

## Optical Realtime Monitoring of Cavitation Induction and Thermal Coagulation with Phase Change Nano Droplet in Tissues

相変化ナノ液滴を用いるキャビテーション生成および加熱凝固の生体組織中でのリアルタイム観察

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### 1. Introduction

In ultrasound echography, microbubbles are the most commonly used contrast agent. They show high echogenicity and characteristic non-linear acoustic responses, enabling their acoustic echo signals to be distinguishable from other signals with appropriate ultrasound exposure sequences and filters.

Recently, it has been revealed that microbubbles have possibilities to be used as 'sensitizers' for HIFU therapy because they have been found to enhance temperature rise induced by tissue absorption of ultrasound energies. [1-3]. However, a serious problem in utilizing microbubbles is that their sizes (several microns in diameter) are too big to leak into tissues from blood vessels when administered intravenously.

To solve the problem, we are developing a nano-sized ultrasound contrast agent which turns into microbubbles upon the exposure of ultrasound pulses and refers it as phase change nano droplet (PCND).

We aim to administer PCND and change their phase to gas and produce microbubble only at the target inside body. Then we could visualize the target if the droplets are accumulated, and we could then further expose therapeutic ultrasound such as HIFU for site-specific treatment. Because it is an 'on-demand' generation of microbubbles and not requires incubation periods after administration, almost all bubbles are usable for therapy

In this study, we established an experiment system for optical realtime monitoring of the cavitation induction and following thermal coagulation in living tissue while simultaneously observing acoustical changes. With the system, we investigated the relationship between optical and acoustical changes in tissues when they are exposed to 1-MHz ultrasound in the presence of PCND.

### 2. Materials and Methods

#### PCND preparation

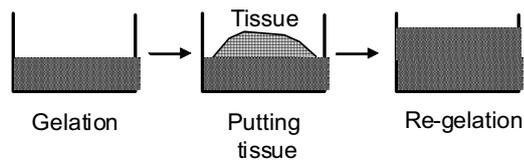
The preparation procedure of PCND was described elsewhere [4]. Briefly, DPPC liposome was prepared and the liposome was further emulsified at high pressure (20 MPa) in the presence of perfluorocarbon liquids. The size distribution of PCND was measured with a LB-550 (Horiba, Ltd., Kyoto, Japan) dynamic light-scattering size analyzer. The mean diameter of the PCND was about 0.2  $\mu\text{m}$ . Tissue samples used in this study were administered 2ml of 0.1%-PCND solutions with syringe and fixed in polyacrylamide gels as shown in Fig. 1-a)

#### Experimental setup for ultrasound exposure

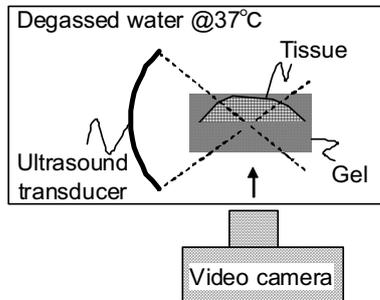
In this study, experiments were carried out with the same setup as previously reported[5]. Focused ultrasound transducer of 1.1 MHz with a diameter of 48 mm were submerged in water tank filled with degassed water kept at 37 °C. Specimen (polyacrylamide gel containing the above mentioned tissue samples) was placed at the focus of the transducer. Ultrasound was exposed typically for 60 s. As shown Fig. 1-b), the optical changes in tissues were recorded with a digital video recorder connected to a Windows®-based computer through IEEE1394 and saved as AVI formatted files. Tissue coagulation volumes were calculated by integrating coagulated areas assuming a spheroid shape. A focused type hydrophone was co-focally aligned with transducer and used to detect acoustic signals emitted from tissues. As an index of cavitation, the square of acoustic signal amplitude was used.

### 3. Results and Discussion

Figure 2 shows a typical optical change in a chicken breast tissue fixed in a gel exposed to 1.1 MHz ultrasound at acoustic intensity of 0.7  $\text{kW}/\text{cm}^2$  for 60 s. A triggering ultrasound pulse is exposed every 0.1 s for phase change of PCND to microbubble (1.5  $\text{kW}/\text{cm}^2$ , 50 cycles). It is clearly shown that a white legion is made after ultrasound exposure. The legion represents the thermal damage caused in the tissue. Obtaining such result was



a) Tissue sample preparation



b) Ultrasound exposure setup

Fig. 1 Tissue sample preparation method in this study (a) and experimental setup for ultrasound exposure (b)

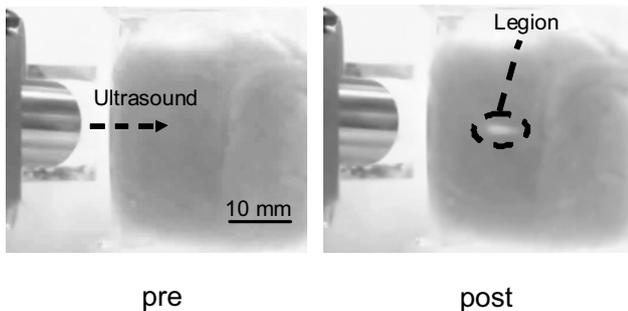


Fig.2 Optical observation of thermal coagulation of chicken breast tissue before and after ultrasound exposure

enabled by following two features of our setup as shown in Fig. 1, 1) tissue surface is formed to be flat upon fixing in a gel, 2) ultrasound is exposed to the interface of gel and tissue. The latter feature is important to monitor optical changes in tissues as well as elevating tissue temperature in water suppressing the influence of the heat convection induced by surrounding water. Figure 3 shows a result of simultaneous optical and acoustic observation of a tissue change while ultrasound is exposed. Fig. 2-a) shows the coagulation volume calculated as described in the previous section. It is clear that coagulation starts at about 40 seconds after exposure begins. As time exceeds, the coagulation volume increases almost linearly. Fig. 2-b) shows the change in acoustic signal intensity, possibly the degree of cavitation. Apparently, the time course is almost chaotic and no clear tendency can be seen. However, it is indicated that after optically significant coagulation start, the acoustic signal intensity is decreased. The mean intensity value is reduced to a third of that before coagulation

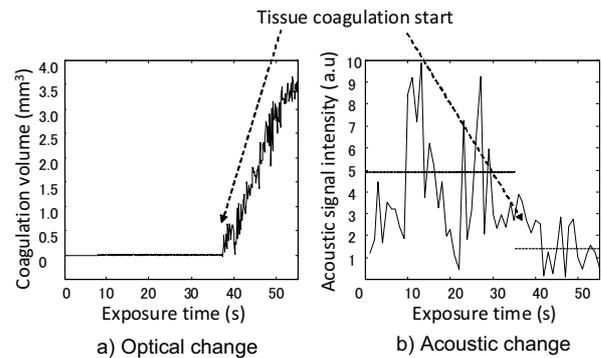


Fig.3 Simultaneous observation of optical and acoustic changes of chicken tissue with ultrasound exposure

starts (dashed lines). Microbubbles are considered to be generated totally during the ultrasound exposure, thus acoustic signals from them should be constant or increased. The tendency in the figure is actually the reverse. Such a result seems to be related to the dynamics of PCND-derived microbubbles. We speculate that the change in their circumstances is the cause. Before coagulation starts, the bubble-surrounding tissues are relatively soft. When coagulation start, the tissues are becoming harder, which may cause the reduced amplitude of bubbles' oscillations. A similar result was obtained in our previous study that acoustic signal intensities obtained upon the phase change of PCNDs decrease as the elasticity of surrounding media increases.

The results obtained may lead to a novel approach for a realtime monitoring of ultrasonic therapy process with PCND that can determine when to stop exposing ultrasound by detecting the decrease of acoustic intensities from tissues. Currently, such therapy monitoring is only available with MRI thermometry. If ultrasound-based monitoring method were enabled, that would make a ultrasound therapy system more moveable and affordable.

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