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Correlation of Rupture Dynamics to the Nonlinear Backscatter Response From Polymer-Shelled Ultrasound Contrast Agents

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Abstract

Polymer-shelled ultrasound contrast agents (UCAs) may expel their encapsulated gas subject to ultrasound-induced shell buckling or rupture. Nonlinear oscillations of this gas bubble can produce a subharmonic component in the ultrasound backscatter. This study investigated the relationship between this gas-release mechanism and shell-thickness-to-radius ratios (STRRs) of polymer-shelled UCAs. Three types of polylactide-shelled UCAs with STRRs of 7.5, 40, and 100 nm/ μ m were studied. Each UCA population had a nominal mean diameter of 2 μ m. UCAs were subjected to increasing static overpressure ranging from 2 to 330 kPa over a duration of 2 h in a custom-designed test chamber while being imaged using a 200 $\times$ magnification video microscope at a frame rate of 5 frames/s. Digitized video images were binarized and processed to obtain the cross-sectional area of individual UCAs. Integration of the normalized cross-sectional area over normalized time, defined as buckling factor (B_f), provided a dimensionless parameter for quantifying and comparing the degree of pre-rupture buckling exhibited by the UCAs of different STRRs in response to overpressure. The UCAs with an STRR of 7.5 nm/ μ m exhibited a distinct shell-buckling phase before shell rupture ($B_f < 1$), whereas the UCAs with higher STRRs (40 and 100 nm/ μ m) did not undergo significant pre-rupture buckling ($B_f \approx 1$). The difference in the overpressure response was correlated with the subharmonic response produced by these UCAs. When excited using 20-MHz ultrasound, individual UCAs ($N = 3000$) in populations that did not exhibit a buckling phase produced a subharmonic response that was an order of magnitude greater than the UCA population with a prominent pre-rupture buckling phase. These results indicate the mechanism of gas expulsion from these UCAs might be a relevant factor in determining the level of subharmonic response in response to high-frequency ultrasound.

I. Introduction

Ultrasound is a widely used imaging tool for medical diagnosis. The small differences in acoustic impedance between tissue constituents produce distinct ultrasound echo signals that represent variations in the local mechanical properties and structure of tissue. Stabilized, micrometer-scale spheres composed of a thin biocompatible shell that encapsulates an inert gas are employed as ultrasound contrast agents (UCAs) [1]. UCAs provide increased sensitivity because of their high echogenicity relative to surrounding tissue [2]. Nonlinear oscillations of UCAs may generate a subharmonic of the incident ultrasound that can be detected to enhance the contrast-to-noise ratio [3]–[5].

UCAs may also be destroyed with acoustic forcing with sufficiently high pressure amplitude, which results in the release of the encapsulated gas. This forced release of gas results in bubbles whose subsequent oscillations in response to ultrasound are another source of subharmonic backscatter [6]–[9]. Typically, ultrasound can destroy UCAs in two ways: shell buckling [10], [11] or shell rupture [8], [9]. For UCAs with relatively compliant shells, such as those made from lipids, buckling resulting from shell oscillations and subsequent compression-only behavior was observed to be an energetically favorable process [12], [13]. The appearance of wrinkles on the surface of the UCAs in a post-buckled state also has been observed on lipid-shelled UCAs undergoing dissolution [14]. UCAs with relatively rigid shells, such as those comprised of a thick (>20 nm) polymer layer, are more robust under compression and maintain their structural integrity up to a specific acoustic pressure threshold, above which they rupture [6], [8], [15].

The pressures at which the UCAs buckle or rupture are correlated with the shell-thickness-to-radius ratio (STRR) [11], [16]–[18]. The manufacturing process involved in producing polymer-shelled UCAs is amenable to customizing the STRR of a UCA population for a polydisperse size distribution [19]. Therefore, polymer-shelled UCAs potentially can be designed to rupture at a prescribed acoustic pressure by choosing appropriate shell parameters such as shell elasticity and STRR, irrespective of their size distribution, which is especially advantageous for applications involving UCA destruction, such as localized drug delivery [20] or perfusion imaging [21].

Previous efforts to characterize these parameters and relate them to UCA behavior include high-speed video-microscopy of UCAs [6], [8], [22] and studies characterizing acoustic backscatter from UCAs [7], [23]–[25]. Although these techniques provided sizes of single agents and insight into the dynamic response of UCAs to ultrasonic excitation, absolute quantitative parameters of the material properties of the UCA shell were not reported. Quantitative parameters, such as the elastic modulus of the shell of individual UCAs, were obtained using an atomic-force microscope (AFM) by pressing on the UCAs with the AFM tip and measuring the shell deformation resulting from this external force [26]. Characterizing the rupture threshold of UCAs, defined for our purposes as the total destruction of the UCA shell, in response to static overpressure has been demonstrated as a cost-effective tool for simultaneously measuring mechanical properties of a large number of individual UCAs [16], [21]. UCA-rupture thresholds measured in this manner also can be used as a proxy to assess propensity for ultrasound-mediated destruction [16], [18].

Despite these advances, a mechanistic understanding of the interaction between polymer-shelled UCAs and ultrasound remains incomplete. For instance, polymer-shelled UCAs have been shown to produce a subharmonic response when excited using high-frequency (>20 MHz) ultrasound (HFU) [18], [25]. Results from our previous study indicated that the strongest subharmonic backscatter in response to 20-MHz excitation was observed from a UCA population with the highest STRR, which has the least propensity for ultrasound-mediated destruction [18]. This observation at 20 MHz was in contradiction to the rupture-based mechanism observed in studies conducted using low-frequency (<10 MHz) ultrasound [6], [8]. Therefore, we previously concluded that polymer-shelled UCAs responding to 20-MHz ultrasound might not undergo rupture and that the subharmonics were generated by a different mechanism [18]. However, recent theoretical and experimental studies [11], [17] that investigated the differences between buckling and rupture of polymer-shelled UCAs as two distinct mechanisms of gas expulsion presented an alternate hypothesis: UCAs with high STRR undergo abrupt rupture resulting in free gas bubbles that respond nonlinearly to incident ultrasound and generate a subharmonic response, whereas the UCAs with low STRRs slowly release their gas during a pre-rupture buckling phase and the subsequent shell rupture does not produce free gas bubbles. Investigation of this hypothesis required a means to study the distinct phases involved in UCA destruction and was the motivation of the present work.

In this study, we conducted a series of new overpressure studies to elucidate the subtle but important differences between shell buckling and shell rupture. To achieve this aim, we improved the temporal resolution of the video microscope in our previous study [16] to identify and study different phases of UCA response to overpressure. We also investigated the relationship between UCA-destruction mode and the nonlinear response of polymer-shelled UCAs to 20-MHz ultrasound. These nonlinear interactions were assessed by measuring the subharmonic signal in the backscatter from individual UCAs in a wall-less flow phantom. The correlation between shell-rupture mode and subharmonic response was examined to gain deeper mechanistic insight into the generation of subharmonic response from these UCAs when excited by HFU.

II. Materials and Methods

A. Polymer-Shelled UCAs

Three types of UCAs, all with poly-L-lactide shells, were used in this study. The UCAs in each group had a nominally constant STRR. The first type, PB127, was manufactured by Point Biomedical (San Carlos, CA, USA; intellectual property transferred to the University of Pittsburgh, Pittsburgh, PA, USA); the other two types, PH37 and PH43, were manufactured by Philips Research (Eindhoven, The Netherlands). The manufacturing methods for the Point UCAs (PB127) are proprietary and the Philips UCAs (PH37 and PH43) were synthesized as described previously [19]. The relevant parameters for the three UCA populations are given in Table I.

B. Overpressure Study

1) Experimental Setup—A custom-designed aluminum test chamber was employed for the study (Fig. 1). The chamber was cylindrical in shape and had a permanent clear glass window at the bottom. A removable graduated microscope reticule on the top side of the chamber, secured by a metallic lid and rubber O-rings, was used as a lid. The markings on the reticule served as a reference for measuring the absolute size of individual UCAs. The chamber had inlet and outlet fluid ports. The input port was connected to a syringe pump (BS-8000, Braintree Scientific, Inc., Braintree, MA, USA) that pumped glycerol into the chamber at a desired rate and the output port was connected to a pressure sensor (PM100D, World Precision Instruments, Sarasota, FL, USA) for monitoring the static overpressure within the chamber.

A high-frame-rate camera (X-Stream XS-3, IDT, Tallahassee, FL, USA) with a long working distance, 200 $\times$ objective (EO Infinity-Corrected LWDO, Edmund Optics, Barrington, NJ, USA) was suspended over the pressure-chamber reticule and used as a video microscope. The camera-lens assembly provided a field of view (FOV) of about 140 μ m with a working distance of 13 mm. The video microscope was operated at a frame rate of 5 fps. A halogen-lamp light source (MH-100, Fiber-Lite, Dolan-Jenner Industries, Boxborough, MA, USA) connected with a light guide was used to illuminate the chamber from the bottom. The light was focused using a dual-lens assembly to a spot diameter of 3 mm on the microscope reticule. The pressure chamber and the illumination assembly were placed on a three-axis manual stage.

Initially, glycerol was slowly pumped into the chamber to avoid introduction of air bubbles. Approximately 0.2 mL of distilled water was placed on the surface of the glycerol layer and a small amount of dry-form UCA was added. The mixture of UCA in water was gently stirred to form a uniform layer over the glycerol without mixing both the layers. At this point, the microscope reticule was carefully placed on top, such that no air bubbles were trapped inside the chamber, and firmly secured with the lid. Glycerol was pumped into the chamber at a rate of 5 mL/hr for 2 h, which subjected the UCAs in the test chamber to slowly changing static overpressure ranging from 2 to 330 kPa. Simultaneously, images of the UCAs proximal to the reticule surface were captured using the video microscope to assess the response of individual UCAs to static overpressure. The images were collected in 1024 $\times$ 1280 pixel (pxl) frames for corresponding time and pressure values.

2) Image Processing—The initial position and diameter of all the UCAs in the first frame were recorded using an automated algorithm for finding circles based on the Hough transform, as described previously [18]. Briefly, the images were filtered using a 0.5 $\times$ 0.5 μ m median filter to reduce noise and processed in three steps: 1) binarization of a region of interest (ROI: 100 $\times$ 100 pxl) centered around the UCA of interest; 2) edge detection using the Sobel operator; and 3) determination of position and diameter of the UCA using Hough transform for a circle. Moreover, this algorithm allowed the determination of position and diameter for partially obscured UCAs as well.

Each UCA in subsequent frames was isolated into separate images with smaller square windows of dimensions that were 1.75 times the initial UCA diameter. This image sequence

(for each UCA) was binarized and pixels associated with the UCA were counted using Matlab (The MathWorks Inc., Natick, MA, USA) to accurately measure its cross-sectional area in the presence of overpressure-induced shape deformations. The time-dependent cross-sectional area was normalized using the area of the UCA in the first frame. The resulting area–time data were analyzed to determine the onset of buckling and subsequent UCA rupture. For the purpose of this study, buckling onset was defined as a 3% decrease in the cross-sectional area because this was the smallest change that was visually detectable in the image sequence. The rupture was defined as the complete disintegration of the UCA microbubble, i.e., 100% decrease.

To quantitatively investigate the difference between time scales for shell buckling and shell rupture, a dimensionless parameter hereafter referred to as the buckling factor (B_f), was defined as

$$B_f = \int_0^1 A' d\tau, \quad (1)$$

where $A'(t)$ is the normalized cross-sectional area of the UCA, τ is normalized time ($\tau = t/t_R$), and t_R is the time of rupture.

A B_f value of 1 represents abrupt rupture (once the critical overpressure for rupture is reached) without any buckling and a B_f value of 0 represents instantaneous shell disintegration and dissolution of the gas. Buckling followed by rupture would result in a B_f value between 0 and 1. The B_f and the difference between rupture pressure and buckling-onset pressure (P_{r-b}) were used to compare the differences in buckling behavior for different STRRs.

C. High-Frequency Ultrasound (HFU) Study

1) Experimental Setup—The HFU data were obtained from our previous study [18]. Pertinent details of the methods involved are presented here. The experimental setup consisted of a test tank with a 200- μ m-diameter input flow channel and 3-mm-diameter output flow channel. Both channels were aligned coaxially, so as to achieve a streamlined straight flow from the input channel to the output channel. A 20-MHz transducer (PI 20-2, Olympus, Waltham, MA, USA) with a focal length of 12 mm, an aperture of 6 mm, and bandwidth of 50% was placed perpendicularly above the line of flow at a distance of 2 mm downstream from the tip of the input channel, (Fig. 2). The transducer had a –6-dB lateral beam diameter of 200 μ m. An arbitrary waveform generator (1281, Tabor Electronics, Tel Hanan, Israel) and a 50-dB power amplifier (350L, Electronics & Innovation Ltd., Rochester, NY, USA) were used to excite the transducer. The pulse–echo signal was amplified using a 50-dB signal-conditioning amplifier (AU-1313, Miteq, Hauppauge, NY, USA) with a bandwidth of 5 to 500 MHz and the signal was digitized using an 8-bit digitizer (DC271A, Agilent Technologies, Santa Clara, CA, USA) at a sampling rate of 400 Msamples/s. A fiber-optic hydrophone (Precision Acoustics Ltd., Dorset, UK) was used to calibrate the acoustic pressure output of the transducer.

The input flow channel of the test tank was connected to a reservoir containing a dilute solution of UCAs (approximately 10^4 to 10^5 UCAs/mL) and the output channel to a waste reservoir through a dual-channel tubing pump (REGLO Digital MS-2/8, Ismatec, Glattburg, Switzerland) using tubing with an inner diameter of 2.06 mm (CP-95608-42, Cole-Parmer, Vernon Hills, IL, USA), which facilitated a steady flow of UCA solution at 0.625 mL/min. This custom-designed setup allowed measurement of acoustic responses from individual UCAs under unconstrained conditions in an open fluid environment.

The UCAs were subjected to 20-cycle toneburst excitation at peak negative pressures of 0.3 to 2.3 MPa. This pulse duration was chosen to reliably detect the subharmonic signal in the backscatter data from individual UCAs. (The system was unable to reliably detect subharmonics when the pulse duration was less than 10 cycles.) A custom software package (Lab VIEW, National Instruments, Austin, TX, USA) was used to control the data-acquisition system and to screen in real time consecutively acquired 20-line M-mode data sets for valid backscatter events. Valid signals were chosen as those that did not indicate presence of multiple UCAs in the transducer focus. Presence of multiple UCAs was determined by examining the number of peaks in the envelope of cross-correlation between the backscatter signal and the ideal pulse–echo response of the transducer [25]. A pulse-repetition frequency of 3 kHz was used such that each UCA was exposed to about 6 to 8 pulses. Multiple exposure of each UCA ensured capture of UCA-backscatter measurement when the UCA was located at the transducer focus, i.e., the location corresponding to maximum acoustic backscatter.

2) Signal Processing—A post-processing scheme based on singular-value decomposition (SVD) was employed to compute a subharmonic score (SHS) that represented the overall subharmonic activity of each UCA population. A detailed description of this SVD-based scheme is described in [25]. An SVD-based method is particularly robust in analyzing large data sets generated from similar experimental conditions. For a given set of acoustic parameters, the responses recorded from individual UCAs can be interpreted as realizations of a random process (i.e., UCA response to ultrasound), which can be decomposed onto an SVD-derived base. This approach is statistically optimal in the sense that the greatest variance by any projection of the data are on the first analyzing vector (AV), the second greatest variance on the second AV, etc. [27].

For each acoustic-exposure condition, the 500 UCA backscatter events were recorded and their responses were stored in a matrix, M . SVD analysis was performed on this matrix, which resulted in an AV, sorted in decreasing order of singular values. From this, the first AV that had a Fourier transform (FT) magnitude peaking at 10 MHz (AV10) was selected. SHS was computed as the product of average decomposition coefficient of M on AV10 and the FT magnitude of AV10 at 10 MHz. SHS is a statistical measure of the subharmonic activity in an entire backscatter data set (500 events in each data set) and provides a more robust quantitative measure than the subharmonic magnitude in backscatter from individual UCAs. SHS is dimensionless because each element of the 500-event data set is first normalized before SVD is performed. This score served as a sensitive metric for quantitative analysis of subharmonic activity considering the frequency of subharmonic events and the strength of the subharmonic response in the observed echoes. The conventional quantitative approach

was limited to determining the percentage of backscatter events that contained a subharmonic-signal component that was at least 25 dB greater than the noise level at that frequency. The SVD-derived SHS was empirically determined to be a linear function of the conventional SHS [25]. Comparison of conventional and SVD methods suggested that SVD-based analysis resulted in a more robust quantification of subharmonic activity in comparison to direct measurement of subharmonic peak magnitude, even at low signal-to-noise ratios [25].

III. Results

A. Overpressure Study

Representative sequences of images of the overpressure response of each UCA type are shown in Fig. 3. Although the sequences show similar trends in the rupture dynamics, the buckling phase for the PB127 UCA was more prominent and slower, spanning a period of approximately 120 s. In comparison, the buckling phase for the PH UCAs lasted only 4 to 5 s. This disparity also was evident from the difference between the rupture pressure and the buckling pressure (P_{f-b}), which was 5.4 kPa for the Pb127 UCA and less than 1 kPa for the PH UCAs.

The difference between the buckling-phase duration of each UCA type was quantified by B_f . A representative curve of the normalized area of a PH37 UCA as a function of normalized time exhibited a sharp drop-off indicating abrupt rupture [Fig. 4(a)]. In comparison, the normalized-area curve for a PB127 UCA indicated a buckling phase with a gradual progression toward rupture. One-way analysis of variation (ANOVA) of the B_f values for the three UCAs indicated that the three types of UCAs exhibited statistically different buckling behavior [Fig. 4(b)]. The B_f values for the PB127, PH37, and PH43 UCAs were 0.80 ± 0.09 , 0.91 ± 0.02 , and 0.93 ± 0.02 , respectively, which indicated that the PB127 UCAs exhibited more pre-rupture buckling compared with the PH37 and PH43 UCAs.

The difference in buckling behavior between PB127 and the PH UCAs also was evident from the difference between the rupture pressure and the buckling-onset pressure (Fig. 5). The PH37 and PH43 UCAs have the same buckling and rupture pressures, whereas the buckling-onset pressure for the PB127 UCAs was less than 50% of their rupture pressures.

B. HFU-Backscatter Study

Fig. 6 shows the SVD-derived SHS for each UCA population as a function of peak negative pressure (P_N) ranging from 0.3 to 2.3 MPa. Each data point in the SHS curve represents a mean SHS obtained from six data sets, each containing 500 individual backscatter events. Although PB127 UCAs had a lower acoustic pressure threshold for producing subharmonic activity in comparison to the two PH-UCA populations, its SHS was an order of magnitude lower than PH37 and PH43 UCAs. The SHS of these UCAs in response to 20-MHz excitation appeared to be correlated to their computed B_f , i.e., UCAs with larger B_f values produced more subharmonic activity.

IV. Discussion

Our experimental results indicated that the presence of a dominant buckling phase during overpressure-induced UCA destruction was correlated with the nominal STRR of the UCA population irrespective of the UCA size. The buckling factor (B_f) of the UCAs provided quantitative means for differentiating between UCAs that did not buckle (high STRR, $B_f \approx 1$) and those that exhibited a prominent pre-rupture buckling phase (low STRR, $B_f < 1$). These results are consistent with theoretical predictions [11] and experimental observations [17] of buckling and tension-induced destruction exhibited by polymer-shelled UCAs responding to low-megahertz range ultrasound. These studies showed that below a certain critical value of STRR, UCAs displayed a distinct buckling phase before UCA destruction. Using scanning electron microscopy to measure the STRR of UCAs, Lensen *et al.* [17] determined that this critical value of STRR was approximately 40 nm/ μ m. The PB127 UCAs employed in this study had a nominal STRR of 7.5 nm/ μ m, well below this critical value, whereas the PH43 UCA, which exhibited the least buckling, had an STRR of 100 nm/ μ m, much greater than the critical value. The qualitative agreement between our static-overpressure results and ultrasonically induced buckling results from previous studies suggests that the overpressure-based method of assessing UCA destruction can be used as a proxy to understand and compare the shell destruction (fragility) of different types of UCAs responding to clinically relevant ultrasound parameters. UCAs investigated in the HFU study were exposed to approximately eight 20-cycle pulses at a pulse-repetition rate of 3 kHz (2.6 ms of sonication per UCA). Similar to the overpressure studies, the PB127 UCAs could exhibit a prolonged pre-rupture buckling phase before ultrasound-mediated shell destruction. The lack of significant subharmonic activity from these UCAs could involve two possible explanations: the buckling phase extends for a duration longer than the sonication time of 2.6 ms or the gas in the UCA undergoing buckling leaks and diffuses into solution, thus resulting in a lack of residual free-gas bubbles upon shell rupture. Conversely, the UCAs with high STRR likely do not undergo buckling under the influence of HFU. Rather, they rupture abruptly, albeit at a higher incident acoustic pressure. The destruction of UCAs in this manner is likely to produce residual free-gas bubbles that could nonlinearly respond to incident HFU and produce subharmonics as evidenced in our HFU studies. We postulate that below the acoustic pressure threshold for rupture, these UCAs with high STRRs do not exhibit significant oscillations. The relatively sharp acoustic pressure threshold for generating a subharmonic response is consistent with this conjecture. Furthermore, the resonance frequency derived from the Hoff model with a nominal UCA size and shell properties was 24 MHz for the PB127 UCAs and exceeded 60 MHz for the PH UCAs [18]. The excitation frequency of 20 MHz was therefore well below the resonance frequency and not ideal for generating subharmonics from these UCAs. However, abrupt shell rupture of PH UCAs is likely to produce residual gas bubbles that have a radius of 1 μ m or less (nominal radius for PH UCAs was 1 μ m). Air bubbles in the size range of 0.2 to 1 μ m have a Minnaert frequency ranging from 3 to 15 MHz. An excitation frequency of 20 MHz is appropriate for generating subharmonics from these bubbles [28], which further supports a rupture-based mechanism for subharmonic generation. It should be noted that the backscatter signals did not show any evidence of inertially cavitating bubbles usually indicated by a presence of broadband noise. This observation is consistent with the fact that

the acoustic pressure threshold for inducing inertial cavitation is relatively high when sonicating at 20 MHz.

For low-megahertz range excitations, it was reported that the rupture of polymer-shelled UCAs was followed by the release of gas bubbles, which last for a few milliseconds before dissolution [20]. In our previous study [18], we had concluded that polymer-shelled UCAs excited at 20 MHz might not exhibit the same behavior because UCAs with the least propensity to ultrasound-induced shell rupture (highest STRR) produced the highest level of subharmonic activity, i.e., subharmonic generation by the UCAs was not correlated to their overpressure threshold for rupture. In this work, we examined the subtle differences between the buckling and rupture phases of UCA destruction to better understand this discrepancy. Observations from the present study suggest that an understanding of the mechanisms involved in UCA destruction, which are dictated by the UCA's STRR [11], [17], are necessary to gain insight into the likelihood and level of subharmonic generation in response to HFU. For instance, UCAs with a more prominent buckling phase might be less likely to produce subharmonics, i.e., buckling factor is inversely correlated with likelihood of subharmonic generation. Conversely, UCAs with a buckling factor approaching 1 will likely produce a subharmonic response. Prior work suggested that the onset acoustic pressure threshold for generating subharmonics and the level of subharmonic activity for the PH UCAs were not correlated with STRR or rupture thresholds determined from the overpressure study [18]. However, the subharmonic response of the PH43 UCAs ($B_f = 0.93$) was approximately twice that of PH37 ($B_f = 0.91$) even though their buckling factors were only marginally different. Additional studies with UCAs of different STRRs and means for detecting and sizing the rupture-induced gas bubbles are necessary to elucidate this observation.

V. Conclusion

Our results indicate that applications involving rupture of polymer-shelled UCAs could benefit significantly from optimization of shell material properties, particularly the STRR. The buckling and rupture behavior of a UCA population can be tuned simply by tuning the STRR despite polydispersity in UCA size. An overpressure-based method of characterizing the UCA buckling and rupture thresholds offers a cost-effective and high-throughput means to compare different UCA populations by simultaneously obtaining destruction data from multiple UCAs in each population. This approach also provides a quantitative parameter, the buckling factor, which is useful differentiating between the buckling and rupture phases of UCA destruction and comparing the buckling behavior of different types of UCAs. Buckling and rupture were observed in the UCAs with STRR of 7.5 nm/ μ m, whereas only rupture was observed for UCAs with STRRs greater than 40 nm/ μ m. The likelihood of generating a subharmonic response was inversely correlated with the UCA's propensity for undergoing pre-rupture buckling.

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Fig. 1. Schematic of the experimental setup for the overpressure study. Changes in the morphology of UCAs subjected to static overpressures in a glycerol-filled chamber were observed with a video microscope.

Fig. 2. Schematic diagram of the experimental setup for UCA-backscatter study. Individual UCAs were passed through the focal region of a 20-MHz transducer and their responses to 20-MHz, 20-cycle tonebursts were recorded.

Fig. 3. Sequence of images showing buckling and subsequent rupture with the corresponding pressure values for the three types of UCAs.

Fig. 4.

(a) The area under the curve of normalized area versus normalized time gives the buckling factor (B_f). Illustration of the difference in buckling factors for UCAs with lower STRR (PB127) and higher STRR (PH37). (b) ANOVA analysis of B_f values for the three UCA types.

Fig. 5.
Buckling and rupture pressures for the three UCA types.

Fig. 6. SHS computed from backscatter measurements of individual UCAs for the three UCA types in response to a 20-MHz, 20-cycle tone-burst excitation. Data were taken from [18].

TABLE I

Parameters for the UCAs.

UCA type	Nominal STRR (nm/ μm)	Number of UCAs used	Mean diameter (μm)	Nominal shell thickness (nm) STRR $\times$ mean radius
PB127	7.5	90	3.6 ± 0.7	13.5 ± 3
PH37	40	100	2.2 ± 0.1	44 ± 2
PH43	100	100	2.3 ± 0.1	115 ± 5