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High-sensitivity Measurement Method of Bubble Cavitation Signal Generated from Infinitesimal Amount of Microbubbles

極微量気泡からの気泡キャビテーション信号の高感度測定法

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1. Introduction

To detect infinitesimal amount of microbubbles is becoming more important with development of functional microbubbles and nanobubbles. Microbubbles modified with targeting ligands have a potential in early diagnosis by ultrasound because the targeted-bubble has both a selective property for accumulation in diseased area and a high degree of echogenicity[1]. And the *in vivo* bubble cavitation application, such as sonoporation and drug delivery, is a promising method with combination of targeting microbubbles[2]. However, conventional ultrasonic imaging methods, such as B-mode and ultrasound color Doppler method, need a large amount of contrast agents for imaging because they do not have enough sensitivity for microbubbles when only very small amount of microbubbles exists in ROI.

In order to detect infinitesimal amount of microbubbles, we proposed a novel visualization of bubble cavitation signal (BCS) induced by high intensity US irradiation. In this method, high intensity US (h-US) is irradiated to microbubble with a fixed time delay after introducing an imaging US (i-US) and BCS is detected by power Doppler imaging unit.

2. High-sensitive measurement method of BCS

Fig.1 shows a schematic diagram of the method. To detect irradiation timing of i-US, US wave detector is attached in front of the surface of the imaging probe. Frequency of h-US is chosen around the bubble resonance frequency in order to produce bubble cavitation. There are three different types of US wave signals which are received by the i-US probe. (A) signal caused by microbubble movement, (B) signal by h-US scattered by microbubble and (C) secondary US wave irradiated by bubble cavitation. If h-US wave irradiates simultaneously with an i-US wave by adding some delay, signal (A) produces S-image at the bubble position and signal (C) produces an inherent time-resolved image (T-image) at the position related to the time delay. Signal (B) is suppressed by this irradiation sequence. Now, we consider the RF signal

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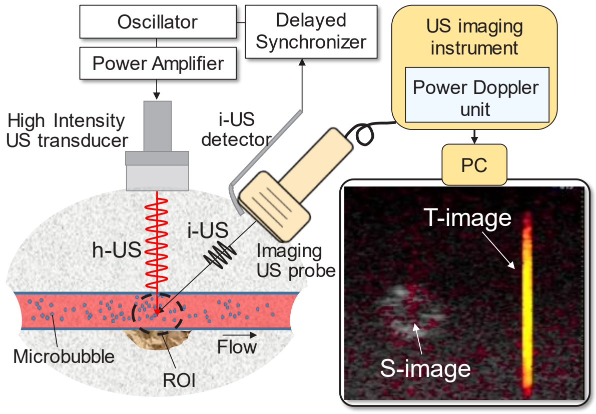

Fig. 1　Schematic diagram of the method.

which is received by i-US probe after the time delay.

$$R_{D,m}(\mathrm{t}) = A_{B,m}(t - T_H) \qquad (1)$$

where, $A_{B,m}$ is the signal which is produced by bubble cavitation and T_{H} is time delay derived from the path difference between h-US and i-US to microbubble. If the received RF signal is fed into a quadrature detector with a reference signal, quadrature detector output signal is given by IQ signals. And if the quadrature detector output signal is fed into MTI (Moving Target Indicator) filter, the filter output signal is written as follows;

$$a_{D,m}(t) = \sqrt{(I_{B,m}(t) - I_{B,m-1}(t))^2 + (Q_{B,m}(t) - Q_{B,m-1}(t))^2} \qquad (2)$$

In usual, since the amplitude of the signal is averaged N times (N: packet size) in power Doppler imaging in US imaging instrument, we obtain

$$< a_{D,m}(t) >= \frac{1}{N}\sum_{m=1}^{N} a_{D,m}(t) = \frac{1}{N}\sum_{m=1}^{N}\sqrt{\left(I_{B,m}(\mathrm{t}) - I_{B,m-1}(t)\right)^2 + (Q_{B,m}(\mathrm{t}) - Q_{B,m-1}(t))^2} \qquad (3)$$

There are three reasons that high sensitive BCS detection is achieved by the proposed method. (I) directly propagated ultrasound wave from h-US transducer to the imaging US probe is suppressed. (II) harmonic frequency components of BCS are detected because the frequency of i-US is much higher than that of h-US. (III) Doppler free geometry is achieved in the same power Doppler image because T-image is constructed not to interfere with the position of S-image.

3. Results

We observed S- and T-images for microbubble suspension which was injected to a small hole in an agarose gel. To avoid bubble destruction by i-US, sound pressure of i-US decreased to 225 kPa by inserting a silicon sheet between probe and gel. Irradiation timing of i-US was detected by thin PVDF film attached in front of the probe. Center frequencies of i-US and h-US were 7.5 MHz and 2.5 MHz. The sound pressure and irradiation time of h-US were set to 1.5 MPa and 30 μs, respectively. We used the microbubble Sonazoid®, which has an average diameter in the range from 2 to 3 μm. Suspensions of microbubbles were prepared at seven levels of concentrations ranging from 8×10^{-9}-8×10^{-3} μL/ml, which was diluted 10^{3}-10^{9} times from the original preparation of Sonazoid.

Fig. 2 shows the extracted result of T-image for various concentration of bubble suspension measured 3 times (id. A, B, C).

Fig.3 shows the result of normalized brightness which is derived from red color of power Doppler image. Not only brightness decrease, but also temporal characteristic change of BCS was observed according to bubble concentration reduction.

Fig.4 shows the brightness of T-image averaged during 30 μs for different microbubble concentrations. When the concentration of microbubble is 8×10^{-9} μL/ml, the averaged brightness is the same with the noise level. The averaged brightness measured at a concentration of 0.08×10^{-6} μL/ml is significantly larger than the noise level.

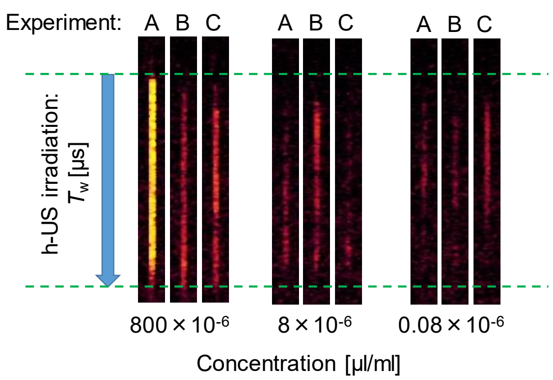

Fig. 2 The recorded T-image for different concentration of microbubble suspension

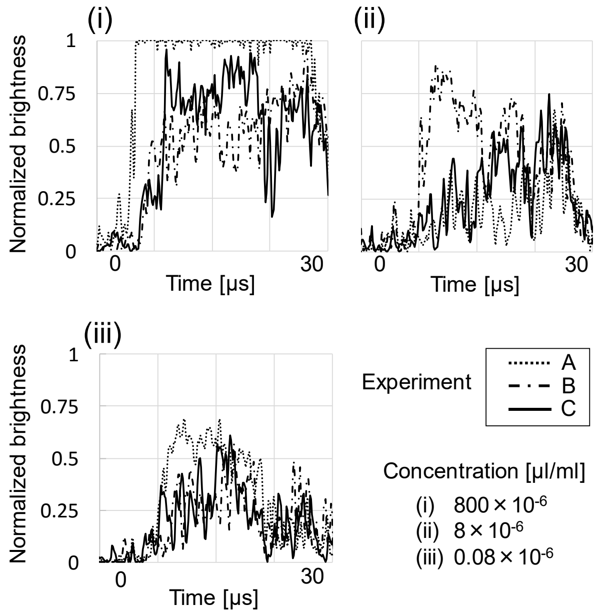

Fig. 3 Analysis result of T-images by normalized brightness of R-value.

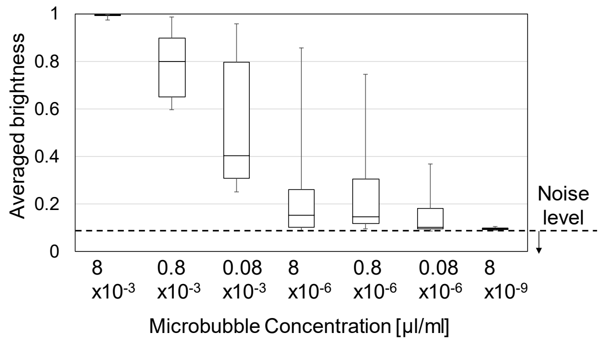

Fig. 4 Average brightness of T-image for different microbubble concentrations

4. Conclusions

In order to detect infinitesimal amount of microbubbles, we proposed a novel visualization of bubble cavitation signal (BCS) induced by high intensity US irradiation. The infinitesimal amount of bubbles, which is 100 times lower than that by conventional method, can be measured by the proposed method.

References

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2. N. Kudo, K. Okada, K. Yamamoto: J. Biophys, **96** (2009) 4866.