Nonlinear behavior of ultrasound-insonified encapsulated microbubbles

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Abstract. Ultrasound contrast agents consist of small encapsulated bubbles with diameters below 10 μm. The encapsulation influences the behavior of these microbubbles when they are insonified by ultrasound. The highly nonlinear behavior of ultrasound contrast agents at relatively high acoustic amplitudes (mechanical index>0.6) has been attributed to nonlinear bubble oscillations and to bubble destruction. For microbubbles with a thin, highly elastic nanoshell, it has been demonstrated that the presence of the nanoshell becomes negligible at high insonifying amplitudes. From our simulations it follows that the Blake critical radius is not valid for microbubble fragmentation. The low maximal excursion observed and simulated for a thick, stiff-shelled microbubble is in agreement with previous acoustic analyses. The ultrasound-induced gas release from stiff-shelled bubbles has been reported. However, we also observed gas release from microbubbles with a thin, elastic shell.

Keywords: Ultrasound contrast agent, encapsulated microbubble, nanoshell
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INTRODUCTION

Ultrasound contrast agents consist of gas microbubbles encapsulated by a nanoshell. Because the resonance frequencies of these microbubbles lie in the clinical ultrasonic range, contrast agents have been used for diagnostic imaging purposes. If a microbubble is subjected to very small pressure changes with an amplitude much smaller than the static ambient pressure, its radial excursion may be considered linear [1, 2]. Contrary to tissue, however, a microbubble exhibits highly nonlinear behavior at higher acoustic amplitudes. With harmonic imaging methods, microbubbles are therefore suitable markers for perfused areas.

We investigate the influence of the nanoshell on the behavior of ultrasound-insonified encapsulated microbubbles. More specifically, we are interested in finding the conditions needed for shell rupture.

OSCILLATING MICROBUBBLES

Let us consider a microbubble with an equilibrium radius R_0 and a shell thickness $h_s \ll R_0$. In equilibrium, the gas pressure inside the bubble p_{g0} can be expressed as:

$$p_{g0} = p_0^\infty - p_v + \frac{2s}{R_0}. \tag{1}$$

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Here, p_0^∞ is the static pressure of the liquid, p_v is the vapor pressure, and s is the surface tension. For an encapsulated gas bubble, the oscillating behavior has been described by a modified RPNNP equation, named after its developers Rayleigh, Plesset, Noltingk, Neppiras, and Poritsky [1, 2]:

$$\rho R\ddot{R} + \tfrac{3}{2}\rho\dot{R}^2 = p_{g0}\left(\frac{R_0}{R}\right)^{3\gamma} + p_v - p_0^\infty - \frac{2s}{R} - 2S_p\left(\frac{1}{R_0} - \frac{1}{R}\right) - \delta\,\omega\,\rho\,R\dot{R} - p_a(t)\,, \tag{2}$$

where $p_a(t)$ is the acoustic pressure in time, R is the instantaneous microbubble radius, S_p is the shell stiffness parameter, δ is the total damping coefficient, γ is the specific heat ratio, ρ is the liquid density, and ω is the angular driving frequency. $R(t)$ is periodic with period $T = T_e + T_c$, where $_e$ stands for expansion and $_c$ stands for contraction. The excursion is defined by $a(t) = R(t) - R_0$. The shell stiffness parameter is given by [3]:

$$S_p = \frac{8\pi E h_s}{1-\nu}\,, \tag{3}$$

where E is Young's modulus, and ν is the Poisson ratio. For albumin and lipid nanoshells, we take $0.499 < \nu < 0.500$. S_p can be estimated from optical observations of radius–time curves or from acoustical data using the relation [4]:

$$\omega_s^2 = \omega_r^2 + \frac{S_p}{4\pi R_0^3 \rho}\,, \tag{4}$$

where ω_s is the angular resonance frequency of the nanoshelled microbubble, ω_r is the angular resonance frequency of an unencapsulated microbubble of the same size.

At high acoustic pressures (mechanical index >0.6) destructive phenomena have been observed, such as microbubble fragmentation, coalescence, and ultrasonic cracking [5]. The critical stress at which a shell ruptures σ_c, is related to Young's modulus by:

$$\sigma_c \approx E\,\varepsilon_c\,, \tag{5}$$

where ε_c is the critical lateral shell deformation. For most biomaterials, $\varepsilon_c < 0.5$. Here, we treat two opposite cases: I. microbubbles with a thin, very elastic shell, and II. microbubbles with a thick, fairly stiff shell.

CASE I: THIN, ELASTIC SHELL

For microbubbles with a thin, highly elastic monolayer lipid nanoshell, like SonoVue™ and other Bracco agents, it has been demonstrated that the presence of the nanoshell becomes negligible at high insonifying amplitudes [5]. Such microbubbles have been observed to expand to more than ten-fold their initial surface areas during expansion. The nanoshell behaves like an elastic membrane that ruptures under relatively small strain [6]. By the time of maximal expansion, therefore, the nanoshell has ruptured, leaving newly formed clean free interfaces. This confirms that these microbubbles may be assumed free (unencapsulated). Similar to inertial cavitation, the relatively slow

TABLE 1. Elastic properties of three contrast agents

	ω_r $[2\pi \times 10^6\,\mathrm{rad\,s^{-1}}]$	$\langle R_0 \rangle$ $[\mu\mathrm{m}]$	S_p $[\mathrm{kg\,s^{-2}}]$	E^* $[10^6\,\mathrm{Pa}]$
Albunex®	2	4.0	10	2
Quantison™	4	1.6	25	2
SonoVue™	3	1.0	1.1	2

* Estimated with $\nu \approx 0.5$

microbubble expansion is followed by a rapid collapse: $T_e > T_c$. The microbubble has a time-varying radius $R(t) > 0$. Because the expansion is virtually unlimited, however, the excursion can be asymmetric as well: $\max(a(t)) > \min(a(t))$.

We analyzed the occurrence of microbubble fragmentation with respect to the intrinsic energy of the bubble [7]. Fragmentation occurs exclusively during the collapse phase. We hypothesize that fragmentation will only occur if and only if the kinetic energy of the collapsing microbubble is greater than the instantaneous bubble surface energy. From our simulations it follows that the Blake critical radius is not a good approximation for a fragmentation threshold.

CASE II: THICK, STIFF SHELL

For microbubbles with a thick, stiff nanoshell, like Quantison™, $a(t) \ll R_0$. From high-speed optical observations, we derived that $\max(a(t)) \leq \mathscr{R}$, where $\mathscr{R} \approx 0.3\,\mu\mathrm{m}$ is the resolution of the optical system. From the difference in resonance frequency between Quantison™ and free gas microbubbles, we determined $S_p = 25$ kg s^{-2} and $E = 2 \times 10^6$ Pa. The critical stress of Quantison™ is $\sigma_c \geq 80$ kPa [8], and thus $\varepsilon_c \geq 0.4$. Taking into account that $\varepsilon_c < 0.5$ and $\langle R_0 \rangle = 1.6\,\mu\mathrm{m}$, it follows that:

$$\max(a(t)) \approx 0.3\,\mu\mathrm{m} = \mathscr{R}\,. \tag{6}$$

Clearly, the acoustic observations are in agreement with the high-speed optical observations. The hypothesis that the rupture of the shell primarily occurs with micrububbles that have tiny flaws in the shell, has been supported by the optical observations of asynchronous cracking and cracking during a subsequent pulse.

SUMMARY OF THE RESULTS

Tabel 1 shows an overview of the shell properties of three contrast agents. SonoVue™ has a thin monolayer lipid shell, Quantison™ has a thick albumin shell, and Albunex® has a thin albumin shell.

Asymmetries with respect to the excursion axis and to the time-axis can be observed with a spherically symmetric oscillating microbubble. Although the ultrasound-induced gas release from stiff-shelled bubbles has been reported, we also observed gas release from microbubbles with a thin, elastic shell (*cf.* Fig. 1).

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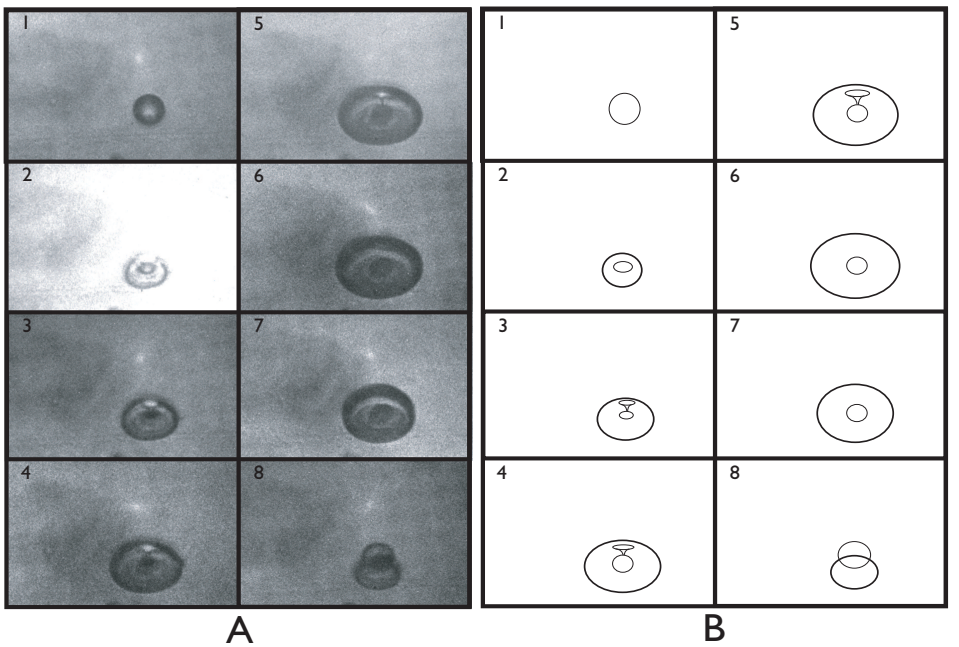

FIGURE 1. Gas release from a lipid-shelled microbubble (A) and a schematic representation thereof (B). The frames were captured at 3 million frames per second. Frame 1 has been taken prior to ultrasound arrival. Frames 2–8 cover one full ultrasonic cycle. Each frame corresponds to a $88 \times 58\,\mu m^2$ area. The images were captured at the Department of Experimental Echocardiography, Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands.