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Microbubble oscillating in a microvessel filled with viscous fluid: A finite element modeling study

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ABSTRACT

Understanding the dynamics of coated-microbubble oscillating in an elastic microvessel is important for effective and safe applications of ultrasound contrast agents (UCAs) in imaging and therapy. Numerical simulations are performed based on a two-dimensional (2D) asymmetric finite element model to investigate the influences of both acoustic driving parameters (e.g., pressure and frequency) and material properties (vessel size, microbubble shell visco-elastic parameters and fluid viscosity) on the dynamic interactions in the bubble–blood–vessel system. The results show that, the constrained effect of the blood vessel along the radial direction will induce the asymmetric bubble oscillation and vessel deformation, as well as shifting the bubble resonance frequency toward the higher frequency range. For a bubble (1.5-μm radius) activated by 1-MHz ultrasound pulses in a microvessel with a radius varying between 2 and 6.5 μm, up to 26.95 kPa shear stress could be generated on the vessel wall at a driving pressure of 0.2 MPa, which should be high enough to damage the vascular endothelial cells. The asymmetrical oscillation ratio of the bubble can be aggravated from 0.12% to 79.94% with the increasing acoustic driving pressure and blood viscosity, or the decreasing vessel size and microbubble shell visco-elastic properties. The maximum compression velocity on the bubble shell will be enhanced from 0.19 to 22.79 m/s by the increasing vessel size and acoustic pressure, or the decreasing microbubble shell visco-elasticity and blood viscosity. As the results, the peak values of microstreaming-induced shear stress on the vessel wall increases from 0.003 to 26.95 kPa and the deformation degree of vessel is raised from 1.01 to 1.49, due to the enhanced acoustic amplitude, or the decreasing vessel size, blood viscosity and microbubble shell visco-elasticity. Moreover, it also suggests that, among above impact parameters, microbubble resonance frequency and UCA shell elasticity might play more dominant roles in dynamic interactions of the bubble–blood–vessel system.

1. Introduction

Encapsulated microbubbles with an insoluble gas core were initially used in clinics as contrast agents for ultrasound (US) diagnostic imaging because of their backscattering properties and higher echogenicity than the background tissues [1,2]. In recent years, microbubbles have also been broadly utilized in the field of ultrasound therapy [3–5]. When injected into a blood vessel, the microbubble oscillations induced by ultrasound excitation will result in the deformation of the blood vessels by making the elastic vessel walls expand and contract. In turn, the microbubble-mediated vessel motions might result in potential therapeutic effects by enhancing the vascular permeability [6–8] and stimulating angiogenesis [9,10]. However, the intense vessel deformations could also be a safety hazard, e.g., cell apoptosis [11], capillary rupture [12], and vascular damage [13–15]. Therefore, there are increasing demands to better understand the interaction between the confined vessel walls and the ultrasound contrast agent (UCA) microbubbles exposed to US pulses, which could be beneficial for the development and optimization of UCA applications in medical ultrasound, especially in therapeutic ultrasound.

Microbubble oscillation, which contains expansion phase and collapse phase, will induce acoustic microstreaming. Subsequently, shear stress can be induced in the surrounding fluid in the vessel. Then, the endothelial cells lining the vessel walls might be affected by the microstreaming-induced shear stress, and the degree of this effect depends on the magnitude of shear stress. Van Bavel et al. reported endothelial cells could lose membrane integrity and eventually detach by sufficiently high shear stress [16]. By using a lithotripter, Ohl and Wolfrum found a shear stress of

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100–160 Pa should be required for detachment of cultured HeLa cells [17]. Miller et al. predicted the lysis of endothelial cells would happen at a shear stress around 800 Pa [18]. Although many efforts have been made to explore the shear stress thresholds relative to the bioeffects of endothelial cells, the determining factors that could dominate the level of shear stress generated by US-induced microbubble oscillations in the elastic vessels have not been well determined.

Besides experimental reports, several numerical models were also proposed in previous studies to simulate the dynamics of a bubble in a confined vessel. For instance, Sassaroli and Hynynen developed a two-dimensional (2D) model to simulate a rectangular bubble oscillating in a rigid vessel [19]. Ye and Bull developed a 2D boundary element model (BEM) to simulate the asymmetric expansion of a free-gas bubble grown from a perfluorocarbon droplet in both rigid and flexible vessels containing an inviscid fluid [20]. Using a lumped-parameter model that takes into account of the bubble shell and the fluid viscosity, Qin and Ferrara studied the natural frequency of nonlinear oscillations of UCAs in a partially compliant vessel and in a vessel with increasing stiffness [21]. After those studies, more asymmetric models were proposed to simulate the asymmetric oscillations and acoustic responses of the bubble in a small vessel, based on BEM, the finite element method (FEM) or the combination of these two methods [22–28]. The results of these numerical studies suggested that the nature frequency and shear stress generated by the bubbles oscillating could be significantly affected due to the presence of the elastic vessel walls. It also predicted that vascular damage could occur during vascular invaginations (viz., the vessel's instantaneous radius is smaller than its initial radius) due to the elevated wall shear stress and circumferential stress.

In general, previous studies have focused more on the impacts of vessel size and stiffness on microbubble oscillations. However, previous studies have mention that the microbubble shell materials will also play a significant impact in the bubble dynamic responses (e.g., acoustic attenuation, scattering, and the generation of harmonics) [29–37]. Moreover, the damping caused by surrounding viscous liquid is another important factor that could affect the bubble oscillations [38]. Therefore, in order to get a more comprehensive understanding of the interactions happening in the complicated bubble–blood–vessel system, more impact parameters (e.g., microbubble shell visco-elasticity and blood viscosity were evaluated regarding their influences not only on bubble behaviors but also on the deformation of blood vessel.

2. Materials and methods

2.1. Theoretical model

The physics of a single microbubble oscillating in a microvessel filled with viscous fluid involves the interaction of a coupled gas–fluid–solid system. Here, the system can be separated into two parts: the interaction between gas and fluid and the interaction between fluid and solid. A homogeneous, incompressible and single-phase Newtonian fluid is assumed to describe the blood environment in the vessel. When the microbubble is activated by ultrasound, the fluid around the bubble should obey the mass and momentum conservation laws [39]:

$$\frac{\partial \rho_l}{\partial t} + \nabla \cdot (\rho_l \mathbf{v}) = \mathbf{0}, \tag{1}$$

$$\rho_l\left(\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v}\cdot\nabla)\mathbf{v}\right) = \nabla\cdot(-p\mathbf{I} + \mu_l(\nabla\mathbf{v} + \nabla\mathbf{v}^T)), \tag{2}$$

where $\mathbf{v}$ is the velocity vector, p is the pressure in the fluid, $\mathbf{I}$ is the identity tensor, ρ_l and μ_l are the density and dynamic of the fluid, respectively.

The gas inside the bubble is assumed spatially uniform and thus obeys the state equation for an ideal gas. Therefore, the gas pressure inside the microbubble is related to the bubble volume,

$$p_g = p_{g0}(V_0/V)^{\gamma}, \tag{3}$$

where p_g is the gas pressure inside the bubble, p_{g0} is the initial pressure, V is the volume of the bubble, V_0 is the initial volume of the bubble and γ is the polytropic exponent of the gas.

If the microbubble is a free gas bubble, the gas–fluid interface must obey a velocity continuity condition and a pressure continuity condition, given respectively as follows [40],

$$\mathbf{v}(R) = \dot{R}, \tag{4}$$

$$p(R) = p - \frac{2\sigma_g}{R} - 4\mu_l\frac{\dot{R}}{R}. \tag{5}$$

where σ_g is the interfacial tension of the free gas bubble and μ_l is the dynamic viscosity of the fluid. Most UCA microbubbles, however, are encapsulated with a thin shell made from protein, lipid or saccharide. To account for the presence of the shell, Chatterjee et al suggested that the encapsulation shell of the UCA bubble can be treated as a Newtonian viscous fluid interface with infinitesimal thickness, and the pressure continuity condition can be applied at the interface [41,42]. According to their work, the pressure continuity condition at the gas–fluid boundary of an encapsulated UCA bubble can be written as:

$$p(R) = p_g - \frac{2\sigma_e}{R} - 4\mu_l\frac{\dot{R}}{R} - 4\kappa_s\frac{\dot{R}}{R^2}, \tag{6}$$

where the interfacial tension σ_e and dilatational viscosity κ_s represent the visco-elastic properties of the encapsulated bubble shell, respectively. The gas pressure in the bubble (p_g) in Eq. (6) is defined as,

$$p_g = p_{g0}\left(\frac{R_0}{R}\right)^{3\gamma}, \tag{7}$$

whose initial value (p_{g0}) is determined by the static balance condition [43]

$$p_{g0} = p_0 + \frac{2\sigma_e}{R_0}. \tag{8}$$

As the length of the microvessel is much greater than the microbubble's radius, the fluid at the ends of the vessel will obey the following boundary condition

$$p(\infty) = p_0 - P_{ac}(t), \tag{9}$$

where p_0 is the hydrostatic pressure in the fluid and $P_{ac}(t)$ is the driving ultrasonic pressure pulse.

The 2D geometry of the bubble–blood–vessel system is schematically illustrated in Fig. 1, where the microbubble is located in the center of the microvessel, L is length of the vessel, w is the thickness of the vessel wall, R_{tube} is the initial radius of the vessel and R_0 is the initial radius of the bubble. The origin of the cylindrical coordinate system is at the bubble's center, the radial coordinate is orthogonal to the vessel wall and the axial coordinate is parallel to the vessel wall.

Since the vessel wall is considered as a homogeneous isotropic linear elastic material, it should satisfy the stress–strain condition [24]

$$\sigma_{ij} = \frac{E}{1+\upsilon}\left(\varepsilon_{ij} + \frac{\upsilon}{1-2\upsilon}\varepsilon_{kk}\delta_{ij}\right), \tag{10}$$