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Characterisation of polymer shelled microbubbles in wall less flow phantom using high frequency ultrasound and video microscopy

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Abstract

A high frequency ultrasound pulse echo system and a video microscope were combined to investigate the relationship between backscatter from polymer shelled ultrasound contrast agents (UCAs) and their diameter. Individual UCAs (manufactured by Point Biomedical or Philips Research) were imaged while being sonicated with 40 MHz tone bursts. The backscatter magnitude produced by the Philips UCAs was proportional to UCA size, which is consistent with theoretically predicted behaviour of encapsulated microbubbles driven at frequencies above resonance. Despite being smaller, the Point UCAs produced a backscatter magnitude twice that of Philips UCAs, indicating that Point UCAs might behave quasi-resonantly when excited at 40 MHz.

Keywords

Contrast agents; Polymer shell; High frequency ultrasound

Introduction

High frequency ultrasound (HFU; >20 MHz) imaging facilitates high resolution imaging and diagnosis of the microcirculation critical to the treatment of dermal^{1,2} and ophthalmic diseases.³ It has also been applied to study the normal and abnormal vascular development of genetically engineered mouse embryos and neonates.⁴ In fact, commercial ultrasound machines have been developed specifically for this purpose.⁵ Ultrasound contrast agents (UCAs) optimised for HFU imaging are desired for improving the performance of these methods. Therefore, the response of existing and experimental UCAs to HFU, particularly the generation of subharmonics due to their non-linear response, has gained interest.

A free bubble (no encapsulation) optimally generates a subharmonic response, when it is driven at a frequency twice its resonance frequency.⁶ The resonance frequency of a free bubble depends on the equilibrium radius of the bubble.⁷ Consequently, the propensity of a bubble to generate a subharmonic response depends on the combination of its size and the driving frequency. When a bubble is driven at a frequency much greater than the resonance frequency, the bubble behaves like a rigid scatterer and the magnitude of ultrasonic

backscatter is linearly related to size; the bubble will not generate a subharmonic response in this regime.⁸

When a bubble is encapsulated, the thickness and elasticity of the shell increase its resonance frequency.^{9,10} This attribute makes polymer shelled UCAs,^{11–14} which have a thick and rigid shell in comparison with conventional UCAs, particularly attractive candidates for HFU applications. Low frequency (<10 MHz) studies involving polymer shelled UCAs have indicated that oscillations of free gas bubbles released upon shell rupture could also generate a subharmonic response.^{15,16} Measurements of ultrasonic backscatter with subharmonic content when excited with HFU tone bursts have also been reported.^{17,18}

However, the majority of studies aimed at investigating UCA–HFU interaction have been performed using UCAs with a relatively ‘soft’ shells such as lipids.^{3,19–21} Sprague *et al.*²² investigated the relationship between the non-linear response of individual phospholipid shelled UCAs bound to gelatine and their size using an optical microscope co-aligned with a 30 MHz transducer. For incident pressures <400 kPa, they observed that the subharmonic response of the UCAs was the highest when the UCA size corresponded to a resonance frequency that was half the excitation frequency (30 MHz). At pressures between 400 kPa and 1 MPa, they reported that the UCAs exhibited non-linear response over a broad range of sizes. Their findings alluded to two distinct pressure regimes: one where the UCAs oscillated to produce nonlinear behaviour but did not rupture; and one where the UCAs ruptured and released a gas bubble that oscillated to produce the non-linear response.

Similar to unencapsulated microbubbles, the magnitude of the ultrasonic backscatter from UCAs is proportional to UCA size when the excitation frequency is significantly higher than the resonance frequency.^{9,10} Maresca *et al.*²³ demonstrated that lipid shelled Definity UCAs ranging in diameter from 1.5 to 6 μm satisfied this criterion when excited at 25 MHz; they also demonstrated the feasibility of using HFU backscatter to acoustically infer the UCA size, which was consistent with optically determined UCA size.

The present study was motivated by the continuing need for a mechanistic understanding of the interaction between polymer shelled UCAs and HFU, which is crucial for developing optimal UCAs for specific HFU applications. In particular, correlation between the UCA parameters (UCA radius, shell thickness and shell elasticity) and ultrasonic backscatter resulting from 40 MHz excitation was examined. The feasibility of acoustically sizing the polymer shelled UCAs was also investigated.

Materials and methods

Experimental set-up

Two types of UCAs were employed in this study: a polycaprolactone shelled, nitrogen filled Point 1466 agent (originally manufactured by Point Biomedical, now produced for research purposes by University of Pittsburgh) which had a nominal mean diameter of 1.1 μm ; and a polylactide shelled, nitrogen gas filled agent (Philips Research Laboratories, Eindhoven, The Netherlands) with a nominal mean diameter of 2 μm . The Point and the Philips UCAs had a mutually common design specification of a constant shell thickness to radius ratio (STRR) with nominal values of 7.5 and 40 $\text{nm } \mu\text{m}^{-1}$ respectively. The UCAs were reconstituted and diluted in a 60 mL syringe containing distilled water. A magnetic stirrer in the syringe gently agitated the solution to keep the UCAs uniformly dispersed in solution.

A customised test tank with ports to allow access for imaging was employed to investigate the UCAs (Fig. 1a). A glass micropipette (inner diameter: 30–40 μm) was mounted at the bottom of the tank in a vertical orientation. A syringe pump (BS-8000; Braintree Scientific,

Inc., Braintree, MA, USA) introduced the dilute UCA solution through the micropipette at a flowrate of 3 mL h⁻¹. The pressure induced by the constricted flow was determined using a pressure monitor (PM15D; World Precision Instruments, Sarasota, FL, USA); this pressure remained under 15 kPa and likely did not result in UCA damage before ejection into the test tank.²⁴ A × 100 water immersion objective (LUMPlan FI 100; Olympus America, Center Valley, PA, USA) attached to a high speed camera (FASTCAM APX; Photron USA Inc., San Diego, CA, USA) was aligned with the tip of the micropipette to image UCAs immediately after ejection. Image acquisition of UCAs close to the micropipette tip was necessitated by the submicrometre depth of field of the objective and the unpredictable divergence of the UCA trajectory from the vertical axis. A 40 MHz transducer (PI50-2; Olympus-NDT, Waltham, MA, USA) with a focal distance of 12 mm was aligned from above with the micropipette tip from above. The peak tensile pressure at the focus was measured using a calibrated needle hydrophone (HPM04; Precision Acoustics, Dorchester, UK); the UCAs were subjected to 20 cycles tone bursts with a peak negative amplitude of 0.43 or 0.89 MPa.

Precise synchronisation between transmission of the ultrasonic pulses and UCA images was achieved by developing an autonomous set-up that obtained 40 lines M scans of ultrasound backscatter at a pulse repetition frequency of 1 kHz and eight video images/M line at a frame rate of 10 000 frames/s. The ultrasound data were processed in real time to identify backscatter events from individual UCAs; if a distinct backscatter event from a UCA (separated in time from the micropipette echo) was detected, the radio frequency (RF) data for the entire M scan and 24 images centred around the M line of the UCA were recorded.

The images and the RF backscatter data were postprocessed using MATLAB (MathWorks, Natick, MA, USA). Images that captured a UCA in focus were chosen manually. For these cases, the UCA size was estimated using a semiautomated algorithm involving: a 0.5 × 0.5 μm median filter for noise reduction; binarisation of a region (30 × 30 μm) centred around a user specified UCA; edge detection using a Sobel operator;²⁵ and the generalised Hough transform for a circle.²⁶ Images of 2 μm latex beads were used for calibrating the UCA size and for quantifying the uncertainty associated with optical sizing, which was empirically determined to be ±0.5 μm (distance corresponding to half the number of pixels between region positively identified as the bubble interior and exterior). The backscatter RF signals corresponding to the manually selected images were processed to obtain the amplitude and the power spectrum of the UCA echo. The high frequency backscatter was compared with the theoretical predictions of the response of acoustically driven polymer shelled bubbles.

Theory

The theoretical model for ultrasonically driven polymer shelled microbubbles developed by Hoff *et al.*¹⁰ was used to predict the nominal response of the Point and the Philips UCAs. The model assumes that the polymer shell is thin compared with the radius and depends on the viscous and elastic properties of the shell. Theoretical calculations were performed in the regime where the bubble oscillations were expected to remain linear unless the incident acoustic pressure induced shell rupture. The scattering cross-section σ_s of an encapsulated bubble predicted using the Hoff model can be expressed as

$$\sigma_s = \frac{\Omega^4}{(\Omega^2 - 1)^2 + \Omega^2 \delta^2} = 4\pi a_e^2 \frac{|p_s|^2}{|p_A|^2}$$

$$\omega_0 = \frac{1}{2\pi a_e} \left[\frac{1}{\rho_L} \left(3\kappa p_0 + 12G_s \frac{ds_e}{a_e} \right) \right]^{1/2}$$

$$\delta = \frac{4\mu_L}{\omega_0 \rho_L a_e^2} + \frac{12\mu_s (ds_e/a_e)}{\omega_0 \rho_L a_e^2}$$

where a_e is the equilibrium radius of the bubble, $\omega_0=2\pi f_0$, f_0 is the UCA resonance frequency, $\Omega=2\pi f$, f is the excitation frequency, p_A is the incident acoustic pressure, p_s is the scattered pressure, ρ_L is the liquid density, κ is the polytropic constant, p_0 is the ambient pressure, G_s is the shear modulus, d_{s_e} is the equilibrium shell thickness, μ_L is the liquid viscosity, μ_s is the shear viscosity and δ is the viscous dampening term.

The shell material properties for theoretically calculating the response of polymer shelled UCAs to HFU were estimated from independent measurement of response of UCAs to static overpressure^{24,27} and values inferred in previous works.^{9,10,28,29} The specific values for the shell parameters used to model the Point UCAs were as follows: STRR=7.5 nm μm^{-1} ; shell shear modulus=10⁸ MPa; and shell viscosity=0.2 Pa s. The response of Philips UCAs was predicted using the following shell parameters: STRR=40 nm μm^{-1} ; shell shear modulus=10⁷ MPa; and shell viscosity=0.1 Pa s.

Results

Experimental results

Experiments with each UCA type were repeated five times. The UCAs that appeared to be in focus were manually selected for processing; this resulted in datasets for 41 Point UCAs and 122 Philips UCAs. Images, backscatter RF signals and the corresponding power spectra from two UCAs that were representative of data from the Philips UCAs are shown in Fig. 1. Image analysis indicated that the two UCAs were 1.7 and 3.5 μm in diameter. The larger of the two UCAs produced an echo signal of approximately twice the amplitude of that from the smaller UCA. In each of these cases, the spectra obtained from the windowed echo signal (shown in red) did not contain significant (within 20 dB of the fundamental) harmonics or subharmonics.

Correlation between the relative amplitude of the backscatter signal and the UCA diameter was investigated. Figure 2 shows the scatter plots of the backscatter signal voltage with respect to the UCA diameter, linear fit between the two measurements and the corresponding root mean squared error (RMSE) for each type of UCA when excited with 40 MHz tone bursts of 20 cycles. The linear fit for the Point UCAs from 0.43 MPa (Fig. 2a) and 0.89 MPa (Fig. 2c) excitation data resulted in $R^2=0.34$ (RMSE=0.05 mV) and $R^2=0.45$ (RMSE=0.07 mV) respectively. Similarly, the linear fit for the Philips UCAs for the two excitation pressures (Fig. 2b and d) resulted in $R^2=0.66$ (RMSE=0.01 mV) and $R^2=0.61$ (RMSE=0.05 mV) respectively. For each UCA population, the backscatter amplitude increased as the diameter increased. However, the backscatter amplitudes generated by the Point UCAs were roughly twice as high as those generated by the Philips UCAs, even though the Philips UCAs had a nominal diameter that was twice that of Point UCAs.

Theoretical predictions

The theoretically predicted responses of Point and Philips UCAs to ultrasonic excitation are shown in Fig. 3. Using the nominal values for equilibrium radius, the scattering cross-sections (normalised to the geometric cross-section) of the two types of UCAs were calculated for a range of driving frequencies, and compared with the scattering cross-section of air bubbles of the same size (Fig. 3a). The peak in each curve represents the resonant behaviour of the bubble. In comparison with air bubbles in water, the elasticity of the polymer encapsulation increases the resonant frequency; the shear viscosity of the shell dampens the response, particularly for the relatively thick shelled Philips UCA. In the super resonant regime (defined as $f \gg f_0$), the scattering cross-section approaches the geometric cross-section (i.e. $\sigma_s/4\pi a^2 \rightarrow 1$). The air bubbles and the Philips UCA fall in the super

resonant regime for 40 MHz excitation. However, the Point UCA ($f_0=33.7$ MHz) does not satisfy this criterion and exhibits quasi-resonant behaviour when excited at 40 MHz.

Figure 3b shows the normalised scattering cross-section of Point and Philips UCAs with respect to the UCA diameter d . The UCA diameters corresponding to the peaks of the curves represent the size at which each UCA will exhibit resonance behaviour (known as the resonant size d_0) when excited with 40 MHz. The Hoff model predicts that UCAs larger than the resonant size ($d > d_0$) will respond like a rigid scatterer and their scattering cross-section will be equal to their geometric cross-section. Based on the nominal diameters of both UCAs, the Hoff model predicts that the Philips UCAs (nominal $d=2$ μm) might behave similar to rigid scatterers when excited at 40 MHz. However, the Point UCAs (nominal $d=1$ μm) will likely exhibit resonant behaviour. Theoretically predicted backscattered pressure at the transducer face (normalised with the incident acoustic pressure amplitude) with respect to the UCA diameter is shown in Fig. 3c. Vertical dashed lines indicate the range of diameters of the UCAs that were experimentally investigated. The theoretical calculation indicated that the Philips UCAs ($d > 1.3$ μm) behave like a rigid scatterer and the resulting backscatter amplitude is linearly correlated with the UCA diameter. However, the calculation for the Point UCAs (0.6 $\mu\text{m} < d < 1.2$ μm) indicated that the backscattered pressure might not have a strong linear relation with UCA diameter.

Discussion and conclusions

Response of polymer shelled UCAs to HFU (40 MHz) was investigated. Clinically relevant levels of subharmonic or harmonic content were absent in the spectra of the backscattered signals for both excitation pressure amplitudes. This indicates that the predominant mechanism of subharmonic generation from Point and Philips UCAs when excited at 40 MHz probably is shell rupture; the incident acoustic pressures employed in this study (0.43 and 0.89 MPa) likely did not exceed the threshold for shell rupture.

The Hoff model¹⁰ predicts that bubbles when excited in the super resonant regime ($f > f_0$) will behave like a rigid scatterer (irrespective of their encapsulation or lack thereof). By extension, the scattering cross-section of such bubbles will simply be their geometric cross-section and their backscatter amplitude will be linearly related to their diameter. Even though the scattering cross-section and backscatter pressure predicted using the Hoff model¹⁰ cannot provide accurate quantitative analysis (without independent measure of shell properties), they qualitatively are consistent with our experimental observations.

The Philips UCAs investigated in this study appear to satisfy this criterion of super resonance behaviour when excited at 40 MHz, i.e. the amplitude of the backscatter signal recorded from the Philips UCAs was linearly related, albeit weakly ($R^2 > 0.6$), to the UCA diameter. On the contrary, the backscatter from the Point UCAs exhibited a poor linear relationship ($R^2 < 0.5$) with the UCA diameter. Furthermore, even though the nominal diameter of Point UCAs was half that of the Philips UCAs, the backscattered amplitude measured from the Point UCAs was roughly twice that from the Philips UCAs. The greater backscatter amplitude exhibited by the Point UCAs cannot be attributed to shell rupture and subsequent oscillations of the free gas bubbles; the resonance frequencies of such gas bubbles are an order of magnitude less than the excitation frequency of 40 MHz. Such oscillations should produce a more linear relationship between UCA size and backscattered signal amplitude.

The backscatter data obtained from both UCAs allude to a difference in the nature of their responses to 40 MHz ultrasound. The calculated scattering cross-section and backscattered pressure indicated that the Point UCAs might behave quasi-resonantly when excited at 40 MHz. Consequently, their scattering cross-section is expected to be greater than the

geometric cross-section, which is consistent with our experimental observations of Point UCAs producing greater backscatter than the Philips UCAs.

The experimental techniques presented in this study facilitated combined HFU and optical characterisation of free flowing UCAs, which is preferable to studies involving bound UCAs (Sprague *et al.*²²) for validating theoretical predictions. Experimental and theoretical results indicated the feasibility of high frequency backscatter measurements at pressures below rupture thresholds for acoustically determining the size of individual polymer shelled UCAs. However, the excitation frequency must be chosen carefully to satisfy the criterion of super resonant behaviour. The experimental methods presented in the current study could also be used to investigate the relationship between acoustic rupture of polymer shelled UCAs (and subsequent harmonics) and their size. The technique could be further improved by using a jacketed flow (section of fluid flowing at slow rate surrounded by fluid flowing at a faster rate) to maintain a predefined trajectory of the UCAs. Such an arrangement will reduce the velocity of UCAs and enable improved accuracy in their optical sizing.

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Fig. 1. *a* The schematic of the experimental set-up. *b–d* The microscope image of the 1.7 μm UCA, the corresponding RF data and the resulting power spectra respectively. *e–g* The image, RF data and the power spectra for the 3.5 μm UCA respectively. The backscatter amplitude from the larger UCA was twice that from the smaller UCA. In both cases, significant harmonics or subharmonics (within 20 dB of the fundamental) were absent

Fig. 2.

Relative amplitude of the backscatter signal measured from individual Point and Philips UCAs with respect to diameter. The UCAs were excited at 0.43 or 0.89 MPa. The Philips UCA backscatter data exhibited a linear trend, indicating that 40 MHz excitation resulted in super resonant response

Fig. 3.

Theoretical predictions obtained using the Hoff model. *a* Scattering cross-sections (normalised to the geometric cross-section) of a Point UCA, Philips UCA and two air bubbles (equilibrium radii of 0.5 and 1 μm) with respect to the driving frequency f . The peak in each curve represents the resonant behaviour of the bubble. *b* Normalised scattering cross-sections of Point and Philips UCAs with respect to UCA diameter ($f=40 \text{ MHz}$). The diameters that corresponded to $f_0=40 \text{ MHz}$ were 0.9 and 1.5 μm respectively. *c* Theoretically predicted, backscattered pressure at the transducer face with respect to UCA diameter ($f=40 \text{ MHz}$). Vertical dashed lines show the size range of the Point and Philips UCAs experimentally investigated