Examination of Amplitude Modulated Wave Irradiation for Bubble Cavitation Position Control

気泡キャビテーション位置制御のための振幅変調波照射の検討

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1. Introduction

The *in vivo* bubble cavitation application, such as sonoporation and drug delivery, is a promising method to enhance permeablity of the drugs. The micropores are produced by a microjet, which is caused by microbubble cavitation; however, sonoporation consists of several mechanisms, which are induced simultaneously [1]. The microbubbles aggregate and form a bubble cloud because of the secondary Bjerknes force acting between neighboring bubbles. Bubble clouds show complex motion in ultrasound acoustic fields because of the action of the primary Bjerknes force. The bubble clouds burst because of the nonlinear oscillation of the bubbles. We have proposed an image reconstruction technique that enables both temporal- and spatial-resolved observation of bubble cavitation dynamics using the back propagation of the acoustic cavitation emission (ACE) signal [2]. Several methods have been reported as microbubble manipulation techniques, for example, utilizing the secondary Bjerknes force which is produced between actual bubbles and the mirror bubbles to promote bubble adhesion to the blood vessel wall [3].

In this study, in order to cause bubble destruction near the blood vessel wall and suppress bubble destruction in the center of the blood vessel far from the wall, we investigate an efficient irradiation sequence using amplitude-modulated waves. The generation of bubble destruction near the blood vessel wall would be a useful mechanism in sonoporation as it increases the biological effect near the target.

2. Experimental set up

Fig.1 shows the experimental setup. We prepared a block of agarose gel as a phantom in which a prism-shaped hole (cross section: 2.0 mm × 5.0 mm) was made in order to inject a bubble suspension. A concave transducer was adopted for pumping US irradiation. The center frequency of pumping US was 2.5 MHz. The focal length of the pumping US transducer [L1 in Fig. 1] was 42 mm

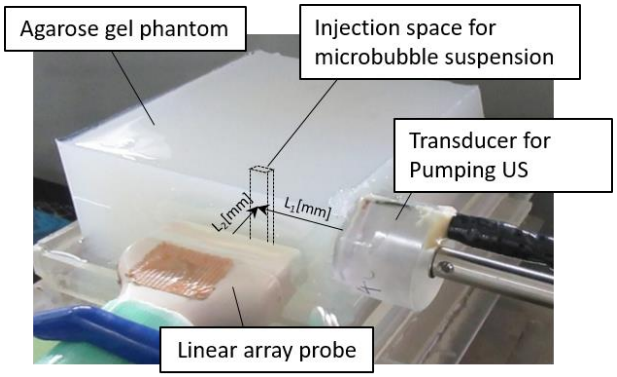

Fig. 1　Experimental set up.

and the beam width of pumping US at the focal point was about 2 mm. The distance of the prism-shpaed hole from the linear array probe [L2 in Fig. 1] was 20 mm.

We used microbbules of Sonazoid (Daiichi Sankyo, Japan), which have a phospholipid shell and perfluorobutane inside with an average diameter of between 2 and 3 μm. The suspension of microbubbles was prepared just before the experiment at a concentration of 1.2×10^6 bubbles / mL, which was diluted 1000 times from the original preparation of Sonazoid.

To record the RF signals, an ultrasound platform (RSYS0003, Microsonic Co. Ltd., Japan) with an imaging linear array probe was chosen. The array has 64 elements with a 7.5 MHz central frequency, a 38.4-mm aperture, and a 0.6 mm element pitch width. In beamforming the received signals, 16 channel data were simultaneously captured, and the frame reconstruction is performed using 32 beamlines. Individual beamlines are formed at intervals with a duration equal to the pulse-repetition time (80 μs). The reconstructed image is obtained at the rate of 390.6 Hz with the irradiation of the pumping US pulse.

We consider the sound input to be a combination of carrier signal (sine wave) of frequency f_c and modulating signal (sine wave) of a frequency f_m having the same amplitude. The amplitude-modulated wave is

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$$s_m(t) = \{1 + cos(2\pi f_m t)\} \times cos(2\pi f_c t) \quad (1)$$

Fig.2 shows the waveform that was input as amplitude modulated signal where f_c is 2.5 MHz, and f_m is 0.15 MHz, which was determined based on λ / 4 resonance with respect to the length of the bubble introduction hole cross section in the pumping US transmission direction.

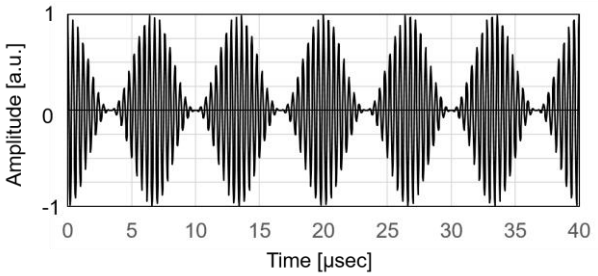

Fig. 2 Waveform of the modulated signal.

The pumping US transducer was driven by a power amplifier (NF Corporation, HSA4101, Japan). The driving signal emitted by the function generator (NF Corporation, WF1968, Japan) was a sine wave and an amplitude modulated wave composed of 40 μs burst length.

3. Results

Fig. 3 shows the reconstructed amplitude signal image which acquired under pumping US exposure with 1st pulse (a) and 16th pulse (b). The sound pressure is modulated to repeat up to 1.4 MPa over a duration of 40 μs. Each frame is displayed with a color bar standardized by its maximum value. In Fig.3(a), the propagation of the bubble cavitation dynamics in the lateral direction is not widely spread and the cavitation distribution appears only near the w1, which is closer to the pumping US wave transmission side, due to the shielding effect of bubbles. In Fig. 3 (b), the cavitation distribution appears alternately in the vicinity of w1 and w2 in synchronization with the sound velocity propagation time.

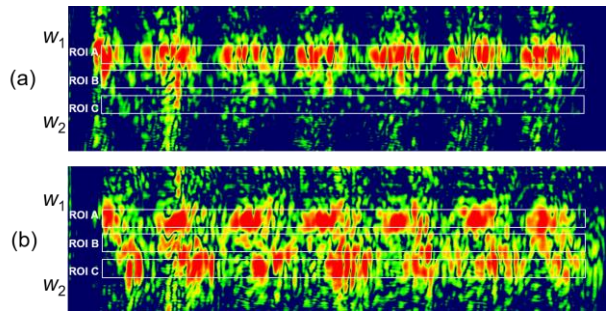

Fig. 3 The reconstructed amplitude signal image which acquired under pumping US with 1st pulse (a) and 16th pulse (b).

In order to examine the difference in cavitation generation efficiency depending on the waveform of the pumping US wave, we compared a sine wave and a modulated wave whose sound pressure was adjusted so that the acoustic energy was uniform. Fig. 4 shows the total signal amplitude of the first 3 frames of the pumping US irradiation and the latter 3 frames of irradiation (16th – 18th frame) measured at each ROI. In Fig.4(a), there is no difference in the tendency of the two irradiation sequences. In Fig.4(b), the total signal amplitude of ROI A and C are larger than that of ROI B, suggesting a more efficient acoustic perforation effect via the blood vessel wall.

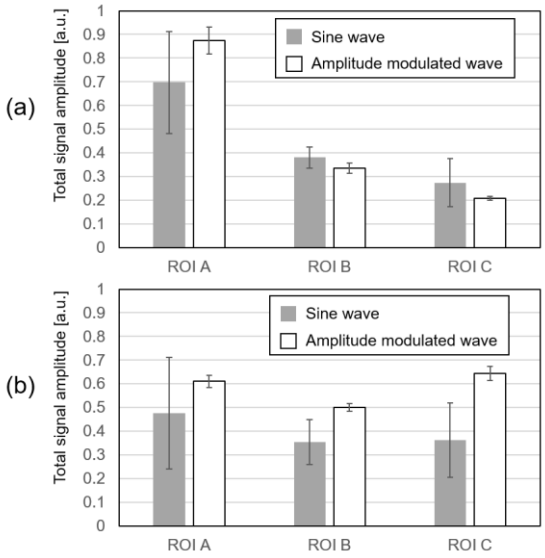

Fig. 4 Total signal amplitude for 3 initial frames (a) and for latter 3 frames (16th – 18th frame).

4. Conclusion

We proposed an efficient irradiation sequence using amplitude-modulated waves for efficient cavitation generation. As a result, it was shown that the occurrence of cavitation near the blood vessel wall was larger than that near the center of the blood vessel, suggesting a more efficient acoustic perforation effect through the blood vessel wall.

References

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