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Frequency-Dependent Phase Change threshold of Perfluorocarbon Nanodroplets

パーフルオロカーボンナノ液滴の相変化閾値の周波数依存性に関する研究

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1. Introduction

Recently, perfluorocarbon nanodroplets are getting much attention as agents for ultrasonic contrast imaging and therapy because they have a size of several handred nanometers and can percolate through neovascular vessels feeding turmors.

Kawabata *et al.*[1),2)] have been developing and reported such nanodroplets, referred as phase change nanodroplets (PCNDs), which can change their phase from liquid to gas by a triggering ultrasound pulse. According to their reports, PCNDs may have potentials to apply to two types of situation, diagnostic and therapeutic, as they can play a role in microbubble precursor. They have investigated that the microbubbles derived from PCNDs could be sustaind by low-amplitude continuous ultrasound after the phase change by the high-intensity triggering pulse[1),3)]. If they have frequency-dependent phase change threshold, we may be able to obtain the phase-changed microbubbles more effectively by optimizing the frequency of the triggering pulse.

In this study, we investigate whether PCNDs have a frequency-dependent phase change threshold by measuring subharmonic signals emitted from the phase-changed microbubbles by using a high-intensity pulse followed by low-amplitude continuous ultrasound.

2. Materials and Methods

2.1 PCND preparation

PCNDs were prepared as described previously[1)]. Dipalmitoyl-phosphatidylcholine (DCCP), dipalmitoyl-phosphatidic acid (DPPA), and pegylated dipalmitoyl-phosphatidylethanolamine (PEG-DPPE) were mixed at molar ration of 8:1:1, and a phospholipid mixture of 8 mM total concentration was combined with 4.5% (v/v) perfluoro-n-pentane (PFP) and 4.5% (v/v) perfluoro-n-hexane (PFH).

2.2 Phantom preparation

Polyacrylamide gel phantoms were prepared as described previously[1)]. An acrylamide solution containing 9.75% (w/w) acrylamide and 0.25% (w/w) bis-acrylamide was degassed for 15 min. The PCND suspension was then added to yield a final perfluoropentane concentration of 12.0 ppm (v/v). After that, 0.5% (w/w) ammonium persulfate and 0.5% (v/v) N,N,N',N'-tetramethylethylenediamine (TEMED) were added to start polymerization. The solution was immediately poured into a container and placed on ice for 5 min to complete the polymerization. The phantom was cuboid in shape (with dimensions of about 4×4×2 cm^3) and placed in a tank with its largest plane facing an ultrasound transducer.

2.3 Experimental setup

Air-backed transducers consisting of piezoelectric ceramic with a resonance frequency of 1.13 MHz, 3.46 MHz or 5.36 MHz, respectively, were used for the exposure. They had a spherical curvature radius equal to diameter of 70, 20, and 20 mm, respectively. One of them was submerged in deionized and degassed water at 36-37 ºC as well as the gel phantom. The oxygen concentration was checked before and after each series of experiments and confirmed to be between 25% and 30%. Subharmonic signals were detected by a focused hydrophone (H10CF, Toray Engineering) with a resonance frequency of 10 MHz. It has a diameter and spherical curvature radius of 10 and 50 mm, respectively (**Fig. 1**). A high intensity burst for 100 μs at 0 to 9 kW/cm^2 was used to produce microbubbles from PCNDs. Immediately after that, CW ultrasound at a peak negative pressure of 2 MPa for 100 ms was irradiated in order to sustain produced microbubbles (**Fig. 2**). These waves were aimed at the gel 10 mm deep from the surface. The

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spectrum was calculated using a Fourier transform for a 1 ms window, starting at 10 ms after the start of sustaining ultrasound exposure. This FFT window was chosen because the microbubbles generated by short-pulsed ultrasound have a short lifetime, typically less than 50 ms[2]. Each series of experiment was done ten times at the same condition. Spatial peak-temporal average intensity (*Ispta*) was calculated from the measurement at low-intensity acoustic pressure with a hydrophone (HGL-0400, Onda) assuming that the output acoustic power from the transducer increases in proportion to the input electric power.

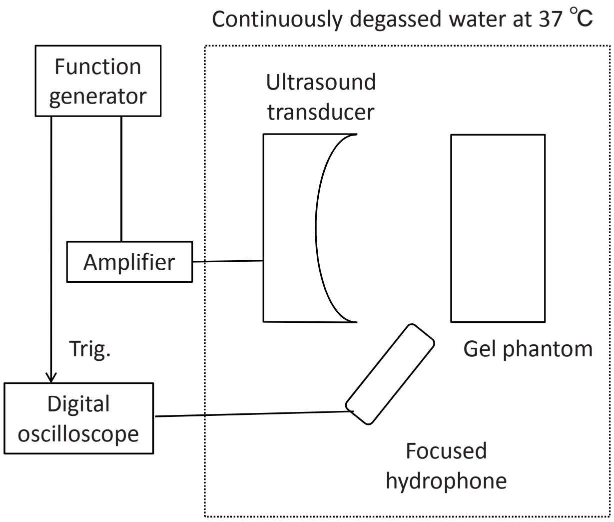

Fig.1 Experimental setup

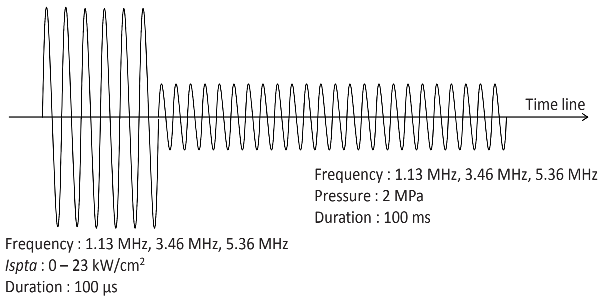

Fig.2 Wave form of microbubble generation and sustaining.

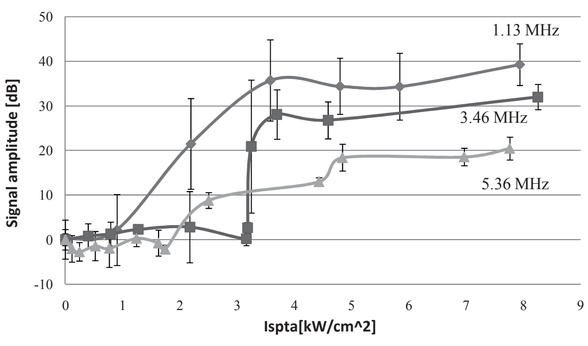

Fig.3 Subharmonic signals from microbubbles induced by high-intensity.

3. Results

Fig. 3 shows dependence of subharmonic signal amplitude from the microbubbles on *Ispta* of the high-intensity triggering pulse. Error bars show the standard deviation. In Fig.3, circles, squares and triangles indicate the subharmonic signal amplitudes emitted from the microbubbles induced by high-intensity ultrasound at 1.13, 3.46, and 5.36 MHz, respectively. The intensity threshold for phase change at 1.13, 3.46, and 5.36 MHz, was around at 1, 3, and 2 kW/cm^2, respectively. Each spectrum runs parallel above the threshold. The highest signal amplitude was observed for a 1.13 MHz pulse. The phase change was induced by a 1.13 MHz pulse at lower *Ispta* than other frequencies.

4. Discussion

The results suggest that PCNDs have a frequency-dependent phase change threshold which is significantly lower at a lower ultrasonic frequency. The subharmonic amplitude at each frequency, at the same sustaining frequency and amplitude, should correlate well with the amount of microbubbles. However, the subharmonic amplitudes at different frequencies from microbubbles sustained at different frequencies are difficult to compare although the amplitude of sustaining ultrasound was kept the same. Further study is needed to compare the amount of microbubbles produced by triggering PCNDs at different frequencies.

5. Conclusion

A frequency-dependent phase change threshold of PCNDs was observed from the measurement of subharmonic signals emitted from the microbubbles which were produced from the droplets triggered by a high-intensity pulse and sustained by low-amplitude ultrasound. In triggering the phase change by a high-intensity pulse, a lower ultrasonic frequency may have an advantage.

References

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