

## **PRESAGE® as a new calibration method for high intensity focused ultrasound therapy**

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**Abstract.** High Intensity Focused ultrasound (HIFU) is a non-invasive cancer therapy that makes use of the mainly thermal effects of ultrasound to destroy tissue. In order to achieve reliable treatment planning, it is necessary to characterise the ultrasound source (transducer) and to understand how the wave propagates in tissue and the energy deposition in the focal region. This novel exploratory study investigated how HIFU affects PRESAGE®, an optical phantom used for radiotherapy dosimetry, which is potentially a rapid method of calibrating the transducer. Samples, of two different formulations, were exposed to focused ultrasound and imaged using Optical Computed Tomography. First results showed that, PRESAGE® changes colour on ultrasound exposure (darker green regions were observed) with the alterations being related to the acoustic power and sample composition. Future work will involve quantification of these alterations and understanding how to relate them to the mechanisms of action of HIFU.

### **1. Introduction**

High Intensity Focused Ultrasound (HIFU) is a non-invasive thermal therapy for treating cancer, which involves the focusing of 0.5-3 MHz ultrasound waves in tumour tissue, from outside the body, to activate cell death pathways. Two mechanisms of action are involved in HIFU treatments: thermal and mechanical. Thermal effects, which are the dominant cause of cell death, arise from the absorption of acoustic energy in tissue, resulting in an increase of temperature, which creates cigar-shaped thermally ablated lesions [1].

The most notable mechanical effect of HIFU is cavitation. This involves the formation and/or activity of gas bubbles in the tissue. If temperatures exceed 100°C then boiling bubbles may be created – this is thermal cavitation. This can cause an undesirable temperature distribution with an irregular shape [2]. A second effect is acoustic cavitation. Here the ultrasonic pressure cycles either nucleate micron-sized bubbles or cause pre-existing bubbles to grow and oscillate. If bubbles become too large, they can implode in a violent, highly localised, collapse causing mechanical disruption of tissue on a subcellular level [3]. However, the effects of HIFU are material (tissue) dependant, making it a challenge to predict the bio-effects and, consequently, to perform treatment planning. It is, therefore,

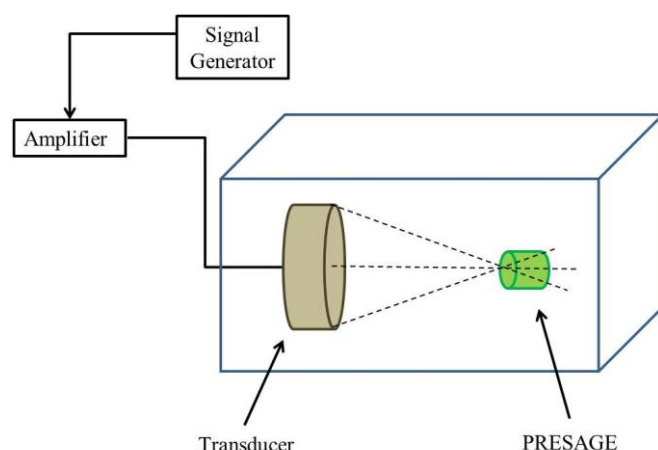


necessary to characterize both the acoustic field at different transducer drive power levels and the tissue attenuation and the absorption within the focal region [4].

PRESAGE® is a volumetric, chemical dosimeter, composed of a solid polyurethane matrix into which is incorporated a leuco-dye reporting agent, which changes colour when exposed to ionising radiation [5-7]. This change can be measured quantitatively in 3D using Optical Computed Tomography (CT). Whilst it has been previously observed that variations in temperature modulate the response of PRESAGE® to radiation [8], the direct production of a spatially resolved colour change by local temperature variations is a novel development. In this work we have tested the viability of using PRESAGE® as a phantom for HIFU beam calibration. Initial results show that colour changes on HIFU exposure and that this is dependent on the ultrasound parameters chosen and the sample composition. PRESAGE® could, therefore, provide a rapid method for performing HIFU calibration.

## 2. Methods

Four cylindrical samples of PRESAGE® (2.2 cm diameter and a minimum of 3 cm height), provided by Heuris Pharma (Skillman, NJ), were exposed to HIFU for 5 seconds, using a single-element transducer (Sonic Concepts, 64 mm outer diameter and 63 mm focal length), driven at 1.7 MHz. For these exploratory experiments, two PRESAGE® formulations with different elastic moduli were selected (“hard” polyurethane SO206 standard PRESAGE formulation with density  $1.07 \text{ g.cm}^{-3}$  (speed of sound of  $2298 \text{ m.s}^{-1}$  and attenuation coefficient of  $9.2 \text{ dB.cm}^{-1}$  at 1.7 MHz) and Shore hardness 80D; “soft” polyurethane CF 95 with density  $1.04 \text{ g.cm}^{-3}$  and Shore hardness 95A (speed of sound of  $2130 \text{ m.s}^{-1}$  and attenuation coefficient of  $23.3 \text{ dB.cm}^{-1}$  at 1.7 MHz)). Two samples of each composition were exposed to free field peak negative pressures of 9.95 MPa and 7.87 MPa (measured in water). Each sample was placed in a tank filled with degassed water. The Presage long axis was aligned with the acoustic beam axis, with the focal plane set 5 mm behind the front face, as represented in figure 1. The samples were imaged using Optical CT before and after exposure using the scanner described in [9] and 3D reconstruction was performed using in-house software.



**Figure 1.** Experimental setup for the HIFU exposure of PRESAGE®. The HIFU transducer was driven using an amplified voltage produced by a signal generator. PRESAGE® long axis was aligned with the acoustic beam axis, with the focal plane set 5 mm behind the front face. For the peak negative pressure values used, a 10 mm long and 2 mm wide focus was expected. The transducer and PRESAGE® were immersed in degassed water to couple the ultrasound between the probe and the sample while suppressing the formation of acoustic cavitation bubbles.

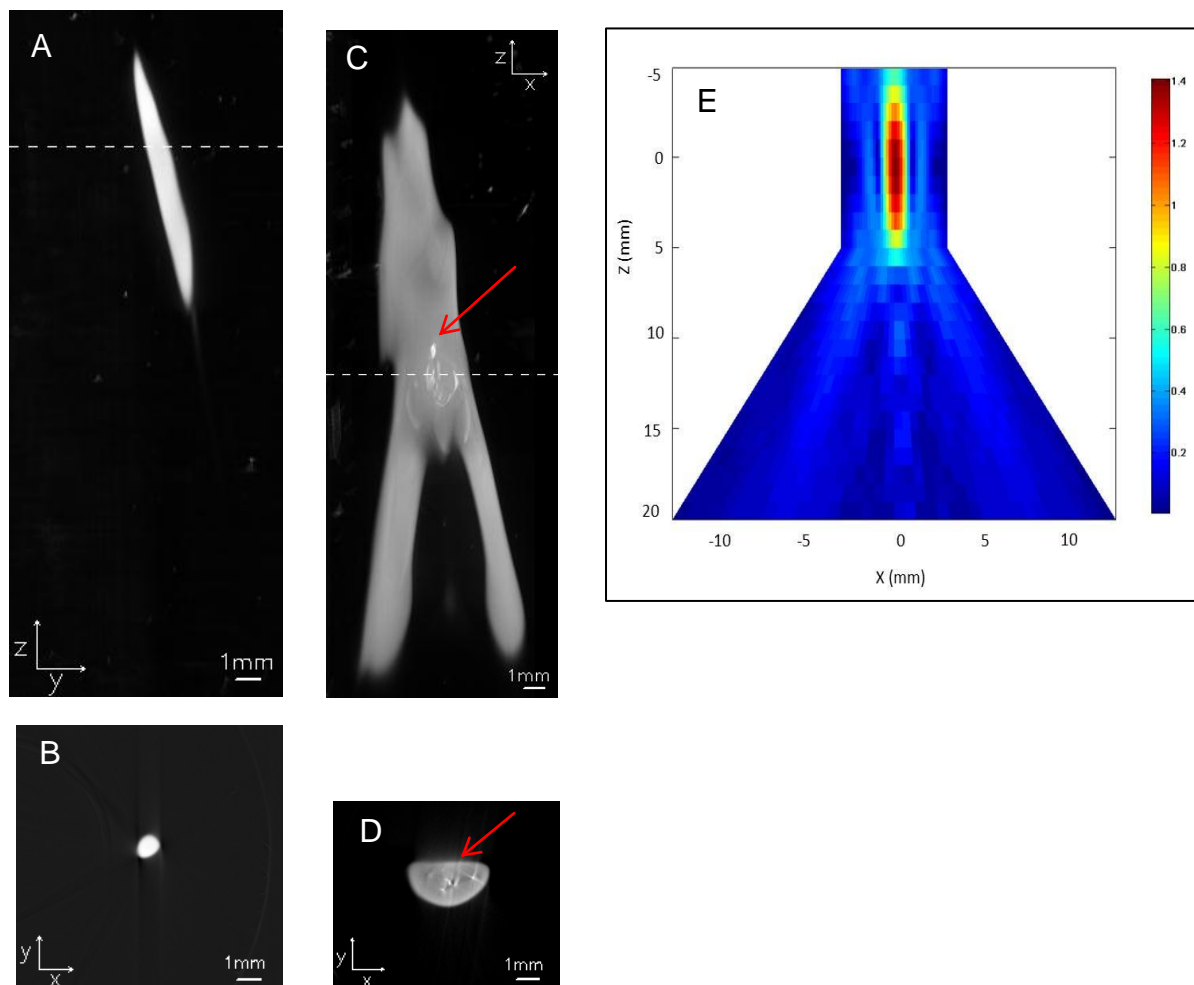
## 3. Results and discussion

All HIFU exposures resulted in an observable colour change in the PRESAGE® (as exemplified in figure 2). These changes were assessed using the optical CT images, represented in figure 3.



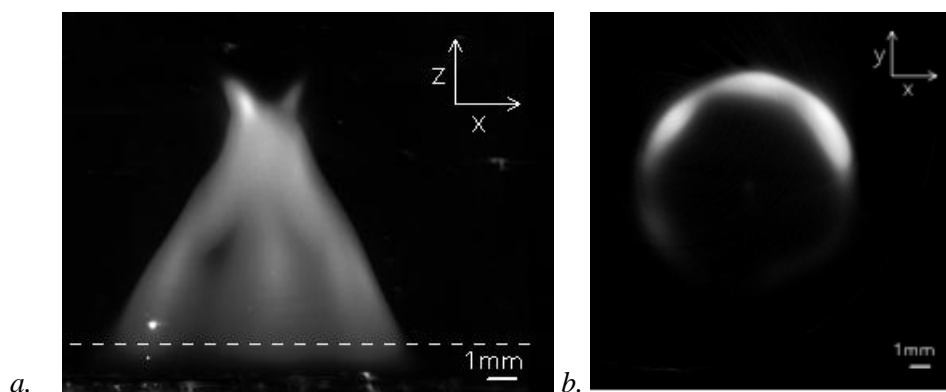
**Figure 2.** Colour changes observed when PRESAGE® was exposed to 7.87 MPa peak negative pressure HIFU. The left sample is a ‘soft’ one made of CF95 polyurethane and the right is the “hard” SO206 polyurethane.

Figures 3 and 4 show a significant difference in size and shape of the HIFU “lesions” obtained with the different acoustic pressures used and the different sample composition. As expected, higher acoustic pressures resulted in larger “lesions”, as more energy is deposited. However, the shapes are also different. Comparing the optical CT images (figures 3A-C) with the beam profile for the Sonic Concepts transducer, (figure 3E), suggests that in figure 3A the focal region can be seen (corresponding to the red region in figure 3E), while in figure 3C the “lesion” seems to be shaped more like the wider (blue) beam profile. Furthermore, in figure 3C, some bubble activity may also be taking place (red arrows pointing for areas of higher greyscale intensity in the image). Further studies will be required to understand the underlying effects causing the changes observed in order to use PRESAGE® as a quantitative HIFU calibration phantom, since one of the key aspects in treatment planning is to distinguish between thermal and mechanical mechanisms. Both “lesions” in figure 3 appear angled, suggesting that the probe might have been slightly tilted in the tank.



**Figure 3.** Optical CT images of PRESAGE® samples exposed to HIFU. z axis is along the direction of ultrasound wave propagation. A: Maximum Intensity Projection (MIP) through a “soft” sample (7.87 MPa ultrasound exposure) in the yz plane (long axis of the sample) showing a roughly cigar shaped lesion. The corresponding reconstruction in the xy plane for the marked slice (dashed line) is shown in B. C: MIP through a “soft” sample (9.95 MPa ultrasound exposure) in the xz plane. The higher power HIFU beam shows a different shape to that in A. Bubbles might have formed inside the PRESAGE® (red arrows) possibly due to acoustic or thermal cavitation in the xy plane reconstruction shown in D. E: beam profile of the transducer obtained in water, as described in [4]. Note: The scale for figure 3E is different from that used in the optical CT images.

Significant differences in beam shape and optical intensity were also observed between “hard” and “soft” samples. Figure 4 shows a clearly different “lesion” from the one in figure 3A, although both samples were exposed to the same acoustic pressure. As in figure 3C, the beam profile seems to have further spread around the focal region. As these were the first experiments of their kind, spare samples from an ionising radiation study were used, but for future studies, it will be important to have a customised and standardised recipe for HIFU experiments, since the results are highly dependent on the composition of the sample. Ideally the PRESAGE® would have a density and sound speed similar to that of water (to optimise acoustic coupling); and acoustic attenuation and absorption and thermal properties (specific heat capacity and thermal conductivity) similar to soft tissues, to mimic treatment exposure conditions. The final “lesion” observed in a “hard” sample exposed to a 9.95 MPa (not shown) was similar to that shown in figure 4.



**Figure 4.** (a) MIP reconstruction in the xz plane for a “hard” sample (7.87 MPa exposure). The optical CT shows a different shape to that seen in figure 3A. A corresponding xy slice is shown in (b). This shows a ‘half-moon’ profile that was also observed in other samples. We would expect a more circular beam profile in water for the transducer that was used, but these shapes might be observed if the acoustic field and/or PRESAGE® sample have some inhomogeneities.

#### 4. Conclusions

Encouraging initial results show a readily measurable HIFU effect on PRESAGE®, which varies with both input power and PRESAGE® composition. Further characterisation of the thermal (specific heat capacity and thermal conductivity) and acoustic (density, speed of sound and attenuation) properties of PRESAGE® is thus the next step. This will then allow us to perform simulations of wave propagation and choose the best composition for future imaging experiments. Furthermore, an existing passive cavitation detection system will be used to determine whether acoustic cavitation is occurring and hence whether the mechanism of colour change is primarily thermal or mechanical. An ultimate goal will be the determination of a quantitative relationship between optical CT image intensity and acoustic HIFU exposure parameters.

#### 5. References

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