Evolution of Acoustically Vaporized Microdroplets in Gas Embolotherapy

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Acoustic vaporization dynamics of a superheated dodecafluoropentane (DDFP) microdroplet inside a microtube and the resulting bubble evolution is investigated in the present work. This work is motivated by a developmental gas embolotherapy technique that is intended to treat cancers by infarcting tumors using gas bubbles. A combined theoretical and computational approach is utilized and compared with the experiments to understand the evolution process and to estimate the resulting stress distribution associated with vaporization event. The transient bubble growth is first studied by ultra-high speed imaging and then theoretical and computational modeling is used to predict the entire bubble evolution process. The evolution process consists of three regimes: an initial linear rapid spherical growth followed by a linear compressed oval shaped growth and finally a slow asymptotic nonlinear spherical bubble growth. Although the droplets are small compared to the tube diameter, the bubble evolution is influenced by the tube wall. The final bubble radius is found to scale linearly with the initial droplet radius and is approximately five times the initial droplet radius. A short pressure pulse with amplitude almost twice as that of ambient conditions is observed. The width of this pressure pulse increases with increasing droplet size whereas the amplitude is weakly dependent. Although the rise in shear stress along the tube wall is found to be under peak physiological limits, the shear stress amplitude is found to be more prominently influenced by the initial droplet size. The role of viscous dissipation along the tube wall and ambient bulk fluid pressure is found to be significant in bubble evolution dynamics. [DOI: 10.1115/1.4005980]

1 Introduction

Embolotherapy is a method of hemostasis where foreign particles (emboli) are introduced into the vasculature via an intravascular catheter to achieve full or partial occlusion of blood flow for treatment of tumors, fibroids, solid organ trauma, gastrointestinal hemorrhage, vascular malformations and aneurysms [1]. Boehm et al. [2] demonstrated that cancer cells can be 'starved' to death by restricting blood flow to tumors, and successful treatment has been reported of cancers such as hepatocellular carcinoma, renal carcinoma and urinary track cancers by the current embolotherapy approach [3]. A variety of embolic agents, such as sclerosants, mechanical coils, balloons, gelfoam, gelatin microsphere and many others, have been used clinically [1]. Most of the current embolization techniques involve procedures that are complicated, requiring either surgical exposure of vessels near the target region or selective catheter placement to minimize embolization of collateral tissue near the tumor, and often requiring prolonged fluoroscopic exposure [1]. One of the major factors in the success of embolotherapy in treating tumors is the ability to direct and confine treatment to the target area. These challenges are partially responsible for embolotherapy being used primarily for cancers that do not respond well to other treatments.

A novel approach, called gas embolotherapy, aims to overcome the challenges of current embolotherapy approaches and is described by Bull [4,5]. In this approach, a site-activated gas bubble, which originates from a superheated microdroplet that is vaporized via an acoustic perturbation is used instead of solid emboli. The proposed therapy is minimally invasive, and provides highly selective delivery of the emboli to the tumor and surrounding vasculature; thus minimizing the risk of infarction of healthy tissues. Gas embolotherapy uses encapsulated liquid droplets of

the perfluorocarbon dodecafluoropentane (DDFP, C_5F_{12}), which has a boiling point of 29°C and is superheated at body temperature (properties in Table 1). The resulting DDFP gas bubbles persist for long times once lodged in vasculature, $O(\text{hours to days})$, providing sufficient occlusion of flow to induce tissue infarction.

The envisioned gas embolotherapy scenario can be seen in Fig. 1. Blood flow carries superheated DDFP microdroplets into the tumor region, where high-intensity ultrasound is used to initiate Acoustic Droplet Vaporization (ADV) [6,7] to form bubbles near the desired occlusion sites. Although the boiling point of DDFP is 29°C at atmospheric pressure, which is lower than body temperature, the superheated DDFP is maintained in liquid droplet form via an albumin or lipid shell. Moreover, since the size of the droplets are in micron range, the surface tension tends to increase the vapor pressure within the droplets; thus increasing the natural boiling temperature of the DDFP droplets thus reducing the level of superheat within the droplet at body temperature. The albumin or lipid shell also reduces diffusion and prevents droplets from coalescing, allowing the stable microdroplets to circulate freely in the circulatory system without lodging until activated by ultrasound.

The proposed use of ADV for therapeutic and diagnostic purpose dates back to Apfel [6] and Quay [7]. Since then it has been used for other applications apart from gas embolotherapy, including aberration correction [8,9], therapeutic drug delivery [10,11], and high-intensity focused ultrasound (HIFU) and lithotripsy-based nucleation agents to enhance thermal delivery and cavitation-based bioeffects [12,13]. Although interest in the therapeutic use of ADV is increasing, the basic understanding of the physical mechanics underlying the ADV phenomena is not well understood.

Earlier experimental investigations [14–18] were primarily conducted from a radiological perspective focused on understanding the effect of various parameters on ADV threshold, identifying the acoustic regime that can be used for clinical applications, and demonstrating based on acoustic signatures that ADV and inertial

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Table 1 Physical Properties of Dodecafluoropentane

Molecular Formula	C ₅ H ₁₂
Molecular Weight (g/mol)	288
Boiling point (°C)	29
Density (Kg/m ³)	1630
Viscosity (N.s/m ²)	0.00652
Surface Tension (N/m)	0.70

Fig. 1 Schematics of the gas embolotherapy procedure

cavitation are distinct. None of the experimental studies were able to estimate the resulting stresses, which can induce a series of bio-effects including vessel rupture, injury to the endothelial layer and changes in vessel permeability [5]. These bioeffects could be deleterious or advantageous, depending on the location and the goal of the treatment. For example, transient increased vessel permeability would be beneficial for drug delivery, but hemorrhage of vessels outside of the tumor might be unwanted. The measurement of stress levels associated with ADV is challenging as it involves processes at microscopic level and at a timescale of microseconds. Additionally, physical understanding of the ADV mechanism and the influence of various parameters on the dynamics of subsequent bubble evolution are not fully understood.

The first investigations of stress levels associated with ADV computationally modeled ADV in rigid [19] and flexible walled vessels [20]. As a simplification, the phase change was considered to occur much faster than the bubble expansion, as appeared to be the case from experiments [14,15], and the expansion of a bubble at an initially high pressure was modeled without modeling the phase change. It was noted that future experiments that focused on the phase change and initial expansion might later be compared to the model results to provide an estimate of the initial bubble pressure. Although the vaporization was not modeled, these studies revealed trends of velocity and stress evolution during bubble expansion phase of ADV.

In subsequent ultra-high-speed camera experiments with an emphasis on the phase change and initial expansion, we demonstrated that expansion of the droplet occurs before vaporization is complete [21,22]. Because only a limited number of images can be acquired at ultra-high-speeds, this was not apparent in the previous experimental studies. Additionally, the experimentally measured bubble/droplet evolution did not agree closely with those predicted by the previous computational models, suggesting that modeling the initial phase change process is important to accurate modeling of the ADV phenomena. We then developed a one-dimensional theoretical model that predicted bubble/droplet growth rate for droplets that were small enough that the final bubble diameter was much smaller than the tube diameter, allowing the bubble to remain spherical throughout the expansion process [23]. Although this provided good agreement with the experimental growth rates, it did not provide stress information and its application is limited to the smallest droplets.

Therefore, the goals of the current study were to (1) develop a model of ADV that incorporates the phase change dynamics, allows for a non-spherical bubble/droplet, and provides stress and

velocity field information, (2) examine bubble evolution dynamics, and (3) determine the stress levels associated with ADV. Additionally, we compare the model predictions to a representative set of droplet/bubble growth data from the previous experimental studies [22], and discuss the ADV initiation mechanism that is indicated by the experiments and supported by the agreement with the new model predictions.

2 Experimental Procedure

The experiments used for validation of the model were previously described [22] and the procedure is briefly summarized here. The schematic of the experimental setup is shown in Fig. 2. A rigid micro-dialysis tube (internal diameter of 200 micron, Spectra/Por, Spectrum Labs, Rancho Dominguez, CA, USA) was utilized for the experiments. The tube was immersed in a water bath that was maintained at 37°C. The droplets used in our experiments were prepared by mixing 75% (volume) saline-albumin solution of 5 mg/mL concentration with 25% (volume) DDFP (CAS #678-26-2) which was sealed in a 3 mL auto sampler glass vial. The mixture was shaken for 30 s at 5000 cpm in a mixer (Wig-L-Bug, Crescent Dental Mfg. Co., Elgin, IL, USA), resulting in a droplet emulsion containing approximately 9.5×10^9 droplets per mL. The droplet emulsions were stored in a refrigerator at 4°C. A small volume of 0.1 mL of the droplet emulsion was injected into one port of the T-connector, after which the port was closed, and the other inlet port was opened to inject water to dilute the droplet emulsion. Subsequent gentle pressing of the water syringe was sufficient to transport the droplets into the hollow fiber and to get the desired inter-droplet spacing. A single acoustic pulse was produced by an immersion ultrasound transducer (3.5 MHz, single-element, 0.75" element diameter, 1.5" focal distance, focal diameter of 600 μ m, A381S, Panametrics-NDT, Olympus, Waltham, MA, USA).

The entire ADV event was recorded using an ultra-high-speed framing camera (SIM802 Model, Specialized Imaging Ltd, Hertfordshire, UK). An industrial microscope (Eclipse infinity series system with a modular focus mount, Nikon, Melville, NY, USA) with 10x or 20x water immersion objectives (Nikon, Melville, NY, USA) was used to achieve the final desired magnification. The triggering signal was critically positioned on the timeline in the ultra-high speed camera software, so that the entire imaging event was well coordinated. The light and ultrasound arrive at the appropriate times, and the camera captures the images at the right moment. The images obtained from camera were analyzed and the bubble time evolution data in terms of effective bubble radius [22] was obtained for a series of experiments.

3 ADV Initiation Mechanism

It has been observed that an acoustic pressure threshold exists, above which ADV occurs. Previous studies [14–17] reported that the vaporization threshold is dependent on the peak rarefaction pressure and the frequency of the acoustic wave. For frequencies

Fig. 2 Schematics of the experimental setup

between 1.5 and 8 MHz, the vaporization threshold decreases with frequency from 4.5 to 0.75 MPa peak rarefactional pressures. Although the mechanism of ADV is not well understood, several mechanisms for droplet vaporization may exist [18]. These likely include (1) perturbation of the superheated liquid DDFP to induce growth of a bubble within the droplet that then consumes all of the liquid DDFP, (2) rupture of the albumin shell prior to phase change of the DDFP, and (3) cavitation of the liquid surrounding the encapsulated droplet, which in turn leads to rupture of the droplet's shell. Ultra-high speed imaging of droplet vaporization [14,15,22] revealed that focused ultrasound beams produce nano-nucleation sites inside the microdroplets, which trigger the vaporization and subsequently consume the liquid inside the droplet forming a gas bubble. This indicates that the first ADV mechanism in the list above appears to be the route to droplet vaporization for the acoustic parameters that we used here and typically use in gas embolotherapy. For other acoustic parameters, other paths to ADV may occur [18].

It is noteworthy that ADV is distinct from acoustic cavitation because ADV involves vaporizing a superheated liquid. Although explosive boiling [24–26] appears to be the closest phenomenon that can be related with ADV, there are some fundamental differences between these phenomena. In explosive boiling droplets (not stabilized by a shell) are suddenly and massively heated by immersion in a hot medium [24], by laser heating [27] or by passage through a shock wave [28]. However, in ADV, the droplets are maintained in superheated state, which are stabilized by albumin or lipid shells. The level of superheat in ADV at body temperature is much less than in explosive boiling studies [24]. The acoustic wave, which is comprised of rarefaction and compression waves when focused at a point do not produce significant temperature gradients instantaneously. Although several studies [29,30] have demonstrated that prolonged high intensity focused ultrasound can produce a temperature rise in theinsonified media, the time scale required to achieve significant rise in temperature of the media is of the order of several minutes or longer. In the ADV process the acoustic wave acts on the droplet for less than 2 μ s, too short of a timescale to elevate temperature, suggesting that ADV is not a thermally initiated process as opposed to explosive boiling. The fundamental difference between ADV and explosive boiling lies in the method of initiation of vaporization. Explosive boiling is thermally initiated usually under constant pressure whereas ADV is initiated by decreasing pressure (via an acoustic source) in a superheated liquid held at constant temperature resulting in an isothermal process.

Based on the proposed ADV mechanism of perturbation of a superheated fluid to produce nucleation sites within the liquid droplet, we [23] recently presented an analytical ADV model that accurately predicts the vaporization event and the subsequent bubble evolution. The current model is based on ADV originating from nucleation sites within the droplet.

4 Model

The new ADV model presented here combines a theoretical model [23] that includes phase change of the DDFP at early times with a computational model that allows for nonspherical bubble evolution at later times. This model also provides velocity and stress field data in addition to the bubble/droplet evolution.

4.1 Theoretical Model. A theoretical ADV model for a spherical droplet in a microtube was developed to model the bubble evolution after the instantaneous vaporization of the microdroplet as a result of ultrasound impulse. The ADV model derived was a Rayleigh-Plesset type of equation for a bubble within two liquids including vaporization and viscous head from the tube. It was assumed that at time zero the nucleation site is already formed and the vapor inside the nucleation site follows the ideal gas law. Although the theoretical ADV model includes phase change it assumes that the droplet, the initial nucleation bubble and the resulting final bubble (after the droplet has completely

vaporized) remains spherical throughout the expansion process. The evaporation rate was assumed to be constant and equal to its maximal possible value, which is obtained by kinetic theory limit to the mass flux that can be attained in a phase change process [31].

The details of the derivation can be found in Qamar et al. [23]. Consider the droplet of radius R_2 inside the tube with length and diameter L and D respectively. At time $t = 0$, it is assumed that a nucleation site is formed inside the droplet with radius R_1 . For each time step the radial Navier-Stokes is integrated from nucleating radius (R_1) to the droplet surface (R_2) by coupling the mass conservation which include the evaporation rate at the nucleating interface which results in

$$\ddot{R}_1 R_1 \rho_2 \left(1 - \frac{R_1}{R_2}\right) + \dot{R}_1^2 \left[2\rho_2 \left(1 - \frac{R_1}{R_2}\right) + \frac{1}{2}\rho_2 \left(\frac{R_1^4}{R_2^4} - 1\right)\right] + \dot{R}_1 \left[2J \left(\frac{R_1}{R_2} - 1\right) + J \left(1 - \frac{R_1^4}{R_2^4}\right) + \frac{1}{2} \frac{J^2}{\rho_2} \left(\frac{R_1^4}{R_2^4} - 1\right)\right] = P_{R_{1+}} - P_{R_{2-}} \quad (1)$$

Where the subscript $P_{R_{1+}}$, $P_{R_{2-}}$, ρ_2 and J indicates the pressure outside the nucleating interface, pressure inside the droplet interface, DDFP density and evaporation rate respectively. Further, to obtain the velocity of the droplet surface (liquid interface, R_2), unsteady Bernoulli equation with head loss term is utilized to give

$$\frac{16\rho_3}{\beta D^2} \left(\frac{L}{2} - R_2\right) \left[\ddot{R}_2 R_2^2 + 2R_2 \dot{R}_2^2\right] + \frac{512\mu_3}{\beta D^4} \left(\frac{L}{2} - R_2\right) R_2^2 \dot{R}_2 + \frac{1}{2} \rho_3 \left[\left(\frac{D^2}{32\mu_3} \frac{dp}{dx}\right)^2 - \dot{R}_2^2\right] = P_{R_{2+}} - P_{\infty} \quad (2)$$

Where $P_{R_{2+}}$, P_{∞} , μ_3 and ρ_3 is the pressure just outside the droplet interface, pressure at the exit of the tube, viscosity and density of the fluid surrounding the droplet. Equations (1) and (2) are combined using kinematic and dynamic boundary condition at the two interfaces to yield the ADV model equation given by,

$$\ddot{R}_1 R_1 \rho_2 \left[\left(1 - \frac{R_1}{R_2}\right) + \frac{AR_1}{\rho_2}\right] + \dot{R}_1^2 \left[2\rho_2 \left(1 - \frac{R_1}{R_2}\right) + \frac{1}{2}\rho_2 \left(\frac{R_1^4}{R_2^4} - 1\right) + 2AR_2 \left(R_1 - R_1^4 \left(1 - \frac{1}{R_2^4}\right)\right)\right] + \dot{R}_1 \left[2J \left(\frac{R_1}{R_2} - 1\right) + J \left(1 - \frac{R_1^4}{R_2^4}\right) + \frac{2R_2 JA}{\rho_2} \left(2R_1^4 \left(1 - \frac{1}{R_2^4}\right) - R_1\right) + BR_1^2\right] + \frac{J^2}{\rho_2} \left[\frac{1}{2} \left(\frac{R_1^4}{R_2^4} - 1\right) + \frac{2R_2 AR_1^4}{\rho_2} \left(\frac{1}{R_2^4} - 1\right) - \frac{BR_1^2}{J}\right] + \frac{1}{2} \rho_3 \left[\left(\frac{D^2}{32\mu_3} \frac{dp}{dx}\right)^2 - \frac{R_1^4}{R_2^4} \left(\dot{R}_1 - \frac{J}{\rho_2}\right)^2\right] = P_{R_{1-}} - P_{\infty} - \frac{2\sigma_1}{R_1} - \frac{2\sigma_2}{R_2} - \frac{4\mu_2}{R_1} \dot{R}_1 - \frac{4\mu_3}{R_2} \dot{R}_2 - J^2 \left(\frac{1}{\rho_2} - \frac{1}{\rho_1}\right) \quad (3)$$

Where

$$A = \frac{16\rho_3}{\beta D^2} \left(\frac{L}{2} - R_2\right), \quad B = \frac{512\mu_3}{\beta D^4} \left(\frac{L}{2} - R_2\right) \quad \text{and} \quad \dot{R}_2 = \left(\dot{R}_2 - \frac{J}{\rho}\right) \frac{R_1^2}{R_2^2}$$

This ADV model (Eq. (3)) was numerically solved for the parameters corresponding to the experimental cases, while matching the experimental acoustic parameters. The results obtained from this ADV model were compared with the time evolution data from the experiments and were found to be in good agreement (discussed in Sec. 5).

4.2 Computational Model.

4.2.1 Geometry and Assumptions. The expansion of the DDFP bubble, after the instantaneous phase change due to ADV

is modeled by performing Navier-Stokes computations in a moving coordinate system. A single spherical bubble, initially located at the center of the rigid tube is assumed to be axisymmetric about the centerline of the tube, such that all the quantities are uniform in the circumferential direction and the circumferential velocity is zero. A tube with length, L , and internal diameter, D , is assumed to be filled with the Newtonian incompressible liquid (water) which is initially at rest. However, in experiments we used microdialysis tubing, which was submerged in the water bath, no wall deformation was observed in the experiments. Figure 3 shows an image of bubble evolution at different time along with the tube wall. It can be observed that the tube is stiff enough and/or that the surrounding inertia of the water bath is high enough that the tube behaves as a rigid wall. Thus, we assumed tube wall to be rigid and enforced an impenetrable tube wall condition in our model.

The experimental observation (Fig. 3) also reveals that the phase change phenomena which result in subsequent DDFP consumption inside the droplet is $O(10^{-7})$ s. A slight growth from the initial droplet volume is also observed during the phase change phenomena and the consequent DDFP consumption process. Based on these observations, it can be inferred that immediately after the phase change phenomena, the DDFP bubble has high pressure and the bubble interface would achieve a certain velocity. In order to correctly model the bubble evolution, the initial bubble pressure, the initial interface velocity and the bubble size should be predicted correctly. To estimate these quantities, the theoretical ADV model was utilized. Based on the initial droplet size the theoretical model was solved until the DDFP is fully consumed to extract the bubble pressure, the interface velocity and the bubble size at that instant. This bubble pressure, the interface velocity and the bubble size were then used as initial conditions in the computational model to predict the bubble evolution correctly.

4.2.2 Governing Equations. The evolution of the bubble, after the instantaneous phase change due to ADV is governed by the unsteady Navier-Stokes equations. For the incompressible fluid surrounding the bubble, the conservation of mass and momentum on an arbitrary control volume Ω , whose boundaries are moving with time is given by

$$\frac{\partial}{\partial t} \int_{\Omega} \rho d\Omega + \int_S \rho (\vec{V} - \vec{V}_s) \cdot \hat{n} ds = 0 \quad (4)$$

$$\frac{\partial}{\partial t} \int_{\Omega} \rho u_i d\Omega + \int_S [\rho u_i (\vec{V} - \vec{V}_s)] \cdot \hat{n} ds = \int_S (\tau_{ij} \hat{i}_j - p \hat{i}_i) \cdot \hat{n} ds \quad (5)$$

where, ρ represents the density, p is the pressure, τ_{ij} is the stress tensor for Newtonian fluid, $\vec{V}$ is the flow velocity vector, u_i is the i th velocity component and $\vec{V}_s$ is the grid velocity of the moving boundary of the control volume, respectively. For the proper solu-

tion of these conservation laws in moving frame of reference, which involves volume with moving boundaries ($\vec{V}_s \neq 0$), an addition space conservation law (SCL) [32,33] has to be satisfied:

$$\frac{\partial}{\partial t} \int_{\Omega} d\Omega + \int_S \vec{V}_s \cdot d\vec{s} = 0 \quad (6)$$

This SCL describes the conservation of space when the control volume changes its shape or position with time and is a mathematical enforcement from control volume formulation in moving frame of reference. After the phase change, the resulting DDFP vapor inside bubble is considered as inviscid and is governed by the isothermal gas law:

$$P_v v_v = \text{Const}$$

where, P_v, v_v are the pressure and the volume of the bubble, respectively.

The above system of conservation laws is solved subject to the boundary conditions corresponding to physical situation. A no-slip condition is applied on the rigid tube wall. An axisymmetric boundary condition is applied at the centerline of the tube. Free outflow boundary conditions are imposed at the exits of the tube, which are a sufficiently large distance from the bubble surface that the flow is fully developed there. This condition is physically justified because the tubes in the experiments were long. Since the bubble evolution is primarily governed by bubble pressure and liquid inertia, using an outflow condition instead of specifying pressure is an appropriate boundary condition to mimic the physical situation.

At the bubble interface, the mass and momentum conservation give rise to the interfacial jump conditions. If there is no mass transfer across the moving interface, the kinematic condition requires

$$[(\vec{V} - \vec{V}_s) \cdot \hat{n}]_{\text{int}} = 0 \quad \text{or} \quad \dot{m}_{\text{int}} = 0 \quad (7)$$

where, the subscript 'int' represents the bubble interface. This condition states that the normal component of the liquid velocity at the surface is equal to the normal component of the interface velocity. The dynamic condition requires that the net force acting on the liquid at the interface should be in equilibrium. This implies that normal forces on either side of the bubble interface are of equal magnitude and opposite in signs, whereas the forces in the tangential direction are equal in magnitude and direction, which can be mathematically written as,

$$(\hat{n} \cdot \Gamma)_g \cdot \hat{n} - (\hat{n} \cdot \Gamma)_l \cdot \hat{n} + \sigma K = 0 \quad (\text{for } K < 0) \quad (8)$$

$$(\hat{n} \cdot \Gamma)_l \cdot \hat{t} + \frac{\partial \sigma}{\partial t} = (\hat{n} \cdot \Gamma)_g \cdot \hat{t} \quad (9)$$

Fig. 3 Bubble evolution at different time for $R_o = 12.23 \mu\text{m}$

Here, Γ is the stress tensor, σ ; is the surface tension, $\hat{n}$ and $\hat{t}$ are the unit normal and tangential (rotating in clockwise direction) vectors at the interface. The indices 'l' and 'g' denotes liquid and gas, respectively, and K is the curvature of the interface. In present computations, the surface tension is assumed to be constant, and the gas is considered to be inviscid.

4.2.3 Numerical Procedure. An in-house code was developed to solve the system of the governing equation along with the specified boundary conditions. In order to obtain discrete form of the conservation laws [4–6], the solution domain is discretized into a finite number of unstructured quadrilateral control volumes (CV). All dependent variables are stored in a collocated variable arrangement, which allows only one set of control volumes to be generated, as opposed to four sets in the case of staggered arrangement. In the present computations, the grid velocities are not explicitly computed from the SCL, however the volume flux through the CV faces, which results from its motion is calculated using total volume swept by the cell face during that time interval [34]. Convective and diffusion terms are discretized (spatial second order accuracy) on the collocated grid via the procedure given by Demirdzic and Muzaferija [34] and the unsteady term is discretized using a fully implicit time differencing.

After the discretization of the conservation laws [4–6], the system of equations can be assembled in the form of nonlinear algebraic equations which link the value of the dependent variable at the control volume center with its values at the points in the neighborhood. The resulting coefficients can be found in Demirdzic and Muzaferija [34]. These coefficient are obtained by utilizing the collocated version of the semi-implicit method for pressure linked equations (SIMPLE) [35] procedure as given by Demirdzic [36]. The system is linearized and the sets of equation for each dependent variable is temporarily decoupled by assuming that the coefficients and source term are known (based on previous time step), which results in a system of linear algebraic equation for all the dependent variables. In present computations this linear system is solved using conjugate gradient squared stabilized (CGSTAB) method, with an incomplete Cholesky preconditioner. The overall solution algorithm is as follows:

Step 1. Obtain the initial location of the interface and the initial conditions from the ADV model.

Step 2. Construct grid and determine the location of the CV vertices and calculate the total swept volume.

Step 3. Reconstruct the interface in term of piecewise cubic Bezier curve to obtain the local curvature, normal and tangential vectors for each CV at the interface [19].

Step 4. Solve the conservation Eqs. (4)–(6) for the flow variables. While iterating for the current time flow field, the stress jump condition at the interface is monitored locally for each sub-iteration of the current time. The new location of the interface is continuously updated at each sub-iteration [19]. Bubble mass conservation is enforced via a scaling procedure as used by Ye and Bull [19].

Step 5. Repeat the process from *Step 2* until steady equilibrium of the bubble with the surrounding bulk fluid is achieved (Interface velocities $\rightarrow 0$).

5 Results and Discussion

In the present study, the effect of initial droplet size on acoustically initiated droplet evolution and the associated stress distribution inside the tube is studied. The microdroplet preparation technique used in the present study does not produce a mono-disperse solution. Thus, during the experimentation the initial droplet size was not known until the images were processed. The initial droplet size was found to be in the range of 7.5 to 15 μm in radius, approximately. The acoustic parameters used to initiate droplet vaporization were $P_a = 7.7$ MPa (peak rarefaction pressure), $f = 3.5$ MHz (frequency of the acoustic pulse) and $N = 4$ or 7 (number of acoustic cycles in the pulse).

Table 2 Bubble Pressure and Interface Velocity for Three Different Droplets

$R_0(\mu\text{m})$	Acoustic cycles (N)	R_2/R_0	Bubble Pressure (P_{r1-}) (bar)	Interface Velocity (dR_2/dt) (m/s)
7.81	7	1.27	49.35	3.41
10.93	4	1.19	48.98	2.90
14.39	4	1.13	46.22	2.51

Results of three initial droplet radii, $R_0 = 7.81$, 10.93 and 14.39 μm , are presented as representative data for comparing the model predictions with experiments. The full set of experimental data is presented elsewhere [22]. The theoretical model was solved for these three droplet sizes until the DDFP inside the droplet is nearly completely vaporized (98% approximately). The acoustic parameters were kept as those used in the experiments. Table 2 show the summary of the results obtained from the solution of the ADV model.

The ratio R_2/R_0 represents the fraction by which the interface has already displaced while consuming the DDFP due to the vaporization event. This slight initial interface expansion during the vaporization event is evident in our experiments (Fig. 3). The results indicate that for the smaller droplets, higher initial velocity of the interface is achieved compared to the bigger droplets. However, the computed internal bubble pressure is weakly dependent on the initial droplet size for the cases investigated in this study.

To compute the evolving flow field using the Navier-Stokes calculation, the above values obtained from the theoretical model are utilized as the initial conditions. Although the computational model can simulate results without utilizing the information predicted by ADV model as done in Ye & Bull [19,20] (At, $t=0$, $R=R_0$, $dR/dt=0$, $P_{r1-}=P_g$), the results obtained via that approach do not match the experimental data. Additionally, experimental observations indicate that vaporization and expansion occur simultaneously, and the concurrent development of ADV model, which predicted the initial vaporization information, assisted to model the bubble evolution dynamics more accurately. Before the start of actual simulations, time and grid independence studies were performed to limit the truncation errors associated with the discretization of the governing equations. It was deduced that a grid size of (490×150) and a time step $\Delta t = 5 \times 10^{-8}$ s is sufficient to resolve the fluid flow around the evolving bubble accurately.

For the computations, the dynamically evolving flow field inside the tube was investigated by plotting streamlines at various time steps. Although the computations were carried with axisymmetric assumption, the data was mirrored and the plots of full physical space are presented for better comparisons purposes. Figures 4 and 5 as well as Fig. 6 show comparisons of computational results with the images obtained from the ultra-high speed camera during the experimentation at various times for the three droplets. In the experimental images the tube walls are at the top and bottom and the ultrasound approaches the droplet transversely from the right at an angle out of the plane.

Based on the bubble evolution visualization, the growth of the bubble can be divided into three regimes: a rapid spherical growth, a compressed oval shaped growth and finally a slow spherical growth. For all the cases the bubble remains approximately spherical for $t < 1.5 \mu\text{s}$, which corresponds to the rapid spherical growth regime. This stage of growth is primarily governed by the surface tension force, and the pressure difference between the bulk liquid and gas bubble. Since during early time the bubble is relatively small and the associated surface tension force ($2\sigma/R$) is high, it tends to keep the bubble in a spherical shape (Figs. 4(a), 5(a) and 6(a)).

After $t > 1.5 \mu\text{s}$, the preferential growth in the axial direction begins (the compressed oval shape regime), with a relatively high curvature in the lateral direction. Initially as the bubble expands,

Fig. 4 Experimental (left) and computational (right) bubble evolution for $R_o = 7.81 \mu\text{m}$

it pushes the fluid surrounding the bubble radially outward. This radial flow is restricted by the tube wall on the top and bottom, which results in a fluid stagnation point just vertically opposite to the bubble on either side of the tube wall (Figs. 4, 5 and 6). As a consequence of this stagnation point, the pressure on the top and bottom of the bubble remains higher compared to the axial direc-

tion. Since for a given time instant a constant bubble pressure is driving the evolution, it tends to elongate the bubble in the axial direction (Figs. 4(b) and 4(c), 5(b) and 5(c) and 6(b) and 6(c)). For larger droplets ($R_o > 10 \mu\text{m}$) the elongation is in the form 'two lobes' as seen experimentally and computationally (Figs. 5(b) and 5(c) and Fig. 6(b) and 6(c)). In the experiments, the

Fig. 5 Experimental (left) and computational (right) bubble evolution for $R_o = 10.93 \mu\text{m}$

smaller bubble tended to have small crinkles on the surface and an elliptical growth, but not the two distinct lobes apparent in the slightly larger bubbles. This elliptical bubble growth was also predicted by the computational model. Further down the timeline, the internal bubble pressure continuously decays because of the

increasing volume of the bubble. At this point, the bubble growth is typically governed by the competition between liquid inertia and surface tension. The large liquid inertia in the axial direction is balanced by a higher surface tension force associated with higher curvature in the lateral direction, which results in

Fig. 6 Experimental (left) and computational (right) bubble evolution for $R_o = 14.39 \mu\text{m}$

restraining the growth of the bubble in the axial direction. As the bubble growth is restrained in axial direction, the interface velocity in the axial direction also decreases. In most cases, the compressed oval shaped bubble regimes end around $t < 10 \mu\text{s}$. For $t > 10 \mu\text{s}$ (slow spherical growth regime) the bubble grows in radial direction (Figs. 5(d) and 6(d)) and is primarily driven by the remaining pressure difference in the bulk liquid and gas bubble,

which is supported by low liquid inertia and lower surface tension force (small curvature) on the top and bottom of the bubble. This recovery of the bubble back to its spherical shape occurs at a much slower pace compared to the pace at which the bubble was initially elongated in axial direction. For $t > 100 \mu\text{s}$, the bubble eventually reaches its final size in a spherical shape (Figs. 4(e) and 4(f), 5(e) and 5(f) and 6(e) and 6(f)). After that, a very slow

Fig. 7 Bubble evolution comparisons from experimental, theoretical and computational approach for (a) $R_o = 7.81 \mu\text{m}$, (b) $R_o = 10.93 \mu\text{m}$ and (c) $R_o = 14.39 \mu\text{m}$. Note that the computations are stopped at $t = 0.00015 \text{ s}$, based on test runs that showed the asymptotic stage was reached by this time.

Fig. 8 Variation of (a) Peak pressure and (b) Peak shear stress on the tube wall for different initial droplet size

mass diffusion across the bubble interface takes place. This mass diffusion is responsible for the further expansion of the bubble by influx of dissolved gases, and is also largely responsible for the eventual disappearance of the bubbles in the bulk fluid. However, it is not a phenomenon associated with the vaporization and occurs at a much slower (order of hours to days) time scale. Thus it is excluded in our computational model.

To understand the bubble evolution dynamics, the expansion ratio (bubble radius normalized with initial droplet radius) was plotted as a function of time. Figure 7 shows the expansion ratio as a function of time obtained from experimental, theoretical, and computational approach for the three droplets. The results are in close agreement with the experimental results. The expansion ratio data suggest that the expansion of the bubble is almost linear for the rapid spherical growth and the compressed oval shaped growth regime. The slow spherical growth regime is nonlinear, which results in bubble eventually reaching its final size asymptotically between 100 to 150 μs . The final bubble expansion ratio appears to be fairly insensitive to the initial droplet size. A simple theoretical estimate for the final bubble size can be made by applying the Young-Laplace equation across the bubble interface. If the bubble pressure is governed by the ideal gas law under isothermal conditions with instantaneous phase change assumption and the bulk liquid pressure reaches atmosphere when bubble is fully evolved. The Young-Laplace equation results in a nonlinear algebraic equation that can be solved in term of final bubble radius

(R_f). By utilizing properties of DDFP (Table 1) and water, solution to this equation yield $R_f = 5.2R_o$. For all the cases investigated the final average bubble size is found to be approximately five times the initial size of the droplet size, as predicted by the theoretical calculations.

The details of the stress distribution along the tube wall, which may induce bioeffects during ADV, were investigated. Figure 8 shows the variation of maximum pressure and shear stress rise onto the tube wall as a function of time. The rise in the pressure is in the form of short pulse (Fig. 8(a)) for few microseconds, however as the droplet size increases the pressure pulse shifts towards the right with an increasing pulse width. A similar pressure pulse profile was experimentally observed by Frost [37] in explosive boiling of a large superheated droplet ($R_o \geq 1 \text{ mm}$). The results obtained from the present study are not compared with the Frost studies as the droplets are vaporized in large pool of bulk liquid (not inside the microtube) by heating the bulk liquid where the bubble dynamics unfold in a different manner as oppose to ADV.

The shear stress is dependent on the bulk flow inside the tube. In all cases, the shear stress reaches its peak value (Fig. 8(b)) towards the end stages of the pressure pulse, which correspond to the maximum fluid velocities inside the tube. A gradual decay in shear stress is observed after the maximum is reached. Although the shear stress amplitude is strongly dependent onto the initial bubble size compared to the pressure pulse amplitude, the magnitude of shear stress approaches the peak values found in human

Fig. 9 Variation of (a) Peak pressure and (b) Peak shear stress on the tube wall for different initial droplet size

vasculature. Typical average values of shear stress in the major human arteries during basal conditions are 2–20 dynes/cm², with localized increases to 30–100 dynes/cm² near arterial branches and regions of sharp wall curvature [38]. This suggests that the location of droplet vaporization might influence the tendency to induce bioeffects in the vasculature. However, the range of induced stress might be enough to induce bioeffects in some vessels, it might not be sufficient to induce bioeffects in other locations, such as arterial bifurcation branches, where vasculature can withstand higher shear stress.

Finally, to locate the region of maximum pressure and shear stress during the ADV, the pressure and shear stress are plotted along the length of the tube for various times (Fig. 9) for $R_o = 10.93 \mu\text{m}$. The peak pressure for all time is located at stagnation point whereas the peak shear stress is located just adjacent (left and right) to the stagnation point on the tube wall. The region of high shear stress depends upon the bubble interface velocity. As the bubble interface velocity increases more bulk fluid is propelled towards the walls causing a higher shear on wall. Moreover when the interface velocity reaches peak value, sudden jump in

the shear stress profiles are seen for some times instances (7, 9 and 11 μs).

6 Energy Analysis

After evaluating the bubble evolution dynamics inside the microtube, we analyzed the energy distribution for the expanding bubble. We estimate how total input energy into the bubble is converted to various components and which energy components affect the bubble expansion process. When the vapor bubble begins to expand the input energy (E_o) to the system is given by

$$E_o = \int_{V_o}^{V_f} P dV \quad (10)$$

where V_o is the initial bubble volume just after the instantaneous conversion of droplet to the bubble by ADV and V_f is the final bubble volume. This input energy drives the expansion of the bubble against the ambient pressure (E_{P_o}), surface tension (E_σ) and viscous stresses at the bubble interface (E_μ). The amount of energy absorbed in each of the processes can be estimated by

$$E_{P_o} = \int_{R_o}^{R_f} P_o 4\pi R^2 dR = \frac{4}{3} \pi (R_f^3 - R_o^3) P_o \quad (11)$$

$$E_\sigma = \int_{R_o}^{R_f} \left(\frac{2\sigma}{R} \right) 4\pi R^2 dR = 4\pi (R_f^2 - R_o^2) \sigma \quad (12)$$

$$E_\mu = \int_{R_o}^{R_f} \left(\frac{4\mu}{R} \frac{dR}{dt} \right) 4\pi R^2 dR \quad (13)$$

In addition to the energy consumption listed above, a portion of the input energy is converted to kinetic energy in the bulk fluid surrounding the bubble and the remaining energy is lost to viscous friction dissipation along the tube wall. It is worth mentioning here, that although ultrasound energy might appear to contribute significantly for ADV, it merely serves to perturb the superheated liquid and its contribution is negligible for subsequent bubble evolution and fluid movement inside the tube. Previous studies [14–17] have indicated that when ultrasound waves hit the superheated droplet, some of the energy is utilized to oscillate the droplet and a major portion is used to nucleate the droplet to initiate the vaporization. In this present experiment the ultrasound operates at 3.5 MHz with 4 or 7 acoustic cycles. The total time corresponding to seven cycles is less than 2 μs . During this 2 μs phase, the ultrasound energy is used to initiate the nucleation and to consume the entire liquid DDFP inside the droplet. By the time the entire droplet is converted to bubble phase the focused acoustic energy is off. At this point the originated bubble has high pressure, which results in bubble growth and subsequently drives the fluid flow inside the tube.

The average kinetic energy gained by the fluid inside the tube due to the bubble expansion is given by

$$\bar{E}_k = \frac{1}{\Delta t} \int_{t_o}^{t_f} \frac{1}{2} \dot{m} \bar{U}^2 dt \quad (14)$$

where t_o and t_f are the initial and final times for the bubble expansion process, $\Delta t = t_f - t_o$, $\dot{m}$ the mass flow rate and $\bar{U}$ is the average velocity of the fluid inside the tube. The average velocity gained inside the tube is estimated by applying mass conservation in the tube given by

$$\frac{d}{dt} \left[\frac{\pi D^2 L}{4} - \frac{4\pi R^3}{3} \right] = -\beta Q = \beta \bar{U} \frac{\pi D^2}{4} \quad (15)$$

where β represents number of outlets. In our case, since both ends are open, $\beta = 2$. Solving for $\bar{U}$ yields:

Fig. 10 Percentage Energy conversion in ADV for $R_o = 10.93 \mu\text{m}$

$$\bar{U} = \frac{16}{\beta D^2} R^2 \frac{dR}{dt} \quad (16)$$

The mass flow rate inside the tube due to bubble expansion is given by

$$\dot{m} = \rho \frac{d}{dt} \left[\frac{\pi D^2 L}{4} - \frac{4\pi R^3}{3} \right] \quad (17)$$

Substituting the value of $\dot{m}$ and $\bar{U}$ from Eq. (17) and (16) in the kinetic energy expression gives:

$$\bar{E}_k = \frac{1}{\Delta t} \int_{t_0}^{t_f} \frac{512\pi R^6 \rho}{\beta^2 D^4} \left(\frac{dR}{dt} \right)^3 dt \quad (18)$$

To compute the average kinetic energy, the interface velocity (dR/dt) is obtained from the theoretical model. Finally the energy dissipated by viscous frictional loss (E_H) of the tube is computed as

$$E_H = E_o - E_{Po} - E_\mu - E_\sigma - E_k \quad (19)$$

For analysis purposes, the droplet with initial radius, $R_o = 10.932 \mu\text{m}$ is considered. Figure 10 shows the percentage energy distribution of the input energy to the expanding bubble inside the rigid tube. It is observed that the majority of energy (62%) is dissipated as frictional loss, whereas almost (36%) energy is used to push the fluid against the ambient pressure. The energy expended to stretch the expanding interface (E_σ), the energy required to push the viscous fluid surrounding the bubble interface (E_μ) and the average kinetic energy (E_k) gained by the fluid in the tube due to bubble expansion are all negligible. The total energy contribution of these energy components is less than 2%. Thus it can be inferred from this energy analysis that the bubble expansion dynamics are primarily dependent on two factors: (a) the total viscous dissipation of the tube, and (b) the ambient fluid pressure surrounding the bubble. To elucidate the role of these factors on the bubble evolution dynamics, theoretical and computational models are utilized to predict the bubble evolution dynamics by varying these parameters.

6.1 Effect of Viscous Dissipation. The energy analysis shows that most of the input energy is dissipated as viscous loss, suggesting that bubble dynamics can be altered by changing viscous dissipation. Since the total viscous dissipation in the tube depends primarily on the length of the tube, the viscous dissipa-

Fig. 11 Effect of tube length on expansion ratio for $R_o = 10.93 \mu\text{m}$

tion can be altered by changing the tube length. If the tube length is increased it is expected that the bubble dynamics would unfold more slowly given that the rate of strain in the surrounding fluid would be smaller. To show this, theoretical and computational models were solved by varying the tube length. Figure 11 shows the bubble evolution dynamics for droplet of initial radius, $R_o = 10.93$ for the case when the tube length is doubled. Results indicate that the final bubble size is not affected, however a dampening effect is observed for the case when the length is doubled. After the spontaneous conversion of DDFP droplet into a vapor bubble, the initial bubble pressure remains the same in both cases as this initial pressure depends on the vaporization dynamics. For both cases the bubble evolution is almost similar until the bubble reaches approximately three times its original radius. Until this point the bubble evolution is primarily driven by high bubble pressure, however, as the bubble is growing the corresponding bubble pressure is also decreasing because of the corresponding increase in volume. The remaining growth of the bubble is controlled by the fluid pressure outside the bubble and the associated viscous dampening. Since in both cases the outside hydrostatic pressure remains the same, the role of viscous dampening in bubble evolution can be elucidated. Although the final bubble size is not affected by increased viscous dissipation, the time scale required to achieve the final size is significantly alternated (approximately six times).

6.2 Effect of Ambient Pressure. The role of ambient pressure in the bubble evolution dynamics inside the tube is investigated by computing the bubble evolution using theoretical and computational modeling. Figure 12 shows the bubble evolution when the ambient pressure is doubled. It is observed that as the surrounding ambient fluid pressure is increased a significant variation in bubble evolution takes place and a rebound in the bubble evolutions is observed. As the ambient pressure is doubled the bubble interface is exposed to higher pressure on the bulk fluid side. Since the internal pressure remains the same as obtained from the vaporization dynamics, a larger portion of input energy to the bubble is consumed while doing work against the higher pressure in the bulk fluid. As a result of this, the dissipative energy loss at the tube wall decreases and a rebound in the bubble evolution is observed. This suggests that the viscous dampening associated with tube friction is primarily responsible in avoiding rebounds in bubble evolution dynamics in ADV. Moreover, as the

Fig. 12 Effect of ambient pressure on expansion ratio for $R_0 = 10.93 \mu\text{m}$

ambient pressure is increased, the final bubble size is also affected which is in accordance with the Young-Laplace equation.

The qualitative results obtained from the present method suggest that the initial droplet size is an important parameter, which governs the stress distribution during the ADV process. A significantly elevated value of localized normal stress (pressure rise), which is typically four to five times the mean blood pressure (94 mm Hg) is observed during the early stages of the vaporization event. This suggests that the vessel walls are exposed to the highest risk of rupture at the beginning of the bubble expansion. Moreover, to minimize the damage caused by shear stress values achieved during bubble expansion it would be ideal to vaporize the droplet near the arterial bifurcation, where vasculature can naturally withstand higher stresses due to higher structural muscular support. However, if the vaporization is done at the bifurcation the bubble dynamics is expected to evolve in different manner, as vessel bifurcations [39] are known to result in pressure wave reflections and modification of velocity fields in the blood flow.

Further ex vivo and in vivo experiments are required to investigate the bioeffects, which could include extravasations of red blood cells due to hemorrhage, damage to endothelial layer and change in vessel permeability when vessels are exposed to similar stress levels as predicted by this study. Nevertheless it is worth noting that as the blood vessels are compliant, it could potentially alter the wall stresses. Thus, future studies will be focused to investigate the bubble evolution via incorporating bubble fluid-structure interaction in the current model. Also, examining the role of geometric parameters (various size vessel and ADV near bifurcations) and fluid properties (surface tension and non-Newtonian fluid) would be the next step in further development of this combined theoretical and computational approach.

7 Conclusion

A combined theoretical and computational approach is employed to study acoustic microdroplet vaporization in a micro-tube. The theoretical ADV model provides the initial radius and the initial pressure of the originated bubble to the computational model, which then solves the subsequent bubble evolution. The results obtained from the combined approach are compared with the ultra-high speed images of bubble evolution from a series of in vitro experiments. The resulting microscale bubble evolution is

studied in order to assess the risk of vessel damage during a potential gas embolotherapy technique. Three regimes of bubble growth are identified in the evolution process. Although the size of the droplet is small compared to the tube diameter, the influence of tube walls on bubble evolution dynamics is significant and is observed as an elongated shape bubble during early stages of the expansion process. For a given initial droplet size, a pressure pulse is generated with amplitude reaching almost twice as that of ambient pressure at the early stage of the bubble evolution. Potential risk of vessel hemorrhage is predicted at the beginning of the bubble expansion. To minimize the potential of damaging the endothelium, smaller bubbles relative to the diameter of the blood vessel are favored. The overall magnitude of the shear stress is much less than that of the pressure, however shear stress magnitude is found to be more prominently influenced by the size of the initial droplet.

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