Ultrasonic excitation of a bubble inside a deformable tube: Implications for ultrasonically induced hemorrhage

Hongyu Miao

Mechanical Engineering, University of Rochester, Rochester, New York 14627

Sheryl M. Gracewski^{a)}

Department of Mechanical Engineering, Department of Biomedical Engineering, and Rochester Center for Biomedical Ultrasound, University of Rochester, Rochester, New York 14627

Diane Dalecki

Department of Biomedical Engineering and Rochester Center for Biomedical Ultrasound, University of Rochester, Rochester, New York 14627

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Various independent investigations indicate that the presence of microbubbles within blood vessels may increase the likelihood of ultrasound-induced hemorrhage. To explore potential damage mechanisms, an axisymmetric coupled finite element and boundary element code was developed and employed to simulate the response of an acoustically excited bubble centered within a deformable tube. As expected, the tube mitigates the expansion of the bubble. The maximum tube dilation and maximum hoop stress were found to occur well before the bubble reached its maximum radius. Therefore, it is not likely that the expanding low pressure bubble pushes the tube wall outward. Instead, simulation results indicate that the tensile portion of the acoustic excitation plays a major role in tube dilation and thus tube rupture. The effects of tube dimensions (tube wall thickness 1–5 μm), material properties (Young's modulus 1–10 MPa), ultrasound frequency (1–10 MHz), and pressure amplitude (0.2–1.0 MPa) on bubble response and tube dilation were investigated. As the tube thickness, tube radius, and acoustic frequency decreased, the maximum hoop stress increased, indicating a higher potential for tube rupture and hemorrhage.

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I. INTRODUCTION

Biomedical ultrasound is widely used for diagnostic imaging because it is inexpensive, relatively portable, and can generate real time dynamic images. In some cases, echo contrast agents, which are essentially stabilized microbubbles, are injected into the vasculature to improve the image contrast of blood flowing through organs such as the heart. However, a number of studies also indicate that ultrasound-induced hemorrhage could be enhanced by the presence of contrast agents (e.g., Miller and Gies, 1998; Miller and Qudus, 2000; Miller and Gies, 2000; Wible *et al.*, 2002; Li *et al.*, 2003, 2004).

Two main hypotheses have been proposed to explain how acoustically excited bubbles can cause hemorrhage (e.g., Zhong *et al.*, 2001; Hwang *et al.*, 2006; Hu *et al.*, 2005). One hypothesis is that vascular damage is caused by the local high pressures and temperatures or by high-speed liquid jets that are generated by the inertial collapse of the bubbles. The second hypothesis is that vessel rupture occurs as the bubble expands. To understand more precisely potential hemorrhage mechanisms, Zhong *et al.* (2001) used a high-speed camera to observe the behavior of contrast agent bubbles flowing within a submerged hollow fiber subject to

lithotripter shock waves. Fiber rupture was observed when a microbubble was present inside the fiber for certain lithotripter shock waves, and no rupture was found in the absence of such bubbles under the same excitation. Zhong *et al.* (2001) concluded that lithotripter shock waves can cause the large expansion of intravascular bubbles that can lead to vessel dilation and eventually vessel rupture. In this paper, a simulation model is used to investigate the interaction between an acoustically excited bubble and a deformable vessel.

Numerous mathematical models have been developed to investigate bubble dynamics. Classical cavitation models, such as the Rayleigh–Plesset equation (Leighton, 1994; Young, 1989) and the Gilmore equation (Gilmore, 1952), describe well the spherically symmetric bubble responses to acoustic excitation in an infinite liquid domain. However, if the bubble is constrained by neighboring objects such as a blood vessel, the bubble motion will become asymmetric and a high-speed liquid jet may form. Therefore, an understanding of asymmetric bubble dynamics is needed to investigate possible mechanisms of ultrasound-induced hemorrhage in tissues containing ultrasound contrast agents.

A number of studies have been reported on asymmetric bubble expansion and collapse near rigid boundaries. Most of them investigated laser- or spark-generated bubbles (e.g., Shima *et al.*, 1981; Vogel *et al.*, 1989; Tipton *et al.*, 1992; Harris *et al.*, 1999; Brujan *et al.*, 2002; Tomita *et al.*, 2002).

^{a)}Author to whom correspondence should be addressed; electronic mail: grace@me.rochester.edu

Only a few studies have been reported on the bubble behavior near rigid boundaries in an oscillating pressure field (Sato *et al.*, 1994; Krasovitski and Kimmel, 2001; Brujan, 2004). For these numerical investigations, the boundary element method has been successfully employed to simulate asymmetric bubble motion, assuming that the bubble is in an incompressible and inviscid liquid. For ultrasonically excited bubbles, the work of Sato *et al.* (1994) and Krasovitski and Kimmel (2001) indicated that as the ultrasound frequency increases or the distance from the bubble to the rigid boundary decreases, the bubble collapse is mitigated.

The effect of the deformation of nearby structures on bubble behavior has also been investigated. The behavior of a laser-induced bubble near a deformable gel sample was observed using high-speed photography by Brujan *et al.* (2001a, 2001b). Also, experimental observations of interactions between ultrasonically excited bubbles and cells (Wolfrum *et al.*, 2002; Kudo *et al.*, 2002) or tubes (Zheng *et al.*, 2007) have been reported. A numerical investigation of bubble interaction with nearby deformable structures was conducted by Chahine and Kalumuck (1998), Duncan *et al.* (1996), and Klaseboer *et al.* (2005). Numerical techniques, such as the fluid-structure coupling procedures in Chahine and Kalumuck (1998) and Duncan *et al.* (1996), were used to develop the simulation models used in the current study.

Recently, a number of papers that present numerical investigations specifically developed to investigate the asymmetric oscillations of an intravascular bubble have been published. Hu *et al.* (2005) developed a theoretical model, including effects to second order, for asymmetric bubble oscillations inside a rigid tube with a radius much larger than the bubble radius. The asymmetric oscillations of a bubble inside a deformable tube excited by a short lithotripter pulse simulated using a finite element technique and a finite volume technique were described in Qin *et al.* (2006) and Gao *et al.* (2007), respectively. In both of these papers, the shock wave pressure was applied at the bubble surface. Qin and Ferrara (2006) used the finite element program COMSOL to model the response of a bubble in an incompressible, viscous liquid to a single sinusoidal cycle acoustic excitation. The effect of the tube was approximated by a nonlinear boundary condition. These papers presented predictions of the resulting pressure on the inner tube surface or the transmural pressure across the vessel wall. Qin and Ferrara (2006) predicted that an acoustic excitation with a frequency of 1 MHz and an amplitude of 0.5 MPa would be sufficient to rupture small vessels with a diameter less than 15 μm . In the current paper, a harmonic acoustic pressure excitation is applied at infinity, similar to the Rayleigh–Plesset model, and the surrounding vessel is modeled with finite elements so the internal stresses can be determined.

An understanding of interactions between ultrasonically excited contrast agents and nearby tissues and vessels is needed to determine damage mechanisms and provide guidelines for safe usage of diagnostic ultrasound. The goal of this investigation was to further explore the possible damage mechanisms of ultrasound-induced hemorrhage when contrast agents are present. A coupled finite element and boundary element code was employed to investigate the axisym-

metric ultrasonically excited bubble-vessel interactions. In particular, simulations were used to investigate the hypothesis that tube rupture occurs due to bubble expansion. The finite element model of the vessel can predict not only vessel deformation but also stresses induced in the vessel, and therefore the potential for vessel rupture can be assessed. The effects of a range of vessel material properties (Young's moduli from 1 to 10 MPa), vessel dimensions (vessel lengths from 30 to 60 μm ; vessel wall thicknesses from 1 to 5 μm ; inner vessel radii from 2 to 8 μm), and acoustic excitations (frequencies from 1 to 10 MHz; pressure amplitudes from 0.2 to 1.0 MPa) on bubble behavior and tube dilation and internal stresses were investigated. Implications of the numerical results for ultrasound bioeffects are discussed.

II. COUPLED BOUNDARY ELEMENT–FINITE ELEMENT MODEL

A coupled finite element and boundary element code has been developed to solve axisymmetric gas-liquid-solid interaction problems to predict the response of acoustically excited bubbles. The gas within the bubble is assumed to be spatially uniform and to obey the polytropic gas law (Prosperetti, 1991),

$$p_b = p_v + p_g = p_v + p_{g0} \left(\frac{R_0}{R} \right)^{3\Gamma}, \quad (1)$$

where p_g is the gas pressure inside the bubble, R is the equivalent instantaneous bubble radius, R_0 is the equilibrium bubble radius, p_{g0} is the equilibrium gas pressure inside the bubble, Γ is the polytropic exponent (equal to the ratio of the specific heats of the gas for an isentropic process), p_v is the constant vapor pressure, and p_b is the sum of the gas pressure and the vapor pressure within the bubble. In addition, a surface tension σ at the bubble liquid interface is considered in our model. The liquid is assumed to be incompressible, irrotational, and inviscid, and therefore modeled in terms of the potential flow equations using the boundary element method. The first two assumptions are consistent with the Rayleigh–Plesset model, which adequately models the bubble expansion and early collapse phases of the bubble considered in this paper. The main effects of compressibility and viscosity occur during inertial collapse, which is not the focus of this paper. Therefore these effects have not been included for simplicity. Viscosity may also reduce the maximum bubble expansion and will therefore be investigated in future work. Since velocity potential in the liquid ϕ_L satisfies the Laplace equation, the governing equation of liquid is given in the cylindrical coordinates as

$$\frac{\partial^2 \phi_L}{\partial r^2} + \frac{1}{r} \frac{\partial \phi_L}{\partial r} + \frac{\partial^2 \phi_L}{\partial z^2} = 0. \quad (2)$$

The acoustic pressure is applied at infinity as in the Rayleigh–Plesset equation for a spherical bubble response to acoustic excitation (Leighton, 1994). The vessel is modeled as a linear elastic solid using a finite element method. Traction and normal velocity are assumed continuous across the fluid-solid boundary to couple the finite element and bound-

FIG. 1. Schematic illustration of the axisymmetric geometry of a bubble within a finite tube length.

any element domains. For details of theoretical issues, numerical techniques, and validation of this code, the reader is referred to Miao and Gracewski (2008).

The following investigation focuses on interactions between a tube and a bubble located at the center of the tube. A schematic illustration of the problem geometry is given in Fig. 1, where R_0 is the initial bubble radius, r_i is the inner radius of the tube, w is the tube wall thickness, A_i is the midpoint on the inner tube surface, and A_o is the midpoint on the outer tube surface.

For numerical simulations, the equilibrium bubble radius, $R_0=1.5\ \mu\text{m}$, was chosen to represent the average size of typical ultrasound contrast agents (Bouakaz and De Jong, 2007). The average inner radius of capillaries is about $4\ \mu\text{m}$. However, to investigate the influence of the vessel inner radius on bubble oscillations, simulation results were obtained for $r_i=2, 4$, and $8\ \mu\text{m}$. Considering the average dimensions of microvessels such as capillaries, the length of the elastic tube should be much greater than the size of the bubble. However, due to limited computing resources, a length of $30\ \mu\text{m}$, ten times the initial bubble diameter, was actually employed. The implications of this limitation will be discussed later in the paper. The average thickness of a capillary wall is about $1\ \mu\text{m}$ (Megerman and Abbott, 1983). Since capillaries are generally surrounded by other tissues such as muscle, the effects of larger wall thicknesses were also investigated as a simplified model of a vessel surrounded by tissue. The related computing costs increase dramatically with increases in vessel wall thickness. Therefore simulations were done mainly with 1 and $5\ \mu\text{m}$ wall thicknesses. Increasing the wall thickness further does not significantly affect the bubble and tube responses for the cases with an acoustic pressure amplitude equal to $0.2\ \text{MPa}$ considered in this paper, as suggested by our preliminary results (not shown).

Blood vessel walls generally consist of multiple layers with different mechanical properties, and experimental measurements indicate that vessel materials exhibit viscoelastic characteristics (Fung, 1981). However, to obtain the general characteristics of the effects of vessel deformation on the bubble response, a simplified homogeneous, isotropic, and linear elastic model was used. Specifically, the linear elastic constitutive equation is given as

$$\sigma_{ij} = \frac{E}{1+\nu} \left(\varepsilon_{ij} + \frac{\nu}{1-2\nu} \varepsilon_{kk} \delta_{ij} \right), \quad (3)$$

where δ_{ij} is the Kronecker delta ($\delta_{ij}=1$ if $i=j$ and $\delta_{ij}=0$ if $i \neq j$) and σ_{ij} and ε_{ij} are the ij th components of the stress and strain tensors, respectively. The material parameters are Young's modulus E and Poisson's ratio ν .

The Young's modulus, the Poisson's ratio, and the density of the vessel wall material need to be specified. From previous experimental measurements vascular materials are known to be nearly incompressible (Fung, 1981), so a Poisson's ratio of 0.49 is used (Melbin and Noordergraaf, 1971). The value of Young's modulus of vascular materials may vary between $0.98\ \text{MPa}$ (or lower) and $9.6\ \text{MPa}$ (or higher) (Yamada, 1970; Duck, 1990; Rowe *et al.*, 2003; Snowhill and Frederick, 2005) for vessels within different organs. In the numerical simulations, Young's moduli of $1, 5$, and $10\ \text{MPa}$ were employed to span a range of Young's moduli relevant to vascular materials. A vessel wall density of $1100\ \text{kg/m}^3$ was used in all the simulations (Megerman and Abbott, 1983).

The tensile strength of vessels also varies between $0.46\ \text{MPa}$ (or lower) and $3.6\ \text{MPa}$ (or higher) (Yamada, 1970; Rowe *et al.*, 2003; Snowhill and Frederick, 2005). The longitudinal tensile strength is generally greater than the circumferential tensile strength. For example, Rowe *et al.* (2003) measured cerebral arteries and obtained a longitudinal strength of $3.6\ \text{MPa}$, which is greater than the circumferential strength of $2.4\ \text{MPa}$. Rowe *et al.* (2003) explained that this difference is due to the multidirectional layered structure of vessel wall. In addition, for the fiber rupture observed by Zhong *et al.* (2001), the cleft was along the axial direction of the fiber, which indicated that the failure of the fiber was due to the circumferential or hoop stress. Therefore, in this investigation of ultrasonically excited bubble-vessel interactions, the hoop stresses inside vessel walls were calculated and compared to the circumferential tensile strength of vessels to predict the damage threshold.

The bubble and the tube were excited by an acoustic source with a frequency of $1, 5$, or $10\ \text{MHz}$ and a pressure amplitude of $0.2, 0.5$, or $1.0\ \text{MPa}$ to investigate the effect of the excitation parameters on the bubble response. The continuous sinusoidal acoustic source was applied at infinity using the same assumptions as those of the Rayleigh-Plesset model. This range of pressure amplitudes was chosen because $0.2\ \text{MPa}$ is just above the inertial cavitation threshold predicted by the Rayleigh-Plesset model (Young, 1989) for an excitation frequency of $1\ \text{MHz}$. The acoustic excitation begins with the tensile phase, which causes the bubble to initially expand. Gravity was not considered in this model, and other constant parameters used for numerical simulations were $\rho_l=1000\ \text{kg/m}^3$, $p_v=2300\ \text{Pa}$, $p_0=101\,230\ \text{Pa}$, $\sigma=0.0717\ \text{N/m}$, and $\Gamma=1.4$, where ρ_l is the liquid density, p_v is the vapor pressure, p_0 is the ambient pressure, σ is the surface tension, and Γ is the polytropic exponent of the gas set equal to the ratio of specific heat capacities for air.

FIG. 2. Comparison of equivalent bubble radius vs time for (a) $r^*=4/3$ with bubble-tube contact during bubble expansion and (b) $r^*=16/3$ without bubble-tube contact during bubble expansion ($w=1 \mu\text{m}$, $E=10 \text{ MPa}$, $f=1 \text{ MHz}$, and $p_a=0.2 \text{ MPa}$).

III. BUBBLE-TUBE INTERACTIONS

In this section, some general characteristics of bubble-tube interactions are described by considering typical simulation results. Results are compared for vessel wall thicknesses $w=1$ and $5 \mu\text{m}$ and inner tube radii $r_i=2, 4$, and $8 \mu\text{m}$ with ratios $r^*=r_i/R_0=4/3, 8/3$, and $16/3$, respectively. The ultrasonic excitation used has a frequency of 1, 5, or 10 MHz and an amplitude of 0.2 MPa. More details about the effects of vessel wall thickness, Young's modulus, and acoustic frequency and amplitude on the interactions between the vessel and the bubble will be discussed in the next section.

General characteristics of the bubble-tube interaction depend on whether or not the bubble comes in to contact with the tube during the bubble expansion phase. The bubble is more likely to touch the inner tube surface for (1) r^* closer to 1, (2) stiffer vessels, and (3) higher amplitude acoustic excitations. Characteristics of bubble responses with and without touching are discussed by comparing the response of a bubble in a stiff tube with Young's modulus equal to 10 MPa and a thickness of $1 \mu\text{m}$ for two different inner radii, corresponding to $r^*=4/3$ and $r^*=16/3$. For both simulations, the acoustic excitation used has a frequency equal to 1 MHz and an amplitude equal to 0.2 MPa.

In Figs. 2(a) and 2(b), typical equivalent bubble radius versus time curves are depicted for $r^*=4/3$ and $r^*=16/3$, respectively. The equivalent bubble radius is the radius of a sphere with the same volume as the bubble and is used here to allow comparisons to results obtained from the Rayleigh-Plesset model. For the oscillation of a single bubble in an infinite liquid domain subject to the same acoustic excitation, the maximum bubble radius R_{max} is equal to $3.7 \mu\text{m}$. For

FIG. 3. Time sequence of bubble and tube shapes for (a) $r^*=4/3$ and (b) $r^*=16/3$ ($w=1 \mu\text{m}$, $E=10 \text{ MPa}$, $f=1 \text{ MHz}$, and $p_a=0.2 \text{ MPa}$). Note that tube ends may be truncated to fit into the frames. In addition, jet penetration denotes the moment when the water jet penetrates the opposite bubble boundary.

$r^*=16/3$, the bubble does not touch the tube wall, and $R_{\text{max}}=3.2 \mu\text{m}$ is $\sim 15\%$ smaller than that for a bubble in an infinite liquid domain. For $r^*=4/3$, the bubble touches the tube during expansion and $R_{\text{max}}=2.0 \mu\text{m}$, almost 50% less than the free field value. Compared to the bubble collapse for $r^*=16/3$ indicated in Fig. 2(b), the bubble collapse for $r^*=4/3$ is mitigated due to a smaller value of R_{max} , as indicated in Fig. 2(a). In addition, the bubble radius versus time curve in Fig. 2(a) is still smooth (first-order differentiable) although the bubble touches the inner tube surface during bubble expansion.

In Fig. 3, a series of bubble and tube shapes are depicted for the same parameters used in Fig. 2. Figures 3(a) and 3(b) are for $r^*=4/3$ and $r^*=16/3$, respectively. The time points are spaced evenly with an increment of $0.1 \mu\text{s}$ except for some important moments, such as the time points of maximum bubble wall velocity, maximum tube dilation, bubble-vessel contact, if it occurs, and maximum bubble radius. For

FIG. 4. Hoop stress distribution in the tube wall during bubble expansion at the moment of peak hoop stress for $r^*=4/3$ ($w=1\ \mu\text{m}$, $E=10\ \text{MPa}$, $f=1\ \text{MHz}$, and $p_a=0.2\ \text{MPa}$). The maximum hoop stress of 1 MPa occurs on the inner tube wall at the location of the bubble.

the smaller ratio of $r^*=4/3$, the bubble touches the inner tube surface at $t=0.445\ \mu\text{s}$. No contact occurs for the larger ratio of $r^*=16/3$.

Note that the maximum hoop stress occurs during the tensile portion of the acoustic pulse, well before the bubble reaches its maximum radius. In Fig. 3(a), between $t=0.24\ \mu\text{s}$ and $t=0.445\ \mu\text{s}$, the tube contracts as the bubble expands. The gas pressure p_g in the expanding bubble is nearly zero. Therefore the bubble nearing maximum expansion could not “push” on the vessel wall if the stress outside the vessel were not tensile. Figure 4 gives the hoop stress distribution within the tube wall at $t=0.24\ \mu\text{s}$, the moment of peak hoop stress during bubble expansion, for $r^*=4/3$. The parameters used in Fig. 4 are the same as the values in Figs. 2(a) and 3(a). The higher hoop stresses occur at the inner tube surface near the middle of the tube (this is the area that deforms the most and is closest to the bubble). The hoop stress distribution in the tube wall at the moment of maximum tube dilation during bubble expansion is similar for all cases considered in this paper.

The ratio r^* is not the only factor that determines whether the bubble will touch the inner tube surface. For instance, if Young’s modulus is changed from $E=10\ \text{MPa}$ to $E=1\ \text{MPa}$ for the ratio $r^*=4/3$, with all other parameters the same, the bubble will not touch the wall upon bubble expansion due to the dilation of the compliant tube wall, as indicated in Fig. 5. For this more compliant tube, the maximum radius $R_{\text{max}}=2.5\ \mu\text{m}$ is greater than the original tube radius. However, the tube expands appreciably as the bubble expands, so they never touch. For this case, results are only shown for the bubble expansion phase because the vessel wall maximum strain is on the order of 0.1. This exceeds the small deformation assumption and leads to an accumulation of numerical errors such that the numerical results for the collapse stage become unreliable. Figure 6 shows the equivalent bubble radius versus time curve during bubble expansion for the same parameters used in Fig. 5.

FIG. 5. Time sequence of bubble and tube shapes for a more compliant tube during bubble expansion for $r^*=4/3$ and $E=1\ \text{MPa}$ ($w=1\ \mu\text{m}$, $r_i=2\ \mu\text{m}$, $f=1\ \text{MHz}$, and $p_a=0.2\ \text{MPa}$).

For all three cases, as shown in Figs. 2(a), 2(b), and 6, the peak hoop stress occurs well before the bubble reaches its maximum radius. Even though the peak hoop stress occurs at the same time as the maximum bubble wall velocity in Fig. 2(b), this is not true in general. For example, the peak hoop stress occurs before and after the moment of maximum bubble wall velocity in Figs. 2(a) and 6, respectively.

During the bubble expansion phase, the maximum principal stress in the vessel wall is the hoop stress. In Fig. 7, the maximum hoop stress $(\sigma_{\theta\theta})_{\text{max}}$ is plotted versus time during the bubble expansion stage for different inner tube radii r_i and acoustic frequencies f . Here, $(\sigma_{\theta\theta})_{\text{max}}$ is the maximum value of $(\sigma_{\theta\theta})_i$, where $(\sigma_{\theta\theta})_i$ is the hoop stress of element i . For all cases shown, $(\sigma_{\theta\theta})_{\text{max}}$ occurs at point A_i . The parameters of these six cases in Fig. 7 are intentionally chosen to be as diversified as possible. For example, the tube wall thickness for Fig. 7(a) is $w=1\ \mu\text{m}$, which is intentionally different from the wall thickness $w=5\ \mu\text{m}$ for Fig. 7(b). Figure 7 indicates that, as the bubble expands, $(\sigma_{\theta\theta})_{\text{max}}$ increases from zero to a maximum value and then decreases down to almost zero. In Fig. 7(a), as the inner tube radius increases from 2 to 8 μm , the peak value of the maximum hoop stress decreases from 1.7 to 1.1 MPa. In Fig. 7(b), as the ultra-

FIG. 6. Equivalent bubble radius vs time during bubble expansion for $r^*=4/3$ and $E=1\ \text{MPa}$ ($w=1\ \mu\text{m}$, $r_i=2\ \mu\text{m}$, $f=1\ \text{MHz}$, and $p_a=0.2\ \text{MPa}$), corresponding to the time sequence of Fig. 5.

FIG. 7. Maximum hoop stress $(\sigma_{\theta\theta})_{\max}$ vs time for (a) different inner tube radii ($w=1 \mu\text{m}$, $E=5 \text{ MPa}$, $f=1 \text{ MHz}$, and $p_a=0.2 \text{ MPa}$) and (b) different ultrasound frequencies ($r_i=4 \mu\text{m}$, $w=5 \mu\text{m}$, $E=5 \text{ MPa}$, and $p_a=0.2 \text{ MPa}$).

sound frequency increases from 1 to 10 MHz, the peak value of the maximum hoop stress decreases from 1.2 to 0.3 MPa.

Since the hoop stress is the maximum stress component during bubble expansion, vessel rupture is predicted when the hoop stress exceeds the circumferential strength of the vessel wall material. This numerical prediction is consistent with the experimental observation of tube rupture patterns by Zhong *et al.* (2001). In their experiments, a cleft was found along the axis of the hollow fiber, which indicated that the tube was ripped open as the hoop stress exceeded the circumferential tensile strength.

An important question is what causes the increase in hoop stress during bubble expansion shown in Fig. 7, or, in other words, what causes tube dilation as the bubble expands. The answer to this question is critical to determine the damage mechanisms of vessel rupture. Zhong *et al.* (2001) observed the response of echo contrast agent bubbles confined within tubes subject to lithotripter shock waves and claimed that the large bubble expansion causes vessel dilation. However, in their experiment, the bubble with an equilibrium radius of $1 \mu\text{m}$ expands to almost 200 times its initial radius, which results in a low pressure inside the bubble at the maximum bubble radius (about $1/10^7$ of the initial equilibrium pressure inside the bubble). Such low pressure is unlikely to push the vessel wall and cause rupture. Instead, Gracewski and Miao (2006) reported that the bubble can expand to meet the vessel wall during the tensile portion of the lithotripter shock wave. At this time, the pressure in the bubble is almost zero so the external radial tensile stress is not balanced by an internal radial tensile stress as it would be for a liquid-filled vessel. Therefore, it was hypothesized that vessel rupture in lithotripsy occurs because the tensile force of the shock wave pulse stretches the vessel, producing a

FIG. 8. Time traces of the gauge pressure p_i at point A_i (solid), the gauge pressure p_o at point A_o (dotted), and the pressure drop across the tube wall $(p_i - p_o)$ (dashed) for $w=1 \mu\text{m}$, $r_i=8 \mu\text{m}$, $E=10 \text{ MPa}$, $f=1 \text{ MHz}$, and $p_a=0.2 \text{ MPa}$. These are the same parameters as in Figs. 2(b) and 3(b). A positive pressure drop will cause the tube to dilate. Note that the pressure drop becomes negative at $\sim 0.4 \mu\text{s}$, well before the maximum bubble radius at $0.57 \mu\text{s}$.

large hoop strain and a hoop stress that exceeds the strength of the vessel. This simple model neglects inertia effects. Therefore, the current simulations, which account for inertia effects, can add more insight into the mechanisms of tube rupture.

For this investigation, the acoustic excitation amplitude is not as high as for lithotripter shock waves, so the bubble may not expand to touch the tube wall. However, during the time when the negative acoustic pressure is being applied, the bubble could expand rapidly and create a velocity field in the liquid around the bubble. The liquid directed to the inner tube wall surface can generate a positive dynamic pressure on the inner wall surface. Much of the bubble expansion occurs during the tensile portion of the acoustic excitation; therefore, the pressure on the outer tube surface could be negative, increasing the pressure drop across the tube wall. This pressure drop would cause the vessel to dilate, thereby generating a hoop stress in the vessel wall.

Figure 8 shows typical plots of the gauge pressures p_i at point A_i on the inner surface and p_o at point A_o on the outer surface of the tube wall (as indicated in Fig. 1). These pressures and the pressure drop $(p_i - p_o)$ across the tube wall are plotted versus time for $w=1 \mu\text{m}$, $r_i=8 \mu\text{m}$, $E=10 \text{ MPa}$, $f=1 \text{ MHz}$, and $p_a=0.2 \text{ MPa}$, the same parameters as in Figs. 2(b) and 3(b). As indicated in Fig. 8, the time trace of the gauge pressure p_o at point A_o is very close to the time-dependent acoustic excitation pressure, indicating a negligible influence of bubble motion on the pressure on the outer tube surface. However, the gauge pressure p_i at point A_i deviates significantly from the acoustic excitation pressure due to the close proximity of the bubble. The curve for p_i qualitatively matches the pressure curve (not shown) predicted by the Rayleigh–Plesset model for a point near a spherically oscillating single bubble in an infinite liquid domain.

The positive peak of the pressure drop curve occurs at $t=0.21 \mu\text{s}$, close to the time of the peak hoop stress at $t=0.28 \mu\text{s}$. The pressure drop across the wall then decreases, becoming negative at $t=0.39 \mu\text{s}$ before the bubble reaches its maximum radius at $t=0.57 \mu\text{s}$. The nadir of the pressure drop curve occurs at $t=0.71 \mu\text{s}$, and then the pressure drop

FIG. 9. Maximum principal stress $\sigma_{\max}$ in the vessel wall vs time for different acoustic pressure amplitudes ($w=5 \mu\text{m}$, $r_i=4 \mu\text{m}$, $E=10 \text{ MPa}$, and $f=1 \text{ MHz}$). The black square on each curve indicates the moment of maximum bubble radius.

rapidly increases as the bubble collapses. This plot is consistent with the tube behavior shown in Fig. 3(b).

Usually the collapse stage attracts more attention from researchers due to the formation of a high-speed water jet that can damage nearby structures. However, in this investigation, the collapse stage is less interesting since the hoop stress in the tube wall during the collapse stage is generally significantly less than the stress during the expansion stage, as indicated in Fig. 9. Some typical plots of the maximum principal stress versus time are presented in Fig. 9 for different pressure amplitudes. The results indicate that even though the acoustic pressure increases from 0.2 to 1.0 MPa, which leads to a more violent expansion and collapse of the bubble, the maximum principal stress $\sigma_{\max}$ at the collapse stage is less than 20% of the value at the expansion stage. Although water jets form during bubble collapse, the current model is axisymmetric such that two opposing water jets form and mitigate the impact of each other, as indicated in Figs. 3(a) and 3(b). The jet direction could be along the axis of symmetry or perpendicular to the tube wall, depending mainly on whether the bubble touches the inner tube surface during the bubble expansion phase. To investigate the influence of water jets, a three-dimensional model needs to be developed to allow the bubble to be located off the axis of symmetry. Therefore, the following numerical investigation and discussion will mainly focus on the bubble expansion stage.

IV. EFFECTS OF PARAMETERS ON TUBE DILATION

In this section, the influence of parameters, such as tube geometry, Young's modulus, and ultrasound excitation frequency and amplitude, on tube dilation are investigated. The peak hoop stress $(\sigma_{\theta\theta})_{\text{pk}}$ values, defined as the maximum value of the $(\sigma_{\theta\theta})_{\text{max}}$ versus time curve during bubble expansion, are compared for cases with different parameters, as an indicator of tube dilation.

A. Effects of tube geometry on peak hoop stress $(\sigma_{\theta\theta})_{\text{pk}}$

First, the influence of different tube geometries and material properties on tube dilation is investigated. In particular, tube wall thicknesses $w=1$ and $5 \mu\text{m}$ and inner tube radii

TABLE I. Effects of tube geometry on peak hoop stress $(\sigma_{\theta\theta})_{\text{pk}}$ ($f=1 \text{ MHz}$, $p_a=0.2 \text{ MPa}$). Values given in the table for $(\sigma_{\theta\theta})_{\text{pk}}$ are in MPa.

E (MPa)	w (μm)	r_i (μm)		
		2	4	8
1	1	1.3	1.0	0.5
	5	1.3	0.8	0.3
5	1	1.7	1.7	1.1
	5	1.5	1.2	0.6
10	1	1.7	1.6	1.2
	5	1.2	1.2	0.6

$r_i=2, 4$, and $8 \mu\text{m}$ are considered for Young's moduli $E=1, 5$, and 10 MPa . A fixed ultrasonic excitation with a frequency $f=1 \text{ MHz}$ and a pressure amplitude $p_a=0.2 \text{ MPa}$ was used in the simulations.

In Table I, the values of $(\sigma_{\theta\theta})_{\text{pk}}$ are listed for all combinations of the parameters mentioned above. In general, as the wall thickness increases from 1 to $5 \mu\text{m}$, the value of $(\sigma_{\theta\theta})_{\text{pk}}$ decreases, even as much as 50% for a stiffer tube ($E=10 \text{ MPa}$) with a larger inner radius ($r_i=8 \mu\text{m}$). As the inner tube radius increases from 2 to $8 \mu\text{m}$, the decrease in $(\sigma_{\theta\theta})_{\text{pk}}$ is more noticeable and can be as much as 80%. Zhong *et al.* (2001) experimentally observed that as the size of hollow fibers becomes smaller, the likelihood of ultrasound-induced fiber rupture is substantially increased, consistent with the results obtained here. The numerical results indicate that if all the conditions remain the same except the tube geometry, ultrasound-induced tube rupture during bubble expansion is less likely to occur for thicker and larger tubes.

B. Effects of tube geometry on peak hoop strain $(\epsilon_{\theta\theta})_{\text{pk}}$ and pressure drop across the tube wall $(p_i-p_o)_{\text{pk}}$

The peak values of the hoop strain $(\epsilon_{\theta\theta})_{\text{pk}}$ and the pressure drop across the tube wall $(p_i-p_o)_{\text{pk}}$ are listed in Tables II and III, respectively. To understand these results, it is instructive to compare them with the theoretical solution for a

TABLE II. Effects of tube geometry on peak hoop strain $(\epsilon_{\theta\theta})_{\text{pk}}$ ($f=1 \text{ MHz}$, $p_a=0.2 \text{ MPa}$).

E (MPa)	w (μm)	r_i (μm)		
		2	4	8
1	1	0.60	0.50	0.27
	5	0.28	0.20	0.08
5	1	0.11	0.16	0.13
	5	0.05	0.06	0.04
10	1	0.05	0.07	0.07
	5	0.02	0.03	0.02

TABLE III. Effects of tube geometry on pressure drop across the tube wall $(p_i - p_o)_{pk}$ ($f=1$ MHz, $p_a=0.2$ MPa). Values given in the table for $(p_i - p_o)_{pk}$ are in MPa.

E (MPa)	w (μm)	r_i (μm)		
		2	4	8
1	1	0.143	0.099	0.052
	5	0.154	0.106	0.055
5	1	0.153	0.100	0.052
	5	0.157	0.106	0.055
10	1	0.157	0.102	0.053
	5	0.158	0.106	0.056

circular cylinder with constant internal and external pressures. The equations for the hoop stress and hoop strain are (Ansel *et al.*, 1995)

$$\sigma_{\theta\theta} = \frac{p_i - (r_o/r_i)^2 p_o}{(r_o/r_i)^2 - 1} + \frac{(p_i - p_o)}{[(r_o/r_i)^2 - 1](r/r_o)^2}, \quad (4)$$

$$\varepsilon_{\theta\theta} = \frac{1 - \nu}{E} \frac{p_i - (r_o/r_i)^2 p_o}{(r_o/r_i)^2 - 1} + \frac{1 + \nu}{E} \frac{(p_i - p_o)}{[(r_o/r_i)^2 - 1](r/r_o)^2}, \quad (5)$$

where r_i is the inner cylinder radius, r_o is the outer cylinder radius, p_i is the internal pressure, p_o is the external pressure, and r is the radius ($r_i \leq r \leq r_o$). Note that these equations neglect the inertial effects and the variation of pressure along the cylinder axis. The hoop strain predicted by Eq. (5) decreases from its maximum at the inner wall, consistent with Fig. 4.

For a given inner radius and applied pressures, as the thickness of the tube increases, the hoop strain and tube dilation decreases. Numerical results for the bubble-tube interaction are consistent with this prediction. Table II shows a decrease in $(\varepsilon_{\theta\theta})_{pk}$ by more than a factor of 2 as w increases from 1 to 5 μm . In addition, the hoop force is supported by a larger area. Therefore, the maximum hoop stress decreases as the wall thickness increases. However, the decrease in hoop stress is not as pronounced for the numerical simulations because the smaller dilation of a thicker tube will affect the bubble expansion and the resulting internal pressure on the tube.

For a given tube thickness and applied pressure, the hoop stress increases as the inner radius increases. However, the bubble has a smaller effect on the internal tube wall pressure in larger tubes, producing a smaller pressure drop across the tube wall, as shown in Table III. Therefore, for the current simulations, hoop stress decreases as the inner radius increases, as shown in Table I.

Finally, for a pressurized cylinder the hoop strain and dilation are inversely proportional to Young's modulus, while the hoop stress is independent of Young's modulus. The maximum hoop strains in Table II show a decrease with increasing Young's modulus that approximately follows this inverse relationship. The bubble response will be affected by a decrease in dilation. Therefore the numerical results in

FIG. 10. Comparison of equivalent bubble radius vs time curves for $f=5$ MHz and $f=10$ MHz ($w=5$ μm , $r_i=4$ μm , $E=5$ MPa, and $p_a=0.5$ MPa).

Table II show that the hoop stress is affected by Young's modulus. If the bubble does not touch the tube, in general, a higher pressure and thus a higher hoop stress will be generated for a tube with a larger Young's modulus. Contact with the tube will mitigate the bubble expansion further. The effect of Young's modulus on hoop stress becomes negligible if the Young's modulus is high enough such that the dilation is negligible.

C. Effects of excitation parameters and tube stiffness on bubble and tube response

To determine the influence of acoustic frequency and pressure amplitude on tube dilation, bubble responses in a tube with wall thickness $w=5$ μm , inner radius $r_i=4$ μm , and Young's modulus $E=1, 5$, or 10 MPa are compared. The ultrasound frequencies considered are $f=1, 5$, and 10 MHz, and the pressure amplitudes are $p_a=0.2, 0.5$, and 1.0 MPa.

In Fig. 10, typical curves of equivalent bubble radius and maximum hoop stress $(\sigma_{\theta\theta})_{max}$ versus time for ultrasonic excitation with higher frequencies ($f=5$ and 10 MHz) are plotted. Since the driving frequency is higher than the natural frequency of the bubble, the forced oscillation of the bubble is modulated by the natural frequency. The first peak value is not necessarily the highest one. Instead, the highest peak value can be found after a few cycles of the ultrasonic excitation. However, for this research, the peak value within the first cycle of the ultrasonic excitation is considered since the investigation of the effects of pulse duration on tube dilation is beyond the scope of this research. However, the response to a single pulse is typically a good indicator of the magnitude of the bubble response to multiple pulses at the same frequency, except when the bubble is excited near resonance. As indicated in Fig. 10, as the frequency increases, the maximum bubble radius during expansion decreases, which mitigates the bubble collapse. Therefore, the peak value of $(\sigma_{\theta\theta})_{max}$ within the first period of the acoustic excitation for $f=5$ MHz is greater than the value for $f=10$ MHz.

To better understand the influence of frequency and amplitude on tube dilation, in Table IV, the peak value of $(\sigma_{\theta\theta})_{max}$ is listed during the first cycle of the acoustic excitation for all combinations of the parameters mentioned above. The numerical results indicate that if all the conditions remain the same except the acoustic excitation parameters, ultrasound-induced vessel rupture during bubble ex-

TABLE IV. Effects of ultrasound frequency (f), pressure amplitude (p_a), and Young's modulus (E) on the peak hoop stress $(\sigma_{\theta\theta})_{pk}$ during the first cycle of ultrasound waves ($w=5\text{ }\mu\text{m}$, $r_i=4\text{ }\mu\text{m}$). Values given in the table for $(\sigma_{\theta\theta})_{pk}$ are in MPa.

p_a (MPa)	E (MPa)	f (MHz)		
		1	5	10
0.2	1	0.8	0.2	0.1
	5	1.2	0.7	0.3
	10	1.2	1.0	0.5
0.5	1	1.4	0.5	0.3
	5	3.1	1.6	0.9
	10	3.1	2.5	1.2
1.0	1	1.7	0.7	0.5
	5	5.3	2.7	1.3
	10	6.3	4.5	2.2

pansion is less likely to occur for higher ultrasound frequencies and lower pressure amplitudes. Note that this investigation does not consider ultrasound waves with frequencies equal to the natural frequency of the bubble, so further work is required to investigate resonance effects.

Tables I and IV indicate that if all the conditions remain the same except Young's modulus, the peak value of $(\sigma_{\theta\theta})_{max}$ generally increases as Young's modulus increases. Qin *et al.* (2006) investigated the dynamic pressure on the inner tube surface for bubble-tube interactions exposed to a very short shock wave pulse. They found that the maximum value of the dynamic pressure increased as the tube became stiffer. This observation is consistent with the conclusion drawn from Table IV. However, it should not be concluded that stiffer vessels are more likely to rupture if all other conditions remain the same since generally stiffer vessels have higher circumferential tensile strengths (Yamada, 1970; Rowe *et al.*, 2003; Snowhill and Frederick, 2005).

D. Effects of tube length on the maximum bubble radius and the peak value of $(\sigma_{\theta\theta})_{max}$

Finally, our preliminary results indicated that as the tube length increases, the maximum bubble radius decreases but the peak value of $(\sigma_{\theta\theta})_{max}$ increases. For example, for the case of $w=1\text{ }\mu\text{m}$, $r_i=4\text{ }\mu\text{m}$, $E=5\text{ MPa}$, $f=1\text{ MHz}$, and $p_a=0.2\text{ MPa}$, the results are compared for $L=30\text{ }\mu\text{m}$ and $L=60\text{ }\mu\text{m}$ in Fig. 11. The equivalent bubble radius versus time curves are plotted in Fig. 11(a). As the tube length increases from 30 to 60 μm , the maximum bubble radius decreases from 2.7 to 2.4 μm . The curves of $(\sigma_{\theta\theta})_{max}$ versus time during bubble expansion in Fig. 11(b) indicate that the peak value of $(\sigma_{\theta\theta})_{max}$ increases from 1.7 to 2.5 MPa as the tube length increases. Because the liquid is assumed to be incompressible, the tube dilates and liquid flows from the tube ends as the bubble expands. Longer tubes provide more resistance to liquid motion along the tube length. Therefore, these results should provide a conservative estimate for predicting bubble-capillary response *in vivo*. Due to the limited computing resources, the effects of tube length on bubble-

FIG. 11. Comparison of (a) bubble radius vs time and (b) maximum hoop stress vs time for $L=30\text{ }\mu\text{m}$ and $L=60\text{ }\mu\text{m}$ ($w=1\text{ }\mu\text{m}$, $r_i=4\text{ }\mu\text{m}$, $E=5\text{ MPa}$, $f=1\text{ MHz}$, and $p_a=0.2\text{ MPa}$). The longer tube inhibits bubble expansion.

tube interactions were not thoroughly investigated here but should be addressed in the future.

V. SUMMARY

In this paper, results were presented for a computational model developed to simulate the interactions of a bubble and a surrounding deformable tube subject to acoustic excitation. An axisymmetric geometry was used with the bubble centered within the tube. The effects of tube dimensions and stiffness and the effects of acoustic excitation frequency and amplitude on the maximum bubble radius and tube hoop stresses and strains were investigated. The simulations provide new insight into the mechanism of tube rupture.

The numerical results indicated that the hoop stress is the maximum stress component in the tube during bubble expansion. Therefore, tube rupture is predicted when the hoop stress exceeds the hoop strength of the tube. As shown in Table IV, a peak hoop stress of 3.1 MPa was predicted for an acoustic excitation of 0.5 MPa and 1 MHz for a tube with an elastic modulus of 5 or 10 MPa. This exceeds the published value of vessel wall circumferential strength of 2.4 MPa (Rowe *et al.*, 2003) and therefore indicates that vessel damage may occur at this acoustic excitation level. This value is close to the experimentally measured threshold for petechiae and hemorrhage in a mouse intestine of 0.85 MPa at 1.09 MHz when microbubble contrast agents are present in the vasculature (Miller and Gies, 2000; Miller *et al.* 2008).

It was shown that the maximum hoop stress occurs during the tensile phase of the acoustic excitation as the bubble expands and that the tube begins to contract, well before the maximum bubble radius is reached. During the tensile phase of the acoustic excitation, the external pressure is lower than

the pressure inside the vessel. This results in vessel dilation and a positive hoop stress that could eventually lead to vessel rupture. Due to inertial effects, the bubble maximum occurs during the compressive phase of the acoustic cycle. At this point, the pressure inside the tube surrounding the bubble is low due to the low gas pressure inside the expanded bubble. In addition, the pressure outside the tube increases due to the increasing pressure of the acoustic source. Therefore, the pressure drop across the tube wall causes the tube to contract. For this axisymmetric geometry, the peak hoop stress during the bubble collapse stage is less than the peak value during the expansion stage. Therefore, at least for this axisymmetric geometry, vessel rupture is more likely to occur during bubble expansion.

In addition, the numerical results indicate that ultrasound-induced tube rupture is less likely to occur for thicker and larger tubes and for ultrasound waves with a higher frequency and a lower pressure amplitude. This may indicate that ultrasonically induced hemorrhage is also less likely to occur for these conditions. These trends are consistent with experimental observations. For example, when contrast agents are present, the ultrasound threshold for the production of petechiae and hemorrhages in a mouse intestine increased with increasing ultrasound frequency (Miller and Gies, 2000), and the severity and area of renal hemorrhage in rats increased with increasing transducer power or decreasing ultrasound frequency (Wible *et al.*, 2002). Also, Skyba *et al.* (1998) observed rupture of smaller ($\leq 7 \mu\text{m}$) microvessels when exposing the spinotrapezius muscle in rats to ultrasound after echo contrast agent infusion. Finally, during the expansion stage, the peak hoop stress increased as the vessel material became stiffer. However, since a stiffer vessel usually has a higher circumferential tensile strength, implications for hemorrhage should be drawn with caution.

The tube length for most of the results presented in this manuscript was equal to ten times the initial bubble diameter. As shown in Fig. 11, extending the tube length will further inhibit bubble expansion. For short tubes, liquid can flow along the tube axis as the bubble expands. The longer the tube is, the more resistant it is to this flow. Due to a limitation in computational resources, the effect of the tube length on the bubble response has not yet been investigated in detail. However, in the limit of an infinite tube, tube dilation must accompany bubble expansion if the liquid is incompressible. Therefore, in this limit, tube dilation and bubble expansion must be in phase.

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