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ULTRASONIC CONTRAST AGENT DESTRUCTION MECHANISMS REVEALED BY OPTICAL OBSERVATIONS

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Introduction: Ultrasonic contrast agent (UCA) consists of liquid containing gas bubbles with diameters of a few micrometers, either free or encapsulated by a shell. UCA bubble destruction behavior has been under investigation for its potential application in high MI imaging techniques, noninvasive pressure measurements, neovascularization, and in drug and gene delivery. The success of such new diagnostic and therapeutic techniques is directly related to our understanding of UCA microbubble destruction.

We investigated UCA destruction mechanisms by subjecting two different contrast agents to high-amplitude ultrasound, and optically recording their behavior with a fast-framing camera. Optically observing ultrasound insonified UCA microbubble with a high-speed camera is a promising method for analyzing microbubble oscillation and destruction behavior.

Methods: The fast-framing camera was capable of recording an optical image sequence of eight frames per experiment and operated at a speed of three million frames per second. Each image sequence was taken during one cycle of ultrasound. We recorded 482 image sequences with an experimental UCA (Bracco Research SA, Geneva, Switzerland), freely flowing through a capillary cellulose tube. The microbubbles had a median diameter of 2 μm . The shells were phospholipid monolayers with an estimated thickness of 10 nm. We also recorded 57 image sequences with Quantison™ (Upperton Ltd., Nottingham, UK), poured into a container and covered with a microscopic slip. The microbubbles had a mean diameter of 3.2 μm . The shells consisted of human serum albumin (0.2–0.3 μm).

In all experiments we transmitted 10 cycles of ultrasound with a center frequency of 0.5 MHz. Peak negative acoustic pressures corresponded to mechanical indices (MI) between 0.9 and 1.2.

Results: The optical image sequences revealing destructive behavior were classified as follows.

Coalescence – the fusion of two or more bubbles. This mechanism was only observed while microbubbles were expanding. We recorded 133 image sequences showing experimental UCA microbubble coalescence. The coalescence mechanism was found to be analog to mechanisms described for larger free gas bubbles.

We included bubble coalescence as a UCA microbubble destruction mechanism, since the total number of bubbles in the UCA decreases due to coalescence.

Fragmentation – the fragmentation (fission) of one or more bubbles into smaller bubbles. This mechanism was only observed, as suggested from cavitation bubble theory, around maximum compression. We recorded 83 image sequences showing experimental UCA microbubble fragmentation.

We observed successive coalescence and fragmentation in 12 image sequences.

Sonic cracking – the formation of a bubble shell defect causing gas escape (Takeuchi, 1999). We recorded 17 image sequences showing Quantison™ microbubble cracking. The number of cracking bubbles compared to the number of bubbles visible in the image sequences is low.

We recorded 15 image sequences demonstrating destruction mechanisms that could not be classified into the categories coalescence, fragmentation, and sonic cracking, for example asymmetric collapse without fragmentation. Jet behavior was clearly observed twice. One of these events was previously published (Postema, 2002). Apparently liquid was propelled into the freely flowing microbubble, in the direction of the capillary wall nearby.

Discussion and conclusions: Coalescence we observed in 28% of our high-MI experimental events with a lipid-shelled UCA, when insonifying at 0.5 MHz. We proposed a coalescence mechanism of UCA microbubbles, based on a mechanism of colliding free gas bubbles and the so-called stalk-pore hypothesis. Bubble coalescence was only clearly observed with the experimental UCA, and not with Quantison™. For the bubble concentration used, the spacing between the Quantison™ bubbles was much larger than a maximal excursion, and therefore bubble collision during the expansion phase may not have occurred.

Bubble fragmentation was only observed with the experimental UCA, and not with Quantison™. We conclude that its bubble wall velocity and acceleration are too low to induce instabilities big enough for fragmentation.

The repetitive coalescing and fragmenting behavior recorded suggests that the destruction behavior of contrast microbubbles is more complex than previously assumed (Chomas, 2001).

We showed that sonic cracking is feasible for the hard-shelled contrast agent Quantison™. Tiny flaws in the bubble shell may account for the reason why certain bubbles cracked and others stood intact.

At before-mentioned acoustic frequency and pressures, when not taking into account coalescence as a real destruction mechanism, we found that fragmentation is the primary destruction mechanism for the experimental UCA, in case of destruction during the first cycles of ultrasound insonification. Since we were only looking at early cycles of the ultrasonic waves, this limits our conclusion.

The destruction mechanisms presented have potential clinical applications in high-MI imaging, noninvasive blood pressure measurements, neovascularization, and targeted drug and gene delivery.

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