Acoustic Detection of Microbubble Destruction in Gaseous Contrast Agents

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Abstract--- The nonlinear oscillation and stimulated scattering of the insonified encapsulated-microbubbles during destruction were investigated using both passive and active acoustic detection techniques. The effects of the destruction on ultrasound imaging were also demonstrated.

The destruction of encapsulated contrast microbubbles has attracted much attention recently. This effect can be used to create new imaging modalities and enhance drug and gene delivery. However, it may produce adverse bioeffects as well. In this paper, the nonlinear behavior and stimulated scattering of the insonified encapsulated microbubbles during destruction were investigated using both passive and active acoustic detection techniques.

A high-intensity focused imaging ultrasound field was established using a 2.5 MHz imaging transducer (diameter 25 mm and focal length 42 mm). The transducer was driven by a signal generator through a 500W power amplifier. It transmitted acoustic imaging pulses with a center frequency of 2.5 MHz for activating the pulsation of contrast microbubbles. The acoustic pressure amplitude was calibrated using a 0.5mm diameter needle hydrophone (Precision Acoustics Ltd, Dorchester, England). Isoton II was used as the carrying and propagation medium and was kept in circulation by a magnetic stirrer.

The collective behavior of multiple microbubbles was examined using a passive acoustic detector. The passive detector was composed of a broadband transducer with a center frequency of 25 MHz. It was positioned confocally at right angles with the imaging transducer. With the passive technique, the oscillation and destruction of microbubbles was studied by characterizing the waveforms of received acoustic signals, and by analyzing harmonic and noise generation via the spectra of the signals. The generation of discrete higher harmonics (up to the 20th order), subharmonics and ultraharmonics was observed at low acoustic pressures, as shown in Figure 1(a). The noise floor in the spectrum was raised at high pressures and therefore discrete harmonic structure in the higher-frequency domain was replaced with broad band noise, as shown in Figure 1(b). The noise spectrum in the higher frequency range was found to be broadened as the acoustic pressure was increased.

Figure 1. The spectra of ultrasound signals received by the passive detector. Encapsulated PFCs microbubbles were insonated by 32-cycle 2.5 MHz pulses at (a) 0.38 MPa with 40dB receive amplification and (b) 0.72 MPa with 28 dB.

The individual behavior of single insonified microbubbles was investigated by an active acoustic detector consisting of a 25 MHz transmit transducer and a 25 MHz receiver (both diameter 12 mm and focal length 12 mm). The active detector was based on the design of a similar detector used by Roy and Apfel (1990) for
detecting microparticles. The transmit transducer sent long low-amplitude detection pulses with a center frequency of 25 MHz. Scattered signals were sensed by the receive transducer. The active detector had a very high spatial resolution and detected objects only in the small confocal region of the two transducers. The detector was aligned to the center of the focal region of the imaging transducer. A band-pass filter with a center frequency of 25 MHz was used to remove both low frequency and high frequency noise, and therefore improved the detection sensitivity at 25 MHz. A time modulus was used to synchronize the acoustic detector with the imaging ultrasound pulses. During our experiments, the microbubble suspensions were diluted sufficiently to allow one microbubble at a time to be present in the detection region of the active acoustic detector.

The first 10 sequences of scattered pulses from three individual encapsulated microbubbles were recorded as shown in Figure 2(a), 2(b) and 2(c), respectively. The constant amplitude in Figure 2(a) corresponded to a non-pulsating microbubble with the imaging ultrasound field off. After the imaging transducer was activated with 16-cycle 2.5 MHz pulses, the scattered signals became modulated responding to the microbubble pulsation in Figure 2(b). Both the linear scattering of the acoustic detection signal and the nonlinear scattering of the imaging ultrasound pulses contributed to the modulation. Obviously, this microbubble was not destroyed by the first 10 imaging ultrasound pulses. After exposure to 4 imaging ultrasound pulses of 1.0 MPa and 16 cycles at the PRF of 1 kHz, on the other hand, the microbubble in Figure 2(c) was destroyed and no significant scattered signal was observed afterwards. The scattered imaging signals from contrast microbubbles usually had a length similar to that of the incident ultrasound pulses (16 acoustic cycles at 2.5 MHz), while inertial cavitation from a suspension of 0.1 mm polystyrene particles lasted less than two acoustic cycles.

![Figure 2](image)

Figure 2. The first 10 sequences of scattered signals from three single encapsulated PFCs microbubbles of another contrast agent at (a) 0 MPa (b) 0.66 MPa, and (c) 1.0 MPa.

The destruction rate as a function of imaging pulse firing number was measured. The destruction rate was defined as the percentage of the destroyed microbubbles among all microbubbles detected by the acoustic detector. The destruction rate increased with the number of firings. When 0.66 MPa, 16-cycle imaging ultrasound pulses were transmitted at a repetition frequency of 1 kHz, about 15% of microbubbles were destroyed by a single firing of the imaging pulse. Only 20% of the detected microbubbles survived after exposure to 8 imaging pulses. The destruction rate was also found to increase with the acoustic amplitude, the pulse length, and the pulse repetition interval.

The results from both passive and active detection will be compared and discussed. The effects of the destruction on ultrasound imaging will also be demonstrated. These effects include the enhancement of the first and second harmonic signals, the creation of phase-correlated acoustic emission images and the occurrence of spectral broadening and disappearing artifacts.

REFERENCES