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Observation of continuous variation in size of microbubble aggregations using a broadband sound source

広帯域音源を用いた微小気泡の凝集体サイズの連続変化とその観測

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1. Introduction

Although minimally invasive treatment methods based on the thermal or non-thermal effects of ultrasound with microbubbles (and microcapsules) were being reported [1,2], because microbubbles spread in bloodstream, the density of microbubbles becomes much lower than that of the injection. To solve the problem, we developed a method to control the behavior of microbubbles in flow with multiple transducers by producing acoustic field, and reported that induction efficiency improved by forming aggregations [3]. However, microbubble aggregations have a risk to clog capillaries which locate downstream of the target area. Furthermore, there is another problem that therapeutic ultrasound does not reach to the core of aggregation, which decreases therapeutic efficiency at the target area. Therefore we experimented to control the size of microbubble aggregations by changing amplitude and frequency of acoustic field with a broadband sound source. In this paper we describe variations of aggregation size versus central frequency and exposure time of ultrasound emission.

2. Theory

If two bubbles are located in an even ultrasound field and oscillated, secondary Bjerknes force (SB force) acts on two bubbles as attractive or repulsive force by the reciprocal reflected sound wave, which is given as per the following equation [4], and microbubbles form aggregations [5].

$$\langle F_b \rangle = -\frac{2\pi\rho R_{10}^3 R_{20}^3 \omega^2}{D^2} \varepsilon_{10}\varepsilon_{20} \cos(\varphi_1 - \varphi_2), \qquad (1)$$

where symbol of < > means time integration of the driven ultrasound emission in one period.

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And ρ is the density of the liquid, R_{10} and R_{20} are initial radius, ε_{10} and ε_{20} are oscillation amplitude of the bubble 1 and 2, respectively, ω is angular frequency, D is the distance between two bubbles, and φ_1-φ_2 is the phase difference of the oscillation between bubbles. From equation (1), though the magnitude of SB force is proportional to the square of the frequency, an acoustic field of higher frequency easily produces phase difference of the oscillation between neighboring bubbles, which might not result to increase SB force due to the term of cosine. Fig.1 shows a schematic of the assumption to form microbubble aggregations by SB force under ultrasound exposure. When the frequency is lower, though the magnitude of SB force is lower, phase of the oscillation is uniform between neighboring bubbles to produce greater aggregations. On the other hand, when the frequency is higher, less uniform acoustic field produces less size of aggregation. The following experiment was carried out to confirm the possibility to control the size of aggregations by varying the frequency.

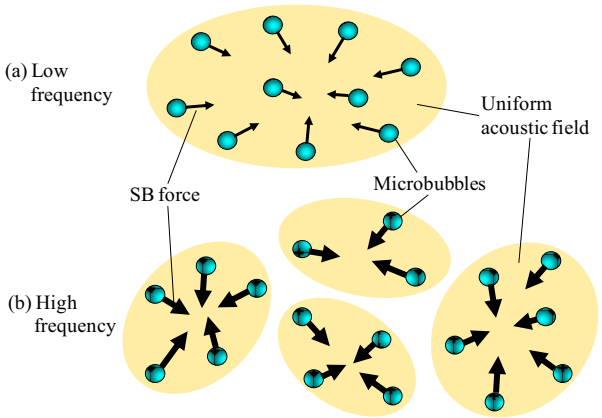

Fig.1 Schematic to form microbubble aggregations by secondary Bjerknes force and variation with frequency.

3. Experiment

We used the F-04E microcapsules (Matsumoto Oil, Co, Ltd), which has a specific gravity of 0.0225 and an average diameter of 2.7 [μm], because of the cost and the stability in room temperature. We selected only those microcapsules with a diameter less than 20 [μm], which resonance frequency is approximated between 5 and 10 [MHz]. We produced a 2 [mm] x 0.3 [mm] channel, which is made of poly(ethylene glycol) with a sound velocity of approximately 1550 [m/s] and a density of 1.27 [g/mL]. It is placed 30 [mm] apart from the bottom of a tank filled with water to avoid the influence of reflected wave. Fig.2 shows the experimental setup.

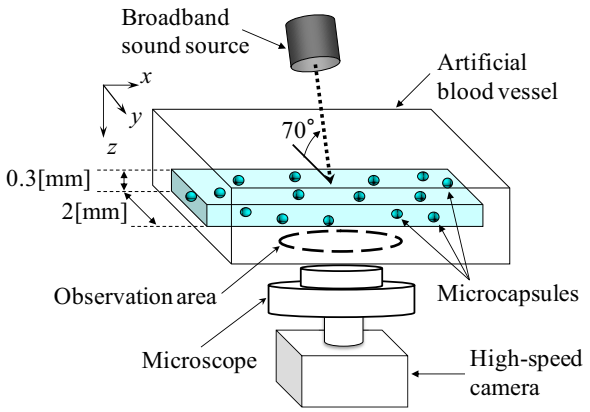

Fig.2 Position relationship between the broadband sound source and observation area in the small channel

The channel was filled with the suspension of capsules of a density of 0.2 [g/L]. The angle of the axis of the sound source, which has central frequency from 2 to 7 [MHz], is set 70 [deg] to the *xy*-plane in Fig.2. The focal point of ultrasound field is set to be in center of the observation area, where behavior of capsules was recorded optically using an inverted microscope and high-speed camera which has frame rate of 500 [fps].

4. Results

First we continued to emit ultrasound with central frequency of 2 [MHz] and the maximum sound pressure of 100 [kPa] to form aggregations. Then aggregations of average area of 1.8×10^{-3} [mm^2] were confirmed. From this condition we started the experiment by changing frequency continuously to 7 [MHz] with keeping maximum sound pressure. Fig.3 shows behavior of an aggregation under the ultrasound emission when the frequency was swept from 2 to 7 [MHz] in 2 [s]. Until 1.502 [s] the area of the aggregation was almost constant, but after then it suddenly collapsed into smaller aggregations.

We also experimented other conditions of sweep time of the frequency. Fig.4 shows the time variations of the average area of the aggregations and the frequency in 3 kinds of sweep times. The time axes are identical in two variations. According to the result, with shorter sweep time, collapse of aggregations shows quicker. Also size of the aggregations shows the dependency on the frequency. Thus the possibility to control the size of aggregations would be realized by sweeping the frequency of ultrasound.

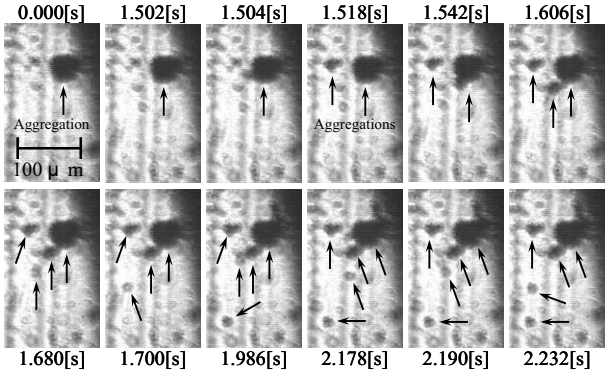

Fig.3 Behavior of the aggregation under the ultrasound emission with sweep time of 2 [s].

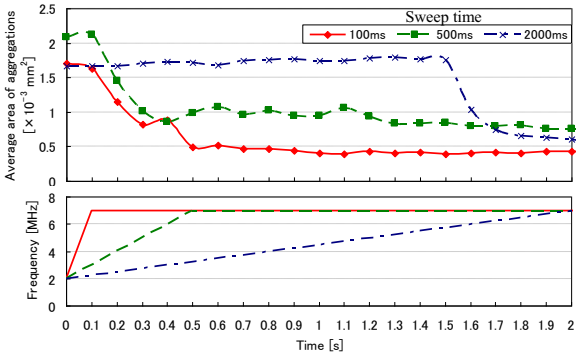

Fig.4 Time variation of the average area of aggregations and the frequency with various sweep time.

5. Conclusion

In this study, we observed continuous variation in size of microcapsule aggregations using a broadband sound source. We confirmed that the size of aggregations depends on the frequency and was able to be controlled by sweeping the frequency. For further analysis, we are going to elucidate appropriate conditions of ultrasound emission to realize precise and quick control of aggregations.

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