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Microbubble characterization based on analysis of echo signal obtained by pulse inversion method

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1. Introduction

In ultrasonography, microbubbles (MBs) coated by a biological membrane such as protein and phospholipid have been used as contrast agents for over 30 years. MBs oscillate and scatter strong signals compared with surrounding blood cells and tissues. Thus, MBs significantly enhance the contrast of B-mode images. When MBs are exposed to ultrasound with a high pressure amplitude, they behave nonlinearly and generate harmonic and subharmonic components in the scattered signal. This nonlinear property has been used to improve the image quality in harmonic and subharmonic imaging techniques.

On the other hand, targeted MBs, which can specifically absorb target molecules via biochemical bonds, have been intensively developed and enable ultrasound molecular imaging. In a previous study, it was demonstrated that there was weak correlation betwenn the amount of absorbed MBs and the concentration of target molecule[1]. This resutls suggests that analysis of number density of MBs possibly develops into the qunatification of molecule expression. As a basic step toward quantitaive molecular imaging, this report investigates how the fundamental component and second harmonic component of echo signal in pulse inversion method change with increasing in the number density of MBs.

2. Methods

Commercial contrast agent (Sonazoid®) was circulated in a flow channel with diameter of 8 mm in Doppler phantom (Model 525, ATS Laboratories). The flow volume was 39.7 ± 0.4 mL/min and the flow velocity at the center of the channel was calculated to be approximately 26.5mm/s. The number density of bubbles were 20, 200 and 2000 bubbles/mm^3.

A modified ultrasonic diagnosis system was employed for the measurement of the echo signal. Ultrasound with a center frequency of 5MHz was emitted from a linear array transducer. The RF signal was recorded at a sampling frequency of 40MHz. The total distance range was 40 mm, and the focal point of the ultrasound beam was located at the center of flow channel. In the pulse inversion mode, in-phase and opposite-phase signals were consecutively emitted. The signal for second harmonic component was acquired by adding both of in-phase and opposite phase signals. The estimation of number density of bubbles was conducted in the different five conditions for negative peak pressure of emitted ultrasound, 0.23, 0.38, 0.68, 087, 1.34, 1.62 MPa. **Fig. 1** shows the waveforms at the focus point and corresponding frequency spectra, where the waveforms are measured by a needle type hydrophone with 0.2 mm diameter (NH02, PAL) in absence of Doppler phantom.

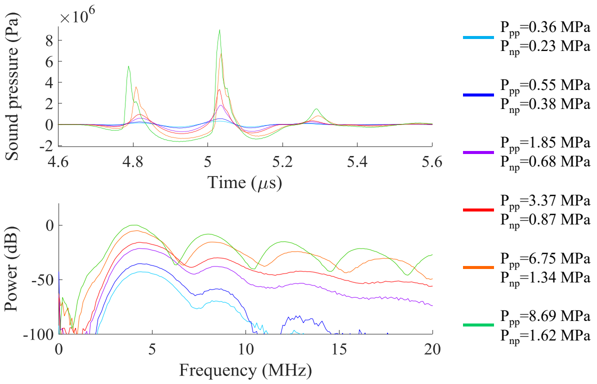

Fig. 1 Waveforms of ultrasound at focus point and frequency spectrum, where P_{pp} and P_{np} mean positive and negative peak pressure, respectively.

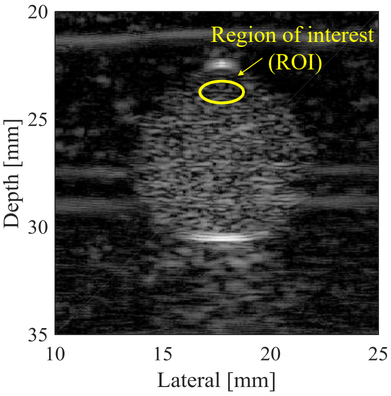

Fig. 2 B mode image of flow channel and shape, size and position of region of interest (ROI) for evaluating echo intensity.

3. Quantification of Echo intensity

Echo intensity was defined as the envelop amplitude evaluated from Hilbert transform of received signal. **Fig. 2** shows B mode image for second harmonic component, where echo intensity was logarithmically compressed. ROI analysis was performed to quantify the echo intensity in the flow channel because echo intensity decayed due to the energy dispersion induced by bubbles. Thus analysis using region of interest (ROI) was performed to avoid the effect of dispersion. The ellipsoidal ROI was located at 1 mm depth from upper of flow channel. The minor and major radii were 1 mm and 2 mm, respectively. The echo was defined as the averaged value in the ROI.

4. Results

First, we investigated the sound pressure range where MBs cannot be destroyed. **Fig. 3** showsthe intensity of fundamental component and as function of peak negative pressure (P_{np}). At $P_{np} < 0.7$ MPa, the intensities of fundamental components seemed to be proportional to P_{np}. At $P_{np} > 0.7$, the intensities decreased with increasing in P_{np}. These results strongly insisted that MBs were destroyed at P_{np} in these experiment conditions. **Fig. 4** shows (a) the intensity of fundamental component and (b) that of second harmonic component as function of number density of MBs at $P_{np} < 0.7$ MPa. It was found that there was proportional relationship between the intensity and number density of MBs except for the result in case of $P_{np} = 0.23$ MPa. The multi-scattering among MBs should complicate the relationship between the echo intensity and number density of MBs. If bubbles with 1 μm radius was distributed in a plane, the effect of multi-scattering become significant in case of number density larger than 2000 bubbles/mm^2.[2] It is supposed that the trend in our experiment, i.e. the proportional relation in 20-2000 bubbles/mm^3 is consistent with the previous study.

4. Summary

For the analysis of number density of bubbles, it was investigated how the echo intensity depend on the number density and sound pressure based on the phantom experiments. The center frequency of ultrasound was 5 MHz. When peak negative pressure was smaller than 0.7 MPa, there was proportional relationship between echo intensity and number density in the range from 20-2000 bubbles/mm^3.

Acknowledgment

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References

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2. [3] O. Couture et al.: IEEE Trans. Ultrason. Ferroelectr. Freq. Control, **46**(1999), 220-232.

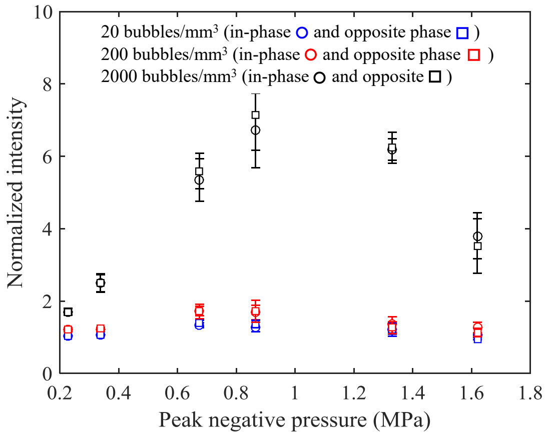
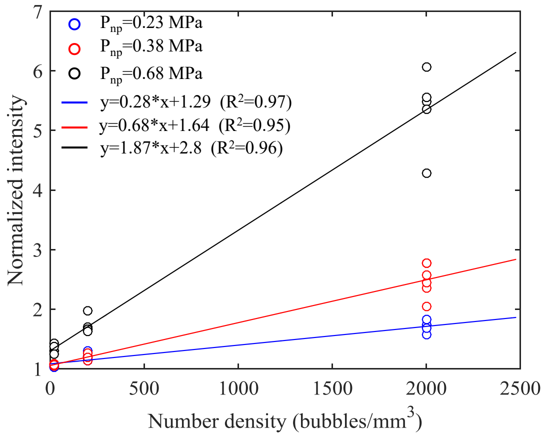
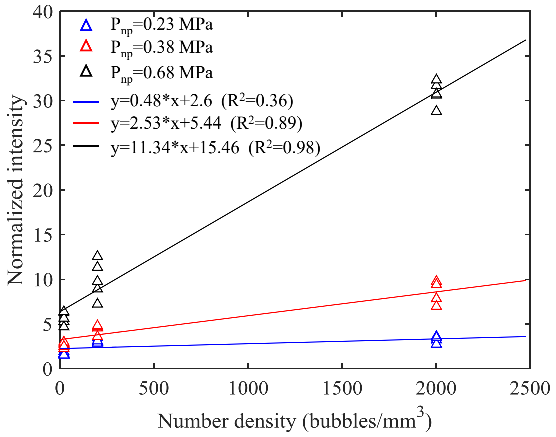


Fig. 3 Echo intensity of fundamental component as function of peak negative pressure, where circle and square plots show intensity of (a) in-phase signal and (b) opposite-phase signal.



(a) Fundamental



(b) 2nd harmonic

Fig. 4 Echo intensity as function of number density of MBs. (a) Fundamental component of in-phase signal, (b) 2nd harmonic component.