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A Reusable Thermochromic Phantom for Testing High Intensity Focused Ultrasound Technologies*

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***Abstract*—High Intensity Focused Ultrasound (HIFU) surgery is a promising technology for the treatment of several pathologies, including cancer. Testing is a fundamental step for verifying treatment efficacy and safety. Ex-vivo tissues represent the most common solution for replicating the properties of human tissues in the HIFU operative scenario. However, they constitute an avoidable waste of resources. Thus, tissue mimicking phantoms have been investigated as a more sustainable and reliable alternative. In this scenario, we proposed a reusable silicone-based thermochromic phantom. It is cost-effective and can be rapidly fabricated. The acoustic, mechanical, and thermal characterization of the phantom are reported. The phantom usability was evaluated with a HIFU robotic platform. 18 different working conditions were tested by varying both sonication power and duration. Temperature and simulated lesions' size were quantified for all testing conditions. An accordance between temperature and lesion dimension trend over time was found. The proposed phantom results a valid alternative to ex-vivo tissues, especially in the early stages of developing novel HIFU treatment paradigms.**

I. Introduction

High Intensity Focused Ultrasound (HIFU) surgery is an emerging, non-invasive therapeutic technology able to revolutionize the treatment of various diseases (*e.g.*, uterine fibroids and tumours of the brain, breast, liver etc.) without the need of any incision, radiation, or drug [1]. HIFU systems usually employ a piezoelectric transducer, which focalizes multiple intersecting beams on the pathological target deep in the human body, with millimetric precision. At the focal point, the high energy density due to the convergence of the US beams induces lethal mechanical and/or thermal effects, thus causing necrosis in the selected target, with no damages to the surrounding tissues. For therapy guidance and monitoring, the treatment has to be performed together with either ultrasound (USgHIFU) or magnetic resonance imaging (MRgHIFU) [2].

The validation of HIFU devices in terms of treatment safety and efficacy is usually carried out either on ex-vivo tissues or by means of Tissue Mimicking Phantoms (TMPs). The former replicate quite well the acoustic and mechanical properties of the living tissues, but the in-vivo translation always involves some features which the ex-vivo tissue cannot mimic. In addition, the use of animal products, such as porcine tissues and organs or chicken breast, represents an avoidable waste of valuable resources. Thus, TMPs seem to be a valid, reliable, and more sustainable alternative. A wide variety of TMPs have been specifically developed for HIFU procedures and – more in general – for thermal therapy studies. They are currently available in liquid, solid, or gel form [3]. TMPs based on polyacrylamide (PAA) are the most widely used in thermal applications. Bovine serum albumin or egg white are usually added to allow real-time visualization of the heated region [4],[5]. However, PAA based TMPs have some limits. First, the lesion induced is irreversible and it occurs at slightly higher temperatures than in the human body. Solutions to obtain reversibility has been proposed, either by using a nonionic surface-active agent as temperature-sensitive indicator [6] or by polymerizing N-isopropylacrylamide with acrylic acid [7]. However, the acrylamide monomer used for PAA TMP synthesis is a cancerogenic dangerous neurotoxin, which requires strict safety rules. Although TMPs based on non-toxic organic substances – *e.g.*, agar, gellan gum and carrageenan – have been proposed, they all suffer from various drawbacks – ranging from fragility, to difficult fabrication and low stability at high temperatures – which limit their usability [8].

Recently, Tissue Mimicking Thermochromic Phantoms (TMTCPs), based on thermochromic additives (powders, inks, or liquid crystals), have been introduced. Their ability to change color – gradually or instantaneously above a given threshold temperature – makes them a valid alternative to the previously presented solutions. Eranki et al. [9] developed a PAA TMTCP with a color gradient between 45 °C and 75 °C, allowing a precise evaluation of the maximal temperature reached. Given the mentioned health risks related to the use of polyacrylamide, Ambrogio et al. [10] proposed a polyvinyl alcohol TMTCP. However, in both cases the dye employed was irreversible. Jiang [11] presented an irreversible – thus, single use – TMTCP made of silicone material. Although its speed of sound and specific heat differ slightly from human tissues values, the silicone represents an attractive material to fabricate TMPs, since it is long lasting, low cost and easily available [12].

To address the need of a reversible TMTCP, we present a novel reusable silicone made phantom for HIFU applications, based on a thermochromic reversible red powder. Reversibility allows for multiple use of the phantom during experimental sessions, thus reducing waste and cost and speeding up the overall testing procedure. An acoustic and mechanical characterization of the phantom was conducted, and its thermal behavior was evaluated. Finally, its usability for HIFU applications was investigated.

II. Materials and Methods

A. Fabrication

The silicone made thermochromic phantom was realized

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by using Ecoflex-30 (Smooth-on Inc., USA), a reversible thermochromic powder (ChromaTemp–Arcacolours, Italy) and Glycerol ($C_3H_8O_3$ 99% extra pure, Sigma-Aldrich, USA). Ecoflex-30 is a room temperature vulcanizing double-component – Part A and the catalysing Part B – silicone, with a curing time of 4 h. The selected thermochromic powder has a transition temperature of 65 °C, where heat-induced chemical structure modifications allow for a change in color from red to white. This threshold was chosen in accordance with the temperature range typically used in HIFU therapy. Glycerol is a non-toxic, colorless liquid, used to increase the speed of sound of the TMTCP. The proposed phantom was prepared in a silicone Part A/Part B ratio of 1:1 w/w. A 30% v/v of Glycerol and a 1% w/w of thermochromic powder were added to Ecoflex-30 Part A. After stirring, Part B was mixed. The mixture was degassed under vacuum for 15 min and then cured at room temperature.

B. *Acoustic and mechanical characterization*

To characterize the acoustic properties of the phantom – *i.e.*, Speed of Sound (SoS), attenuation coefficient (α) and acoustic impedance (Z) – 5 cylindrical samples of 30 mm diameter by 30 mm height were fabricated. A through-transmission technique was utilized for calculating SoS and α, by using deionized and degassed (dd) water as reference material [13]. Each sample was immersed in dd-water and interposed between an US planar unfocused transducer (PA1068 or PA1067 or PA1066 or PA1065, for covering the 1-5 MHz frequency range – Precision Acoustics Ltd., UK) and a needle hydrophone (2 mm, Precision Acoustics Ltd., UK), along the major axis of the US transducer. A wave generator (33220A, Agilent Technologies, USA) connected in series with a 50 dB signal power amplifier (240 L, Electronics & Innovation Ltd., USA) was utilized to drive the US transducer. The produced ultrasonic signal was detected by the hydrophone, and acquired by an oscilloscope (7034B, Infinii-Vision, Agilent Technologies, USA). Signal sampling frequency was set at 40 MHz. Programming and synchronization between the wave generator and the oscilloscope were ensured by a Labview interface. For noise reduction, signals were acquired 10 times and averaged for each measurement. SoS and α at 1-5 MHz with step of 1 MHz, were evaluated as described in Cafarelli et al. [13]. Finally, Z was computed as the product between the density (ρ) and the SoS of the tested sample, where ρ was calculated as the ratio between weight and volume.

To mechanically characterize the phantom, 5 dog-bone shaped samples were fabricated. Measurements were carried out using a mechanical testing machine (Instron Corp., USA) equipped with an electronically calibrated 1 kN load cell. The strain rate was set to 15 mm/min, while the maximum elongation was set at 200% of the initial length of the sample. The 100% Modulus ($E_{100\%}$) was determined as the ratio between the measured stress and the measured strain at 100% sample elongation.

C. *Thermal behavior*

To assess the thermal behavior of the proposed phantom, the specific heat capacity (c_p), the RGB and HSV color components as a function of temperature [10], and the reversibility time were investigated. The c_p was measured on 3 samples by using a Differential Scanning Calorimeter (DSC1, Mettler Toledo, USA) [14]. To evaluate RGB and HSV intensity – thus, color change around the TMTCP transition temperature – the thermochromic solution was molded in five PET tubes (centrifuge tubes – Corning Incorporated, USA) – 12 ml for each tube. A digital hot plate (AREC.X-VELP SCIENTIFICA, Italy) connected to a digital thermoregulator (VPF Vertex-VELP SCIENTIFICA, Italy) was used for creating a controlled water bath. Each tube was immersed in the controlled water bath and the temperature of the molded phantom was monitored with a type K fine wire thermocouple (RS Components, UK). The tip junction of the thermocouple was positioned at the centre of the molded phantom. Temperature measurements were recorded by connecting the thermocouple with a PC through a NI USBTC01 converter (National Instruments, USA), at 1 Hz. The tubes were maintained in the water bath till they reached a target temperature of 55 °C, 60 °C, 65 °C, 70 °C and 75 °C, respectively, and kept at that temperature for 10 min. Then, a picture was taken by using a 12.2 MP camera and a 512x184 pixel ROI was selected using Matlab (Mathworks, USA) for extracting the RGB and HSV color components.

To investigate the reversibility of the proposed phantom, each tube – after having reached the target temperature and maintained it for 10 min – was let to cool at room temperature (25 °C). Temperature variation as a function of time was evaluated through the above-mentioned thermocouple.

D. *Usability test in HIFU application*

To investigate the usability of the phantom in HIFU testing applications, the HIFUSK (High Intensity Focused Ultrasound Surgery based on KUKA robot) platform was used [15]. Figure 1 reports the utilized set-up. The 7 degrees-of-freedom robotic arm (LBR Med 14 R820, KUKA, Germany) mounts the therapeutic HIFU transducer: a 16-channel phased annual array type, with a diameter of 120 mm, a focal length of 120 mm and a central frequency of 1.2 MHz (Imasonic Voray-sur-l'Ognon, France). The HIFU transducer is driven by a 16-channel high-power signal generator (Image Guided Therapy, France). Each channel can reach up to 20 W, thus giving a maximum power of 320 W. A 2D US probe (Analogic

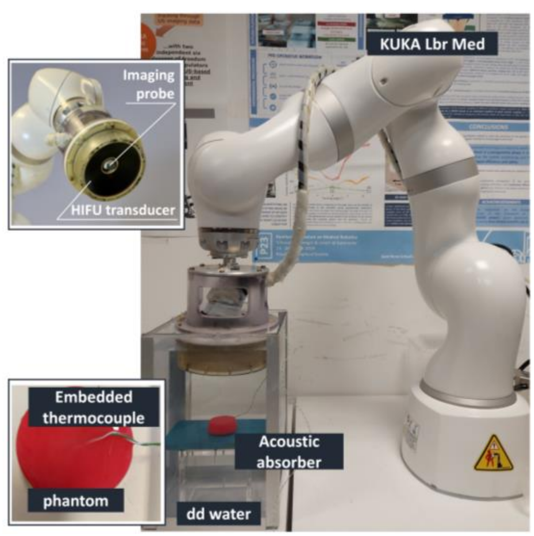

Figure 1. *Set-up - The HIFUSK platform is used for delivering the HIFU sonications. The phantom is immersed in a dd-water tank. A thermocouple is embedded in it for measuring temperature during sonications.*

Ultrasound PA7-4/12, USA) is confocally mounted on the HIFU transducer, for ensuring real-time image guidance during the therapy.

Tests were conducted on a cylindrical phantom (44 mm in diameter, 16 mm in height), placed in a dd-water tank. Sonications were performed by varying both HIFU electrical power – in the range 20-100 W with steps of 20 W – and sonication duration – 5 s, 10 s, 15 s. After each sonication, the phantom was let to cool at water temperature (25 °C). To measure temperature timing (*i.e.*, times related to the temperature rise and descent) during HIFU sonications, the tip junction of the fine wire K thermocouple was fixed just under the surface of the phantom, perpendicular to the axis of the HIFU transducer. Data were acquired at 1 Hz, by connecting the thermocouple to a PC through the NI USBTC01 converter. To compute the area and timing of the lesion (*i.e.*, the phantom color change) during each sonication, a 4K 2160p/30fps video was recorded. A video segmentation algorithm was carried out in Matlab to measure the produced lesion area based on its RGB intensity (using an RGB threshold chosen based on the results obtained in *Thermal behavior*).

III. RESULTS

A. Acoustic and mechanical characterization

The acoustic and mechanical properties of the proposed TMTCP are shown in Table 1: in the first column SoS, α (at 1 MHz) and its power law ($\alpha = x f^{y}$) fitting parameters, Z and $E_{100\%}$ of the proposed phantom are reported. The table shows a comparison with main human tissues [16]–[19].

B. Thermal behavior

Specific heat capacity is reported in the last row of Table 1 and compared with human tissues again [20]. The thermal behavior of the proposed phantom is reported in Figure 2. The graph shows RGB intensity and the HSV color space as a function of temperature, for the five tested values (from 55 °C to 75 °C with steps of 5 °C). For comparison, the RGB and HSV intensity at room temperature (25 °C) is reported. It can be noticed how, as temperature increases, green and blue intensity components increase, until they reach a plateau, towards white color. The recovery time for each of the tested temperatures was evaluated. After being heated and maintained at the target temperature in the range 55-75 °C for 10 min, the phantom shows a recovery time in the interval 15-20 min.

C. Usability test in HIFU applications

The test protocol comprised the evaluation of 18 different sonication conditions. The obtained results are summarized in Figure 3. The first row reports the maximum produced lesion area as a function of the sonication duration, for each of the

TABLE I. ACOUSTIC, MECHANICAL AND THERMAL PROPERTIES OF THE PROPOSED PHANTOM VS HUMAN SOFT TISSUES

	Phantom	*Fat*	*Diseased liver*	*Liver*	*Breast*
SoS[m/s]	1067±1.17	1478	1527	1595	1510
α[dB/cm]	0.67±0.32	0.48	0.58	0.50	0.75
x, y	0.29, 2.3	0.6, 1	-,-	0.9,1.1	0.16,1.7
Z [MRayl]	1.26±0.6	1.40	1.60	1.69	1.54
$E_{100\%}$ [kPa]	24.85±0.7	0.5-3	6-25	8-12	1-3
c_p [kJ/kgK]	3.33±0.06	2.43	3.76±0.07	3.62±0.08	2.22

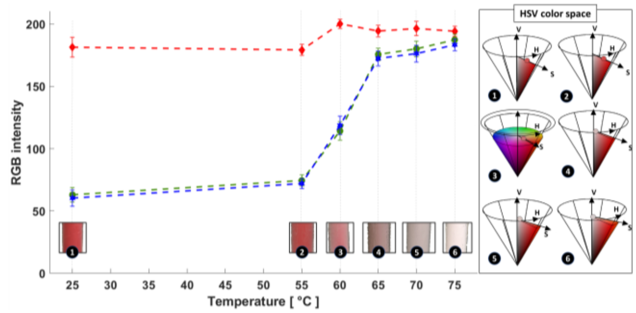

Figure 2. *Phantom RGB intensities and HSV color space at room temperature (25 °C) and after 10 min in a controlled water bath at 55 °C, 60 °C, 65 °C, 70 °C and 75 °C.*

tested sonication power. The corresponding maximum temperature is reported in the second row. The maximum temperature value tends to saturate around 150 °C for a sonication duration ≥ 10 s and a power higher than 60 W. Lesion and temperature timing are reported in the last two rows of Figure 3. Both the lesion and the temperature rise time, *i.e.*, the time where the lesion area and temperature reach their maximum value, coincide with the sonication duration. The lesion descent time, *i.e.*, the time in which the lesion diameter reaches a value lower than 1 mm (area lower than 0.78 mm^2), varies from 18 s (for 20 W, 5 s sonication) to 94 s (for a 100 W, 15 s sonication). On the other hand, the temperature descent time, namely the time in which the measured temperature reaches the water temperature, varies from 3 min (for 20 W, 5 s sonication) to 9 min and 30 s (for a 100 W, 15 s sonication). In addition, results show the same trend between temperature and lesion area variation across time. As an example, Figure 4 reports the lesion area and temperature variation across time for a 60 W, 5 s sonication.

It was previously noticed that powers higher than 100 W cause our TMTCP not to completely recover the original red color after sonication. This can be caused by a thermal damage to the silicone component of the phantom, which reaches the flash point at temperature values higher than 150 °C.

IV. DISCUSSIONS AND CONCLUSIONS

This paper presents a re-usable, cost-effective thermochromic phantom for HIFU applications. The phantom is based on Ecoflex-30, which is a non-toxic silicone material. Its fabrication process is fast and does not require any special equipment or instrumentation. The use of a reversible thermochromic powder allows the phantom to be re-usable. In addition, its rapid reversibility time ensures the user to re-utilize the phantom several times within a single test session.

Some of the phantom's properties were found similar to the ones of human tissues, while other properties (*e.g.*, SoS and $E_{100\%}$) need further investigation on silicone materials and doping agents for their optimization. Thus, the proposed phantom can be considered an affordable, ready-to-use, valid alternative to ex-vivo tissues, in the first phase of HIFU technologies testing.

Phantom color change was analyzed in the range 55–75 °C. A sensitive color variation can be appreciated from 60 °C. This threshold can be tuned by properly selecting the thermochromic powder transition temperature. The relationship between temperature and lesion variation during

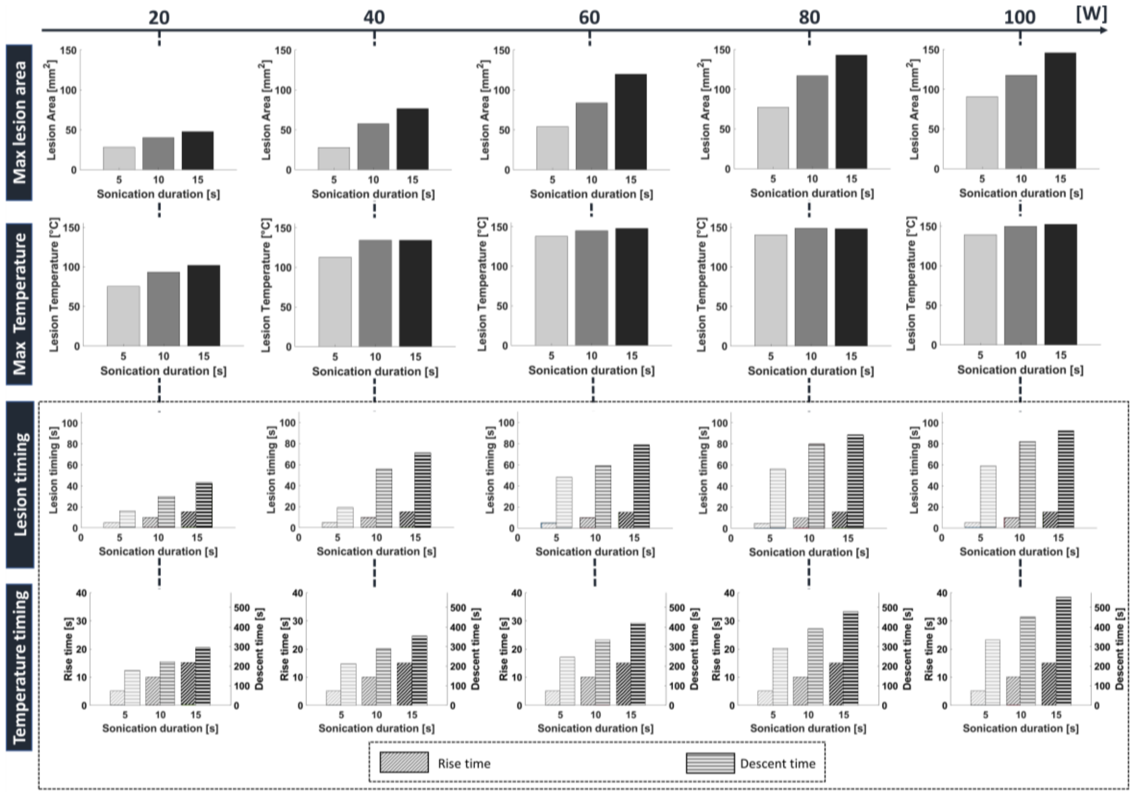

Figure 3. *Maximum lesion area (first row) and maximum reached lesion temperature (second row) as a function of the sonication duration, for each of the tested sonication power. In the third and fourth row, lesion and temperature rise time (light color) and descent time (dark color) are reported.*

HIFU sonications was studied. Lesion variation behavior reflects temperature variation behavior; indeed, lesion dimension provides a real-time information on lesion temperature. In addition, lesion dimensions are proved to be compatible with those ones required in a real clinical scenario to address pathological tissues (of the order of centimeters) [1]. Other kinds of thermal treatment in which our phantom can find applicability could be investigated, *e.g.*, microwave radiofrequency and laser ablation [21].

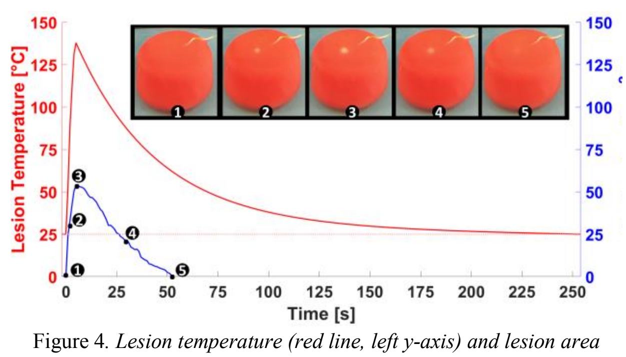

Figure 4. *Lesion temperature (red line, left y-axis) and lesion area (blue line right y-axis) as a function of time, for a 60 W, 5 s sonication.*

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