Effect of duty cycle of ultrasonic exposure sequence on efficiency of sonodynamic treatment method

超音波照射シークエンスにおける照射時間率が音響力学治療法の治療効率に与える影響

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1. Introduction

Sonodynamic treatment (SDT) is one of the non-invasive treatment modalities for cancer. In this treatment, reactive oxygen soecies (ROS) leading cancer cell death are generated by ultrasound and sonosensitizer which enhances the generation.

In this study, high-intensity focused ultasound (HIFU) is used to induce sonochemical reactions. When tissues are exposed to HIFU, cavitation bubbles are generated by a highly negative pressure around the focal point of HIFU. The cavitation bubbles are oscillated and collapsed by HIFU. The collapse of a cavitation bubble makes the gas inside the bubble adiabatically compressed, resulting in an extremely high pressure and tempreture. In such a condition, water molecules in the bubbles are pyrolytically decomposed, and ROS (e.g. hydroxyl radical, singlet oxygen, and hydrogen peroxide) are generated[1)]. Since ROS has cytotoxicity, cancerous tumor around the focal region of HIFU can be treated. In the previous study[2)], it was reported that some drugs called sonosensitizers can enhance the theraputic effect of SDT.

SDT can treat cancer noninvasively, and more effectively than either HIFU or drug alone. On the other hand, focused ultrasound treatment has a disadvantage; smallness of the focal region. Since the size of the focal region of HIFU is on the order of millimeters, it takes long time to treat a cancerous tumor whose size is much larger than the focal region.

To overcome this disadvantage, the efficiency of ROS generation by HIFU is needed to be improved. In this study, ROS generation by several sequences of ultrasonic exposure is investigated to develop a highly efficient HIFU sequence for SDT.

2. Materials and methods

2.1 Trigger HIFU sequence

In previous studies on HIFU treatment, some effective ultrasonic exposure sequences have been developed. Trigger HIFU sequence, one of them, is a sequence which aims to use cavitation bubbles more efficiently[3)]. This sequence consists of two different types of ultrasonic wave; trigger pulse (TP) and sustaining burst (SB). TP, a short pulse with an extremely high intensity, generates cavitation bubbles with its highly negative pressure. SB, a relatively long burst wave with a moderately high intensity, follows TP and continuously oscillates the cavitation bubbles generated by TP.

2.2 Luminol sonochemiluminescence

When luminol reacts with hydroxyl radical, it is excited and emits blue light returning to the ground state[4)]. Applying this, the region where ROS are generated by the collapse and oscillation of acoustic cavitation bubbles can be visualized[5)]. This phenomenon is called sonochemiluminescence.

2.3 Experimental setup

Figure 1 shows the experimental setup. A 2D-array HIFU transducer driven at 1 MHz was attached on an acrylic tank. The focal length and diameter of the transducer were 120 mm and 147.8 mm, respectively. The transducer consisted of 128 elements, enabling electronic scanning of the focus. The tank was filled with degassed water at 19.5 – 20.5℃ with a dissolved oxygen saturation of 20-24%. The HIFU focus was placed in a polyacrylamide gel having soaked in luminol solution (0.7 mM luminol and 6 mM Na_2CO_3) for 24 hours in a dark refrigerator with at about 5℃. Blue light emitted by luminol reaction was captured by a single lens reflex camera (Nikon D500) in a dark room. The ISO sensitivity value of the camera was 5000, and the shutter speed was 30 seconds. The area which has higher brightness than a threshold (15/255) was detected, and the brightness in the region was integrated.

2.4 HIFU exposure sequence

Two types of HIFU exposure sequence used in this study are shown in **Fig. 2**. T sequence consists of only TP (50 kW/cm^2, 0.1 ms) and intervals, and in TS sequence a SB (0.25 kW/cm^2, 10 ms) follows a trigger pulse. T_{TP}, the period between the trigger pulses, was 30, 100, and 300 ms. Each sequence was repeated for 90 cycles. TP was irradiated to the point 3 mm downstream from the focal point of SB. Before the exposure of T and TS sequence, an ultrasonic pulse (5 kW/cm^2, 0.05 ms) was irradiated 20 times to the focal point with a PRF of 1 Hz for removal of the cavitation nuclei.

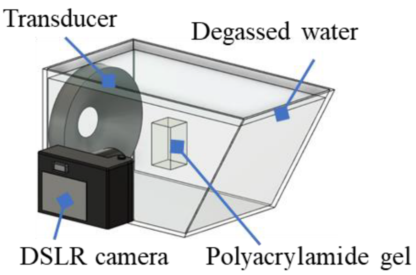

Fig. 1 Experimental setup

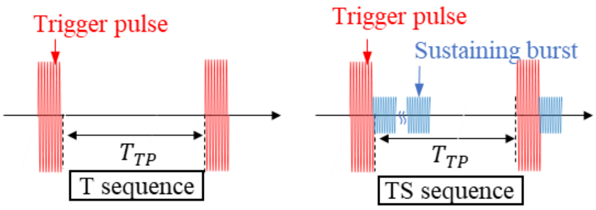

Fig. 2 HIFU exposure

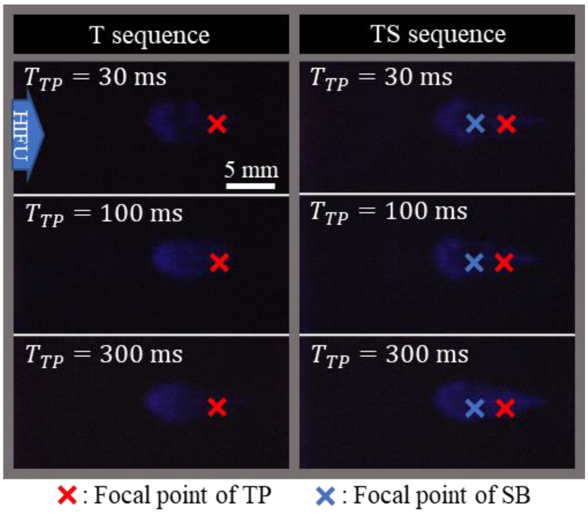

Fig. 3 Images of sonochemiluminescence

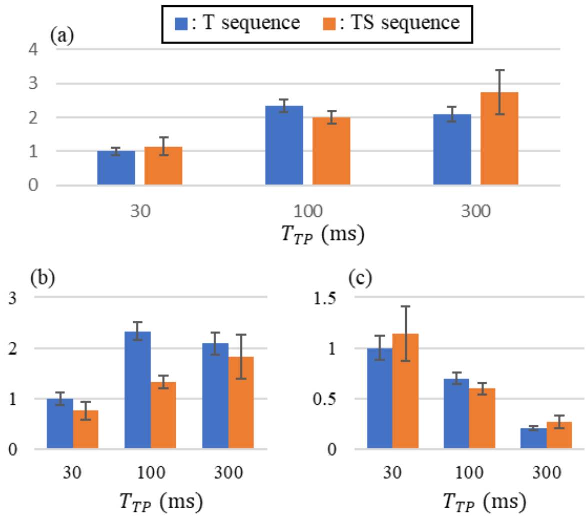

Fig. 4 (a) Integrated brightness, (b) Energy efficiency of ROS generation, (c) Time efficiency of ROS generation

3. Result and discussion

Pictures of blue light emission induced by each of the six sequences are shown in **Fig. 3.** The contrast and brightness of them were adjusted for visibility. The sequence with a longer T_{TP} shows brighter luminescence. The region of ROS generation by TS sequence is seen to have spread downstream.

In **Fig. 4**, the integrated brightness, energy efficiency, and time efficiency of ROS generation are shown. The energy efficiency is the integrated brightness divided by the total acoustic energy. The time efficiency is the integrated brightness per unit time. The values of T_{TP}= 30, 300 ms and that of T_{TP} = 100 ms were averaged for 6 and 3 experiments, respectively. All values were normalized for T_{TP} = 30 ms. It is seen that as T_{TP} increases, the energy efficiency increases, and the time efficiency conversely decreases. TS sequence with T_{TP} of 30 ms shows the highest time efficiency, and T sequences with T_{TP} of 100 and 300 ms show those higher than the other sequences. Considering the use of SDT with electronic focal scanning, e.g. 6 points exposure, longer T_{TP} can improve the time efficiency. There may be a room for improvement for the time efficiency. For example, SB duration can be optimized by considering the dissolution time of bubbles.

4. Conclusion

The effect of duty cycle on the efficiency of ROS generation by the sequence applying Trigger HIFU sequence, was investigated. As the duty cycle of HIFU exposure increased, the time efficiency was improved and the energy efficiency decreased in both T and TS sequences.

References

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