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On microbubble generated from phase change nano droplet

相変化ナノ液滴より生成したマイクロバブルに関する考察

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1. Introduction

Ultrasound can penetrate into living tissues while maintaining low invasiveness and focus its energy into very small regions less than 1 cm^3. Such property is ideal to develp a minimally invasive therapy, which is needed to maintain high quality of life of patients.

HIFU (High Intensity Focused Ultrasound) therapy aims to utilize above advantage of ultrasound for cancer treatments. Its effectiveness on breast and prostate cancer are proven and now used in clinical settings.

However, there are following three major problems in current HIFU therapy systems to be solved to widen applicable situations.

Preliminary studies have shown that local generation of microbubbles only at target will solve above problems and several approachs are ongoing[1].

Our approach is using a liquid 'precursor' of microbuble (phase change nano droplet (PCND)) which turns into microbubble on ultrasonic pulses[2]. We have been shown that PCND can generate microbubbles in tissue phantoms and murine tumor tissues *in vivo*[3].

In this study, we investigated the phenomena taking place in tissue phantoms on ultrasound with relatively long pulse train to obtain optimum pulse exposure method for generation microbubbles.

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 μm. Gel phantom was prepared basically the same procedure as previously reported [4]. In preparation, 5-% albumin solution is included in the gel as the indicator of thermal coagulation.

Experimental setup for ultrasound exposure

In this study, both in vitro and in vivo experiments were carried out with the same setup as previously reported[4]. Focused ultrasound transducer (2.2 MHz with a diameter of 35 mm or 3.3 MHz with a diameter of 48 mm) were submerged in water tank filled with degassed water kept at 37 ºC. Specimen (polyacrylamide gel containing the above mentioned nano droplet or mice injected nano droplet from a tail vein) was placed at the focus of the transducer. Ultrasound was exposed for 3 s.

3. Results and Discussion

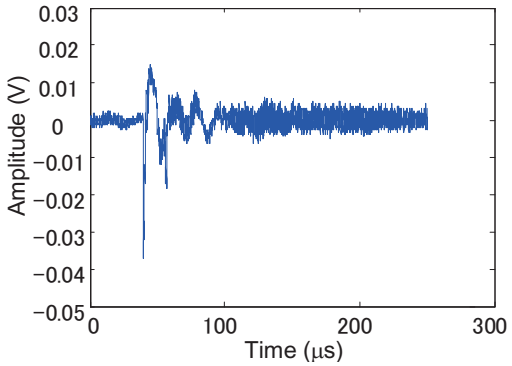

Figure 1 Acoustic signal from PCND

Figure 1 shows typical acoustic signal obtained by the focused hydrophone on exposing ultrasound pulse to a tissue mimicking phantom containing PCND at the concentration of 100 nmol/ml, which roughly corresponding to PCND concentration in murine tumor tissues when 15 minutes after administrated intravenously. In the figure, the process of microbubble generation is clearly shown. On exposing, intense negative pressure is observed and several waves of low frequency components are seen. The former should correspond to the volume inflation due to the phase change from liquid to gas. The latter should be either the movement of generated microbubbles or relaxation of the surrounding media. The time constant is about 20 μs, thus seems to be related to the relaxation otherwise large bubble more than 60 μm is generated (can be denied by optical observation). Figure 2 shows the spectrogram obtained on exposing 3.3 MHz pulse (10,000 cycles) to tissue mimicking polyacrylamide gel containing PCND at amplitude of 2.7 kW/cm^2. The time course

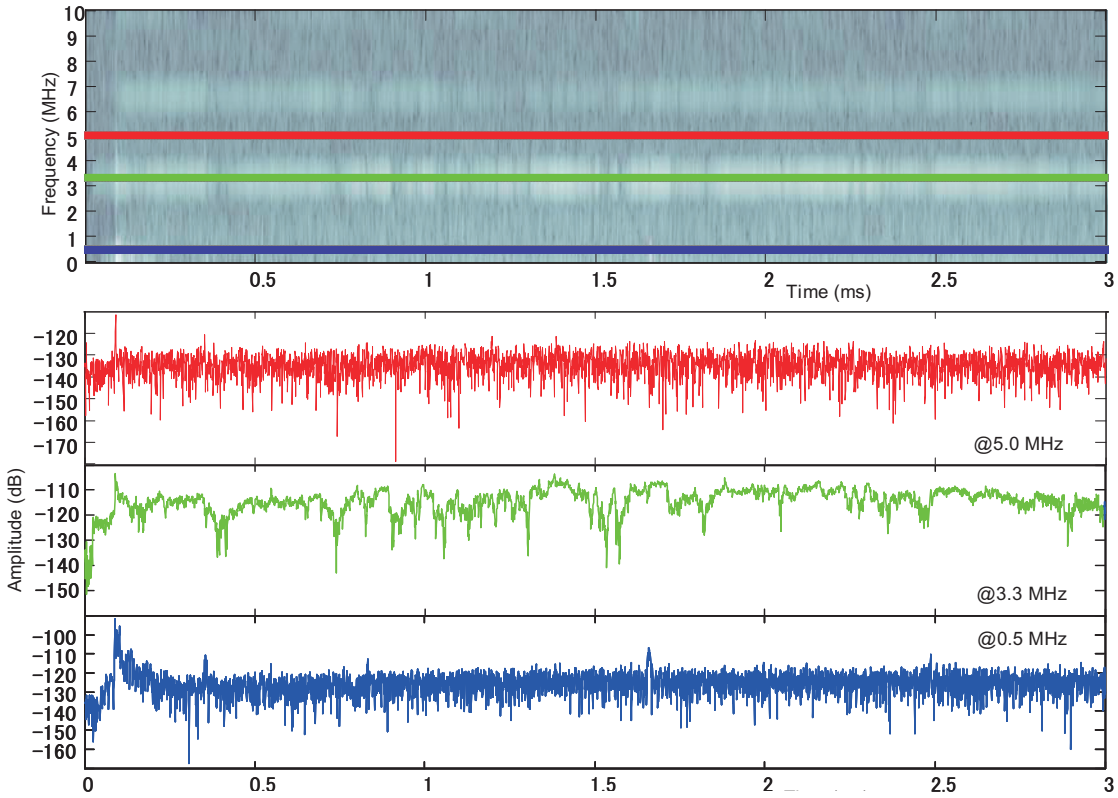

Figure 2 Spectrogram of acoustic signal from PCND

amplitude changes of selected frequency components, at 0.5, 3.3 and 5.0 MHz are also shown in the figure. As control experiments, results with 100 cycles of ultrasound pulse were obtained and confirmed that the length of pulse does not influence the spectrum. As expected from Fig. 1, very broad band signal is detected just after pulsed is started in Fig. 2. Such broad band signal is not observed after the one signal is ceased. Further, the time courses of 3 frequency components were investigated. 3.3 MHz was selected because it is the incident wave. 5.0 MHz was selected as the sign of the presence of the broad band signal. 0.5 MHz component was selected to observe the medium relaxation. No characteristic pattern was found in the 3.3 MHz-component time course except that very strong signal is obtained on exposing ultrasound. 5.0 MHz showed almost the same tendency as 3.3 MHz but more typical. After the broad band signal, every signal amplitude were comparable with noise level. 0.5 MHz was the only exception. It was found that significant signal was observed at least 2 times after the broad band signal. These findings show that significant bubble generation takes place only once in an exposure duration and no successive generation is induced. However, low frequency signals, may be due to the surrounding media relaxation, is observed more than once. Either very fast bubble generation or ceasing process or bubble independent media specific phenomena is taking place. Results obtained this time give information on bubble generation with PCND. To effectively induce microbubbles, the pulse length should not be more than several thousand cycles, or several hundred miliseconds.

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