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1 Optical observations of ultrasound contrast agent destruction

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5 Microbubble destruction has been under investigation for its potential application in drug and
6 gene delivery, and for the improvement of diagnostic ultrasound contrast agent (UCA) detection
7 methods. We investigated UCA destruction mechanisms by subjecting two different contrast
8 agents to high-amplitude ultrasound, and optically recording its behavior with a fast-framing
9 camera. The fast-framing camera was capable of recording an optical image sequence of eight
10 frames per experiment and operated at a speed of three million frames per second. Each image
11 sequence was taken during one cycle of ultrasound. We recorded 482 image sequences with an
12 experimental UCA (Bracco Research SA, Geneva, Switzerland), freely flowing through a
13 capillary cellulose tube. The experimental UCA consists of encapsulated gas bubbles with a
14 phospholipid shell. The microbubbles have a median diameter of 2 μm . We also recorded 57
15 image sequences with Quantison™ (Upperton Ltd., Nottingham, UK), poured into a container
16 and covered with a microscopic slip. Quantison™ consists of air-filled albumin shells. The
17 microbubbles have a mean diameter of 3.2 μm . Shell thicknesses range from 0.2 μm to 0.3 μm . In
18 all experiments we transmitted 10 cycles of ultrasound with a center frequency of 0.5 MHz. Peak
19 negative acoustic pressures applied ranged from 0.64 MPa to 0.85 MPa. We observed the
20 following microbubble destruction mechanisms:

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

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

28 Sonic cracking – the formation of a bubble shell defect causing gas escape. We recorded 17
29 image sequences showing Quantison™ microbubble cracking. The number of cracking bubbles
30 compared to the number of bubbles visible in the image sequences is low. Tiny flaws in the
31 bubble shell may account for the reason why certain bubbles crack and other bubbles stay intact.

32 We observed successive fusion and fission in 12 image sequences. We recorded 15 image
33 sequences demonstrating destruction mechanisms that could not be classified into the categories
34 fusion, fission, and sonic cracking, for example asymmetric collapse without fragmentation.

35 We conclude that fission is the primary destruction mechanism for the experimental UCA, in case
36 of destruction during the first cycles of ultrasound insonification.

37

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