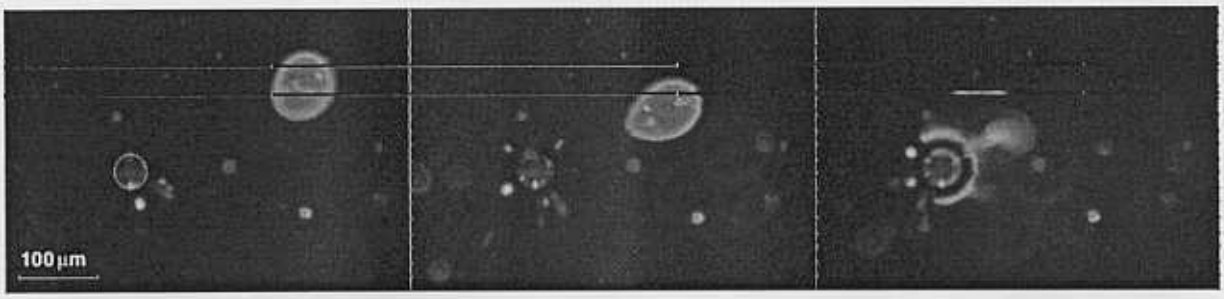

Figure 1.

The effect looks dramatic under the microscope: the vesicles are periodically accelerated towards and repelled from the bubble. In this "bouncing" motion the vesicle is subjected to a shear stress that is reflected in its elongated shape. As this deformation increases (upon increasing driving pressure or adjusting material parameters) the break-up of vesicles is also observed (see Figure 1).

We interpret the motion as acoustic streaming induced by the bubble oscillations, a nonlinear effect creating a steady flow with closed streamlines from periodic driving. A quantitative theory of acoustic streaming is available, enabling us to directly model the streaming flow, vesicle transport, and vesicle deformation. Moreover, because the bubble oscillation amplitudes are actually small, it is possible to control these processes with great accuracy, and improve vastly on current methods relying on inertially collapsing bubbles.

Lipid vesicle deformation and rupture (the vesicle membrane is fluorescence-marked) in the acoustic streaming flow generated by the bubble (white circle).

Optical observations of ultrasound contrast agent destruction

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Microbubble destruction has been under investigation for its potential application in drug and gene delivery, and for the improvement of diagnostic ultrasound contrast agent (UCA) detection methods. We investigated UCA destruction mechanisms by subjecting two different contrast agents to high-amplitude ultrasound, and optically recording its behavior with a fast-framing camera. 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 experimental UCA consists of encapsulated gas bubbles with a phospholipid shell. The microbubbles have a median diameter of 2 μm. We also recorded 57 image sequences with Quantison™ (Upperton Ltd., Nottingham, UK), poured into a container and covered with a microscopic slip. Quantison™ consists of air- filled albumin shells. The microbubbles have a mean diameter of 3.2 μm. Shell thicknesses range from 0.2 μm to 0.3 μm. In all experiments we transmitted 10 cycles of ultrasound with a center frequency of 0.5 MHz. Peak negative acoustic pressures applied ranged from 0.64 MPa to 0.85 MPa. We observed the following microbubble destruction mechanisms:

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

Sonic cracking – the formation of a bubble shell defect causing gas escape. 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. Tiny flaws in the bubble shell may account for the reason why certain bubbles crack and other bubbles stay intact. We observed successive fusion and fission in 12 image sequences. We recorded 15 image sequences demonstrating destruction mechanisms that could not be classified into the categories fusion, fission, and sonic cracking, for example asymmetric collapse without fragmentation. We conclude that fission is the primary destruction mechanism for the experimental UCA, in case of destruction during the first cycles of ultrasound insonification.

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