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Computational simulation of hematocrit effects on arterial gas embolism dynamics

Karthik Mukundakrishnan, Ph.D.¹, Portonovo S. Ayyaswamy, Ph.D.², and David M. Eckmann, Ph.D., M.D.³

¹Dassault Systemes Simulia Corp., Rising Sun Mills, RI, 02919

²Department of Mechanical Engineering and Applied Mechanics, University of Pennsylvania, Philadelphia, PA, 19104

³Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA, 19104

Abstract

Background—Recent computational investigations have shed light into the various hydrodynamic mechanisms at play during arterial gas embolism that may result in endothelial cell (EC) injury. Other recent studies have suggested that variations in hematocrit level may play an important role in determining the severity of neurological complications due to decompression sickness associated with gas embolism.

Methods—Towards developing a comprehensive picture, we have computationally modeled the effect of hematocrit variations on the motion of a nearly occluding gas bubble in arterial blood vessels of various sizes. The computational methodology is based on an axisymmetric finite difference immersed boundary numerical method to precisely track the blood-bubble dynamics of the interface. Hematocrit variations are taken to be in the range 0.2–0.6. The chosen blood vessel sizes correspond to small arteries, and small and large arterioles in normal humans.

Results—Relevant hydrodynamic interactions between the gas bubble and EC-lined vessel lumen have been characterized and quantified as a function of hematocrit levels. In particular, the variations in shear stress, spatial and temporal shear stress gradients, and the gap between bubble and vascular endothelium surfaces that contribute to EC injury have been computed.

Discussion—The results suggest that in small arteries, the deleterious hydrodynamic effects of the gas embolism on EC-lined cell wall are significantly amplified as the hematocrit levels increase. However, such pronounced variations with hematocrit levels are not observed in the arterioles.

Keywords

decompression sickness; numerical; Casson; finite difference; vortex; shear stress

INTRODUCTION

Arterial gas embolism (AGE) can occur as a result of decompression sickness (DCS) attributed to a reduction in ambient pressure, during medical procedures such as cardiopulmonary bypass surgery and angiography (2, 23), and during rapid exposure to

hypobaria such as in high altitude flight or extravehicular activities in space (10). The primary effects of AGE are mainly mechanical in nature, namely, they cause injury to the vascular endothelium while in motion and may occlude arteries. Gas emboli can also lodge in coronary, cerebral, and other systemic arterioles. Coronary artery embolization can lead to myocardial infarction or dysrhythmia while cerebral artery emboli can cause stroke or seizures. Secondary biochemical effects include activation of leukocytes, platelets, complement, and the clotting cascade. In addition, attachment of polymorphonuclear cells and granulocyte-mediated reperfusion injury may also occur (2–3). An increase of vascular permeability occurs due to gas embolism leading to extravasation of plasma and hemoconcentration, an increase of hematocrit. Female divers with hematocrit values 48% or higher were found to be at greater risk of developing neurological DCS, particularly motor weakness and severe sensory symptoms (6). Hematocrit levels also serve as a proxy measure of intravascular hydration. A study of hematocrit levels after a single warm-water scuba dive found statistically significant increases (36). A swine study found that dehydration (leading to hemoconcentration) increased the risk of severe cardiopulmonary and central nervous system DCS and of overall death (15). Conversely, a recent study using human subjects has shown that pre-dive hydration reduces DCS risk (16).

The mechanisms underlying these observations regarding hematocrit variations are either unknown or are poorly understood. Delineating and quantifying the effects of such variations on AGE dynamics are critical to advancing the knowledge of the pathophysiological responses associated with intravascular bubbles, and to the development of new and more effective therapies.

As related to gas embolism, in a series of related studies over the past few years we have experimentally and numerically investigated the motion of a finite gas bubble in the vasculature. On the molecular level, we have previously demonstrated that bubble contact with endothelial cells causes injurious or lethal influx of calcium (22) into the cell. We have also shown that this Ca^{2+} signaling occurs through a stretch-activated channel, such as a transient receptor potential vanilloid (TRPV) family member, triggering the release of Ca^{2+} from intracellular stores via the Inositol trisphosphate (IP3) pathway (31). Moreover, we have proved that this Ca^{2+} transient is the mechanotransduction result of the bubble having imposed a tensile force on a heparan sulfate proteoglycan component of the endothelial cell glycocalyx – most probably the transmembrane syndecan – as proteins ligands bound to the heparan sulfate side chains are pulled into the hydrophobic gas/liquid bubble interface (21). This force physically displaces syndecan, and its actin-associated cytoplasmic domain, which subsequently perturbs cytoskeletal structures and activates a TRPV calcium channel. These responses may be prevented with a surfactant being present to compete with any bubble-glycocalyx or bubble-plasma macromolecule interactions (21). These findings at the molecular scale largely can be interpreted to explain other molecular interactions between bubbles and blood components (12–13). For more macro-scale observations, the role of surfactant is also important in bubble adhesion to (32), and detachment from the vessel wall, as studied *in vitro*, *ex vivo* and *in vivo* (8, 14). In order to model such a complex problem, a novel computational method has been developed to study the motion of gas bubble in a shear-thinning blood-like Casson fluid (37). While the previous work is limited to low fluid to gas viscosity ratios, the numerical methodology has been extended to solve the motion of a real gas bubble (27). The dynamics responsible for causing EC injury due to the motion of gas embolism has been clearly elucidated for the first time (24–26). In (33), the computational simulations of bubble motion included the presence and transport of soluble surfactants both in the bulk and the blood-bubble surface. However, none of these studies has systematically considered the dynamics of the gas bubble under a widely varying hematocrit range that are important in situations where hemodilution and hemoconcentration may occur. The present study addresses this deficiency by characterizing and quantifying the

important hydrodynamic interactions between the gas bubble and vascular endothelium for physiologically relevant hematocrit level variations using computational methods. In particular, the variations in shear stress, spatial and temporal shear stress gradients, and the gap between bubble and vascular endothelium surfaces have all been computed. The results suggest that in small arteries, the deleterious hydrodynamic effects are significantly amplified as the hematocrit levels increase.

METHODS

Computational Model

We consider the axisymmetric motion of a nearly occluding gas bubble in a vessel of circular cross-section of radius R (diameter, d) with the aspect ratio (radius of the bubble to the radius of the vessel) denoted by λ . The primary focus of this paper will be the formulation and evaluation of the bubble motion and interactions with the blood vessel at the macroscopic scale. The microscale phenomena that include the cell membrane and intracellular dynamics will therefore not be considered.

The non-dimensional scaled equations for the conservation of mass and momentum for a single continuum (blood + gas) yield (see, (25) for details):

$$\nabla \cdot \mathbf{u} = 0 \quad (1)$$

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \frac{1}{Re} \nabla \cdot \mu (\nabla \mathbf{u} + \nabla^T \mathbf{u}) + \frac{1}{We} \int_{S(t)} \kappa \mathbf{n}_f \hat{\delta}(\mathbf{x} - \mathbf{x}_f) dS - \frac{l}{Fr^2} \rho \mathbf{e}_z \quad (2)$$

Here, $\mathbf{u} = (v_r, v_z)$ denotes the fluid velocity vector, v_r, v_z the dimensionless velocity components along the radial (r) and axial (z) directions, respectively, t the time, and p the fluid pressure. $S(t)$, dS , κ , $\mathbf{n}_f$ and $\mathbf{x}_f$ denote the instantaneous location, the infinitesimal dimensionless arc length measure, the dimensionless curvature, the unit normal vector pointing into the bulk fluid, and the position vector, of the blood-bubble interface, respectively. $\hat{\delta}(\mathbf{x} - \mathbf{x}_f)$ is the 2D axisymmetric delta function which is nonzero only when $\mathbf{x} = \mathbf{x}_f$ and $\mathbf{e}_z$ is the unit vector along the axial direction. Furthermore, the non-dimensional density ρ and viscosity μ of the bubble-blood medium in equations (1) and (2) are given as follows:

$$\begin{aligned} \rho(r, z, t) &= \Pi(r, z, t) + \frac{\rho_g}{\rho_l} (1 - \Pi(r, z, t)), \\ \mu(r, z, t) &= \frac{\mu_l}{\mu_{ref}} \Pi(r, z, t) + \frac{\mu_g}{\mu_{ref}} (1 - \Pi(r, z, t)), \end{aligned} \quad (3)$$

where, ρ_l is the constant density of blood ($= 1000 \text{ kg m}^{-3}$), $\rho_g (= 1.229 \text{ kg m}^{-3})$ is the gas bubble density, μ_{ref} is the reference viscosity of blood, which is taken to be the average Newtonian blood viscosity ($= 3.5 \text{ cP}$), and $\mu_g (= 0.01 \text{ cP})$, is the gas bubble viscosity. Also, $\Pi(r, z, t)$ is the Heaviside function which takes a value of 1 in the bulk (blood) and 0 inside the bubble. In equation (3), following Sharan and Popel (30), the bulk fluid viscosity μ_l is modeled as a two-layer fluid consisting of a cylindrical core of concentrated red blood cell (RBC) suspension surrounded by a less viscous, thin cell-free layer as follows:

$$\mu_l = \begin{cases} \left[\sqrt{\frac{\mu_{\infty}}{\mu_{ref}}} + \sqrt{\frac{Bi}{|\gamma|}} \left(1 - e^{-\sqrt{m}|\gamma|} \right) \right]^2 & \forall 0 \leq r \leq \frac{(1-\delta)}{2} \\ \frac{\mu_{layer}}{\mu_{ref}} = \frac{\beta \mu_p}{\mu_{ref}} & \forall \frac{(1-\delta)}{2} \leq r \leq 0.5 \end{cases} \quad (4)$$

The cell-free layer is modeled as a Newtonian fluid of viscosity $\mu_{layer}(=\beta\mu_p)$ while the concentrated suspension of RBCs is modeled as a shear-thinning Casson fluid. Here, μ_p is the viscosity of blood plasma ($= 1.2$ cP (1)), and δ represents the non-dimensional thickness of the cell-free layer normalized with respect to the vessel radius R . $|\gamma|$, τ_y and μ_∞ are the local shear rate, yield stress of blood, and the asymptotic Newtonian viscosity at high shear rates, respectively. The factor β depends nonlinearly on δ , the core hematocrit H_C and the discharge hematocrit H_D (30). The values of β , H_C , and δ are obtained based on solving nonlinear coupled differential equations supplemented by experimental data for known values of d and H_D . While we have employed those procedures, the solution methodology is not included here for brevity (see, (25) for details). Table I shows the various evaluated values of H_C , δ , β and μ_{layer} for given values of d and H_D used in the present study.

In equations (1) and (2), the Reynolds number, Re , Bingham number, Bi , Weber number, We , and Froude number, Fr are defined by:

$$Re = \frac{\rho_l d U_{\max}}{\mu_{ref}}, Bi = \frac{\tau_y d}{\mu_{ref} U_{\max}}, We = \frac{\rho_l d U_{\max}^2}{\sigma}, Fr = \frac{U_{\max}}{\sqrt{gd}}$$

The Reynolds number Re is the ratio of the inertial to the viscous forces exerted by the blood, Bi is the ratio of the yield stress of the blood to the viscous forces, We is the ratio of the inertial to the surface tension forces, and Fr is the ratio of the inertial to the gravitational forces. Here, $U_{\max}$ is the maximum inlet flow velocity for a blood vessel of given size with $H_D = 0.45$, the nominal hematocrit value in humans, and σ is the constant surface tension coefficient. Additional non-dimensional parameters can be derived from the combinations of the above parameters. For example, the capillary number Ca , which is the ratio of the

viscous to surface tension forces, is given by $Ca = \frac{\mu_{ref} U_{\max}}{\sigma} = We/Re$. The value of surface tension σ is taken as 3 dyne/cm for $Re = 0.2$ although the air-blood surface tension coefficient is higher ($\sim O(10)$). As pointed out in (25), such reduced values are necessitated by the fact that for low Re and very high σ , numerical noise in the form of parasitic currents (vortices) corrupt the solution at the blood-bubble interface. The reduction in σ value results in an increase in film thickness. Such a reduction in the value of σ is not required at higher Re . The values of various non-dimensional parameters used in the present simulation are given in Table II.

Boundary and initial conditions

The dimensionless boundary and initial conditions for the problem in the presence of the bubble is as follows.

Inlet boundary, $z = 0$: At the inlet, the fully developed two-fluid model axisymmetric Casson flow velocity profile is prescribed (25).

Outlet boundary, $z = L$: Since the flow occurs in a long vessel, for computational purposes it is important to establish geometry with a prescribed location for the outlet boundary. Here, the outlet boundary is set at $z = L/d = 6$ (25). An outflow boundary condition at $z = L$ is prescribed as follows:

$$\frac{\partial \mathbf{u}}{\partial z} \left(r, \frac{L}{d}, t \right) = \mathbf{0} \quad (6)$$

Reflective boundary, $r = 0$: A reflective boundary condition is used at the axis of symmetry, $r = 0$.

$$\begin{aligned} v_r(0, z, t) &= 0, \quad 0 \leq z \leq \frac{L}{d} \\ \frac{\partial v_z}{\partial r}(0, z, t) &= 0, \quad 0 \leq z \leq \frac{L}{d} \end{aligned} \quad (7)$$

Wall no-slip boundary, $r = 0.5$:

$$\mathbf{u}(0.5, z, t) = \mathbf{0} \quad (8)$$

Initial conditions: At $t = 0$, the flow is described by a fully developed velocity profile ($v_z(r)$) obtained by solving a two-fluid model (see, (25) for details). Thus,

$$\mathbf{u}(r, z, t) \rightarrow v_z(r) \big|_{t=0} \quad (9)$$

Numerical Methodology

The present study is based on a front-tracking method coupled with a level contour reconstruction procedure. The details are not included here for the purposes of brevity (see, (25, 27) for details).

System Parameters

The vessel sizes considered in this study are representative of a small artery ($d = 0.2$ cm), a large arteriole ($d = 100$ μ m), and a small arteriole ($d = 40$ μ m) in a normal human. For the present study, two values of λ , namely, 0.9 and 1 are considered that represent nearly occluding bubble sizes. Our recent study (24) has shown that the hydrodynamic interactions between the finite sized bubble and the vessel wall remained nearly invariant for any further increases in bubble size beyond $\lambda > 1$.

Hematocrit levels (H_D , discharge hematocrit) are varied between a lower hemodiluted limit of 0.2 and an upper hemoconcentrated limit of 0.6, including both the limits for the sake of completeness (for example, in (28), the range considered corresponded to $0.3 \leq H_D \leq 0.61$). These limits are chosen specifically to consider dehydration and hemoconcentration that may occur at extreme environments where decompression events constitute a significant physiological risk.

RESULTS

The results from various simulations are presented as follows. For a given blood vessel (i.e. for a given Re) and bubble size λ , the state corresponding to $H_D = 0.45$ is considered as the hematocrit basal state for that Re . The basal state can be considered as a nominal state for most humans (mean H_D for most humans is ~ 0.45). Thus, it serves as a reference state about which variations in hydrodynamical quantities due to the variations in hematocrit levels may be evaluated and compared against. The inlet flow rate corresponding to every other H_D - Re pair is taken to be the same as that for the hematocrit basal state. For all the cases considered here, the gas bubble motion attains a steady state and the results presented pertain to such steady state conditions.

It is useful to analyze the structure of the flow field prevailing near the vicinity of the bubble under steady state conditions. The hydrodynamical flow structure determines the physical state experienced by the endothelial cells lining the vessel walls. In Figs. 1A–C, the flow

field corresponding to a representative case of $Re = 2$, $\lambda = 1$, and $H_D = 0.2$ is shown. The flow fields for other combinations of Re , λ and H_D are qualitatively similar and hence, are not presented for brevity. Fig. 1A displays the flow streamlines as would be seen by an observer situated on the endothelial cell (EC) that is fixed on the vessel lumen (vessel wall; inertial frame). In Fig. 1B, the same streamlines are plotted in a reference frame attached to the steadily moving bubble. The most notable feature as observed in Fig. 1A is the presence of a small recirculating vortex ring in the vicinity of representative point **P** on the lumen. This vortex ring causes a reversal in the direction of the prevailing local velocity field thereby resulting in a reversal of the sign of the associated shear stress at the endothelial cell surface. The exploded version of such a vortex ring is shown in Fig. 1C for clarity.

It is well known that hydrodynamic shear affects the normal functionality of ECs (9, 35) and the characterization of the level of imparted stress is important in gas embolism studies (24–25). It is of interest here to study the variations in the shear stress levels as a function of variations in H_D for each Re and λ . To facilitate comparison, the dimensional shear stress, τ , is now normalized with the basal shear stress τ_{ref} to yield a dimensionless shear stress τ^* . The basal shear stress τ_{ref} is defined as that value of wall shear stress prevailing for the hematocrit basal state ($H_D = 0.45$) in the absence of a bubble and at steady flow conditions. Figs. 2A–C show the variations of τ^* as a function of time at a given point on the endothelial cell surface (denoted by **P** in Fig. 1A) for $Re = 0.2$, 2, and 200, respectively, and for three representative values of $H_D = 0.2$, 0.45, and 0.6, all for $\lambda = 0.9$. Similarly, in Figs. 3A–C, the temporal variations of τ^* are given for the case of $\lambda = 1$. The temporal shear stress profiles for all the cases look qualitatively similar and resemble a solitary wave traveling on the endothelial cell surface. Each solitary wave is characterized by significant departures from a mean quiescent state (the asymptotic constant stress states at the beginning and end of the finite duration shown in Figs. 2 and 3) over a finite time period. Figs. 2 and 3 also demonstrate the rapid reversals in the sign of shear stress for all the cases. Both the departures from the quiescent state and the sign reversals are attributed to the presence of the fluid vortex ring in the vicinity of the bubble and the EC-lined lumen as noted earlier in Figs. 1A and C.

Consider the temporal variation of the normalized shear stress at a given location on the lumen for a representative case of $Re = 0.2$, $H_D = 0.45$, and $\lambda = 0.9$ as given by the solid curve Fig. 2A. Let the minimum and maximum shear stress values over the period of significant stress variations denoted by τ_{min}^* and τ_{max}^* , respectively. Let t_1^* and t_2^* denote the corresponding time instants at which τ_{min}^* and τ_{max}^* occur. Then, the maximum value of the variation of shear stress over the undisturbed mean state is provided by the quantity $\Delta\tau^* = \tau_{max}^* - \tau_{min}^*$. The variations of $\Delta\tau^*$ as a function of H_D for $Re = 0.2$, 2, and 200 and for two values of $\lambda = 0.9$ and 1, are given in Table III. In general, for all the cases, $\Delta\tau^*$ is noted to increase with increasing H_D . However for $Re = 0.2$, corresponding to small arteriole, the variations in $\Delta\tau^*$ are seen to be very small for both $\lambda = 0.9$ and 1. For the case of $Re = 2$, the increase in $\Delta\tau^*$ is slightly pronounced for the case of $\lambda = 0.9$ compared to that for $\lambda = 1$. The increase in $\Delta\tau^*$ with increasing H_D is the highest for the case of $Re = 200$ as seen in Table III. For this case, increased viscous effect in the gap between the bubble and the endothelial cell surface due to an increase in H_D is responsible for the higher $\Delta\tau^*$ variations. It may be seen from Figs. 2C and 3C, that τ_{min}^* decreases while τ_{max}^* increases with increasing H_D for $Re = 200$.

A step change in shear stress has been implicated in increased and sustained plasma membrane fluidity (7, 17). Shear stress gradients together with sign reversals may cause potential disruption of endothelial cell membrane integrity and functionality. From the shear stress temporal variation profiles, an estimate of the maximum temporal gradient of shear

stress experienced by the ECs can be obtained as a function of hematocrit levels. The value

denoted by $\frac{\Delta\tau^*}{\Delta t^*} = \frac{\tau_{\max}^* - \tau_{\min}^*}{t_2^* - t_1^*}$ is given in Table III as a function of H_D for various values of Re and λ . Consider the case of small arteriole ($Re = 0.2$). For $\lambda = 0.9$, $\Delta\tau^*/\Delta t^*$ increases at higher H_D . The increase is more pronounced in the hematocrit range 0.45 – 0.6, with the variation from the hematocrit basal state ($H_D = 0.45$) approximately doubling at $H_D = 0.6$. However, for $\lambda = 1$, $\Delta\tau^*/\Delta t^*$ decreases over the hematocrit range of 0.45 – 0.6. As is shown in Table I, the cell-free layer viscosity is higher at $H_D = 0.6$ than at $H_D = 0.45$. Coupled with the fact that for $\lambda = 1$, the bubble interface is elongated and is in very close proximity to the vessel wall, increased viscous interaction (primarily viscous stretching) of the generated vortex ring (see, Fig. 1C) takes place. A slight increase in the width of the vortex ring translates into an increased time interval between the occurrence of $\tau_{\min}^*$ and $\tau_{\max}^*$. Thus, while $\Delta\tau^*$ increases in this range (see, Table III), the corresponding but larger increase in $t_2^* - t_1^*$ results in a net decrease in $\Delta\tau^*/\Delta t^*$. The maximum decrease at $H_D = 0.6$ is ~ 15% lower than for the hematocrit basal state ($H_D = 0.45$). On the other hand, for $\lambda = 0.9$ and H_D in the range 0.45 – 0.6, the larger gap arising between the bubble interface and the vessel wall leads to a lesser stretching of the vortex ring. The resultant effect is that the increase in $\Delta\tau^*$ is smaller than the corresponding increase in Δt^* . As a result, there is a net increase in $\Delta\tau^*/\Delta t^*$ occurring with hemoconcentration. Also, for the case of $Re = 0.2$, another prominent effect in play is the Fahraeus-Lindqvist effect, which is responsible for increasing the core hematocrit H_C above H_D and creating a cell-free layer composed mainly of plasma near the vessel wall. This effect is mainly due to the tendency for the RBCs to move toward the axis of the tube, leaving a layer of cell-free layer (1). The thickness of the cell-free layer (characterized by δ) is smaller for $H_D = 0.6$ compared to $H_D = 0.45$ as can be seen from Table I due to increased Fahraeus-Lindqvist effect. The decrease in the cell-layer thickness may provide an increased viscous resistance to the motion of the bubble from the RBC-rich core for the case of $H_D = 0.6$ compared to $H_D = 0.45$ thereby resulting in a higher $\Delta\tau^*$. The case of large arteriole ($Re = 2$) is considered next. The variations in $\Delta\tau^*/\Delta t^*$ for both $\lambda = 0.9$ and 1, as given in Table III, are qualitatively similar to those found for the small arteriole. The maximum increase observed in $\Delta\tau^*/\Delta t^*$ appears for $\lambda = 0.9$ and $H_D = 0.6$ and is ~20% higher than that found for the hematocrit basal state. Similar to $Re = 0.2$, a pronounced decrease in $\Delta\tau^*/\Delta t^*$ is found with hemoconcentration ($0.45 \leq H_D \leq 0.6$) due to the reasons stated earlier. The maximum decrease in $\Delta\tau^*/\Delta t^*$ for $\lambda = 1$ and $H_D = 0.6$ is about 10% below the basal state. However, for this case, the inertial forces are an order of magnitude higher than for the case of $Re = 0.2$ for similar viscous conditions. For a small artery ($Re = 200$), as seen in Table III, the variations in $\Delta\tau^*/\Delta t^*$ are most significant and pronounced as H_D increases for both $\lambda = 0.9$ and 1. As much as a three-fold increase in $\Delta\tau^*/\Delta t^*$ is found as H_D increases from 0.2 to 0.6. The dominance of inertial forces at $Re = 200$ is apparent.

The proximity of the bubble interface to the endothelial cells lining the vessel wall is assessed by evaluating the thickness of the fluid film in the gap between the EC surface and the bubble-blood interface. The dimensional thickness is normalized with respect to the thickness of the endothelial surface layer (ESL). The endothelial surface layer (ESL) is an extracellular layer of cell membrane-bound substances that is actively involved in many functions, such as the control and regulation of vascular tone, fluid and solute exchange, haemostasis and coagulation and inflammatory responses. Here, ESL thickness is assumed to be ~ 0.5 μm (29). In Table III, this normalized distance is displayed as a function of H_D for various values of Re and for $\lambda = 0.9$ and 1. Consider first the case of $\lambda = 0.9$. For small and large arterioles ($Re = 0.2$ and 2), the film thickness remains nearly constant for all values of H_D considered. The closest proximity occurs for small arterioles ($Re = 0.2$) followed by that for the large arteriole ($Re = 2$). For small arteries ($Re = 200$), the film thickness increases for $0.45 \leq H_D \leq 0.6$. However, it should also be noted that for small

arteries the bubble interface is far away from the endothelial surface compared to those in arterioles. The inertial effects of flowing blood are high in the arteries and hence the bubble gets stretched and deformed along the axial direction thereby increasing the film thickness (25). For the case of $\lambda = 1$, and for small and large arterioles, the film thickness remains essentially the same in the range $0.45 \leq H_D \leq 0.6$. However, for $0.2 \leq H_D \leq 0.6$, the film thickness increases by approximately 20% in large arterioles. For the flow in a small artery, the film thickness steadily increases as H_D increases from a value of 0.2 with the maximum film thickness occurring at $H_D = 0.6$. This value is about twice as high as that for the case of $H_D = 0.2$. In view of the large film thicknesses observed in small arteries, interactions between the bubble and vascular endothelium occur primarily due to the prevailing hydrodynamics. However, in small and large arterioles direct bubble-endothelium interactions and hydrodynamic interactions may both be at play.

In the case of small arteries ($Re = 200$), given the significant variations of $\Delta\tau^*$, $\Delta\tau^*/\Delta t^*$, and the film thickness with H_D , it is useful to compare the variations of the same quantities with changes in surface tension (or, equivalently, the capillary number Ca) as well. Such a comparison would provide us with insights into potential approaches for effective therapy. In this study, we have assumed the surface tension σ to be constant, and hence Marangoni stresses do not arise. However, the variations in the surface tension σ may occur as a result of changes in plasma protein levels which could lead to an altered protein adsorption at the air-liquid interface. This may also occur as a result of addition of surfactants (8, 13). A detailed numerical study of such phenomena on the bubble dynamics in blood vessels has been carried out by our group (33). In Fig. 4, the variations of the change in shear stress $\Delta\tau^*$, the shear stress gradient $\Delta\tau^*/\Delta t^*$, and variation of film thickness are plotted as a function of Ca for the representative case of $\lambda = 1$ and $H_D = 0.45$. The highest value of $Ca (= 2.45 \times 10^{-2})$ corresponds to a value of $\sigma = 50$ dyne/cm and the lowest value of $Ca (= 1.225 \times 10^{-1})$ corresponds to $\sigma = 10$ dyne/cm. As Ca increases due to a decrease in σ , $\Delta\tau^*$ decreases almost by a factor of two. This may be attributed to a relative increase in both viscous and

inertial effects (due to an increase in $We = \frac{\rho_l d U_{\max}^2}{\sigma}$) compared to surface tension effects. An increased inertial effect tends to stretch the bubble along the axial direction and there is a corresponding contraction of size along the radial direction due to conservation of bubble mass. Such a radial contraction results in an increased film thickness and a corresponding reduction in the velocity gradient in the gap leading to a decreased shear stress. Similarly, the shear stress gradient $\Delta\tau^*/\Delta t^*$ also decreases almost by a factor of two as Ca increases by a factor of five. The film thickness increases by a factor of two as the surface tension is reduced (*i.e.*, as Ca is increased). As stated earlier, the increase in film thickness is a result of an increased bubble deformation due to a decrease in surface tension force compared to the inertial and viscous forces.

DISCUSSION

The major aim of this study is to characterize and quantify the effect of hematocrit variations on arterial gas embolism. Data from recent analysis have shown that increase in hematocrit levels correlated positively with an increase of neurological symptoms of decompression sickness (6, 28). Our model findings for gas bubble motion in arteries ($Re = 200$) provides important insights to help explain these findings, since both the shear stress and its temporal gradients increase with increasing hematocrit values (Table III). Gradients in shear stress cause heterogeneous distribution of increase in plasma membrane fluidity (7). Cell injury may eventually happen through mechanisms involving overload influx of calcium ions, stress failure of the lipid bilayer, alterations induced in cell cytoskeletal elements, and pathways involving changes in focal adhesion sites (18). Additionally, we have now shown experimentally that gas bubble contact with endothelial cells results in calcium signaling

associated with cell death (22). This calcium signaling is definable by specific molecular interactions between the bubble surface and components of the endothelial cell surface layer (21), with mechanotransduction of cell surface layer forces leading to activation of identifiable intracellular biochemical pathways that are interdependent on elements of the cell cytoskeletal structure (21, 31). These may be reasons for the cause of the observed increase in neurological DCS in previous studies such as (6) and (28). If these hydrodynamic effects provide a measure of the symptoms of neurological DCS, our model further suggests that hemodilution may play a beneficial role in treating or managing arterial gas embolism. This fact is confirmed by a recent study that has shown that pre-dive hydration reduces DCS risk in humans (16). It should be noted that hydration results in hemodilution, and this may be a therapeutic or prophylactic approach to dealing with individuals at risk for decompression stress, especially those who may already be dehydrated. Conversely, an increased risk of severe cardiopulmonary and central nervous system DCS and of overall death have been observed in a swine study (15) which also is consistent with our study results. On the basis of this analysis, hemodilution may serve to help minimize the risks of cellular and end organ injury in arterial gas embolism and therefore reduce the occurrence of neurological symptoms of DCS by altering the fluid dynamical effects of bubble transit in close proximity to the vessel wall.

While the detection of catastrophic events, inflammatory response, and resuscitative measurements are well known for air embolism in small and large arteries, little is known about the effects of small emboli in microcirculation such as arterioles and capillaries (2). Our previous models have elucidated many of the mechanical (hydrodynamic) aspects of bubble motion in arterioles, both small and large (24–25). Our present findings have extended these studies to investigate the effect of changes in hematocrit on bubble motion and its influence on vascular endothelium. The flow field responsible for many of the mechanical effects in the vicinity of the gas embolism in a microcirculation as shown in Fig. 1 has been described for the first time. Quantification of the hydrodynamic effects reveals that variations in hematocrit do not play a major role in altering the mechanics of bubble-EC interactions. While there is an increase in shear stress with increased hematocrit levels in arterioles (see, Table III), it is relatively small compared to the increases observed in arteries. Similarly, the changes observed in the temporal shear stress gradients are also smaller compared to those of arteries. Similarly, the proximity to vascular endothelium (film thickness, see Table III) are also less affected by hematocrit changes. It may be concluded that alterations in hydration state leading to either hemodilution or hemoconcentration may not significantly affect the direct mechanical effects of gas embolism on endothelial cellular function in arterioles.

From the analysis of Table III and Fig. 4, it can be seen that both hematocrit and Ca (surface tension) variations have a profound effect on the bubble dynamics in arteries. The change in shear stress $\Delta\tau^*$, temporal shear stress gradients $\Delta\tau^*/\Delta t^*$, and the film thickness are all reduced, both due to hemodilution as well as reduction in Ca . It should be noted that a reduction in Ca can be easily obtained using soluble surfactants. Thus, these two effects can be synergistically harnessed in the design of effective therapies for mitigating gas-embolism induced injuries.

Some of the major limitations of the present model are discussed next. Given the complexity of the air embolism problem, we have chosen to solve an approximate yet meaningful description of the model. Some of the approximations and limitations of the model are listed as follows. A simple circular cylindrical surface has been considered to model the artery and arterioles. Hence, our model does not consider the exact topology of the vascular endothelial cell surface. For small arteries, the bubble surface is not in close proximity to the vascular endothelium (Table III) and the assumption of a smooth vessel wall may be a good

approximation. However, for the case of arterioles and in particular small arteriole, the bubble surface is in close proximity to the EC surface (Table III). Hence, topology of the endothelial cell may affect the outcome of the results. While a detailed computation can be done taking into the EC topology (11, 19), the relative comparison of the results with basal state may not change since the cell topology may affect the outcome of all the results in the same way. A second limitation of the present study is that the effect of normal stresses, mainly pressure gradients, and their associated changes has not been evaluated. These forces have been implicated as the main cause of injury in other cell types such as epithelial cells (5, 20). However, much of the research to date on endothelial cell response to flow has examined only variations of shear stresses since shear is considered to be the primary source of hemodynamic loading. In line with this, we have chosen to focus only on the variations in the shear stresses and its associated gradients on the EC-lined lumen due to bubble motion. However, to the best of our knowledge, there are only a limited number of studies that have begun to unfold the effect of normal stresses (primarily flow induced pressure loading) on the EC cell mechanics. For example, in (34), it has been concluded that the EC response to pressure includes (i) reshaping to minimize drag, (ii) realigning to minimize shear-induced torque, and (iii) minimizing attachment forces required to maintain adhesion. Although the numerical scheme is capable of evaluating the changes in pressure gradients, we have not discussed them due to the lack of information pertaining to the role played by these forces on the EC dynamics, especially as pertains to the very short time course associated with the solitary wave dynamics that occurs with gas embolism bubble transit through a vessel. Another limitation of the present study is the assumption of a uniform surface tension and the presence of a steady blood flow in a rigid wall vessel. Non-uniform adsorption of plasma proteins might result in surface tension gradients and Marangoni stresses. These stresses might influence the flow patterns and wall shear stress values. Also, the compliance of blood vessels may influence the bubble dynamics. In (33), we have already addressed the effect of Marangoni stresses arising as a result of addition of a soluble surfactant. The results from these studies can also be extended to study the influence of non-uniform protein adsorption. Other complexities that have not been considered in the present study include blood flow oscillations during each cardiac cycle, leukocyte/platelet interactions with bubble surface, vessel bifurcations and tortuosities, and the effect of glycocalyx thickness and composition.

The following are the major conclusions of the present study. Detailed computations have been performed to characterize and quantify the important hydrodynamic interactions between a gas bubble and vascular endothelium for physiological variations in hematocrit levels. In particular, the variations in shear stress, spatial and temporal shear stress gradients, and the gap between bubble and vascular endothelium surfaces have all been computed. The results of our models suggest that in arteries, the deleterious hydrodynamic effects of the air embolism on EC-lined cell wall are significantly amplified with an increase of hematocrit pointing to the harmful effects of hemoconcentration in the face of arterial gas embolization. However, such pronounced variations were not observed in the computational results for arterioles over the broad range of hematocrit levels considered. Thus, hemodilution through hydration may be a preventive measure for arterial gas embolism related endothelial cellular injury and related vascular dysfunction. The results from our models provide a better understanding of the possible mechanisms involved in the effects of hematocrit on the dynamics of an air embolism.

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REFERENCES

1. Ayyaswamy, PS. Introduction to Biofluid Mechanics (Chapter 17). In: Kundu, PK.; Cohen, IM., editors. Fluid Mechanics. Amsterdam ; Boston: Academic Press; 2008. p. xxviii, 872 p.
2. Barak M, Katz Y. Microbubbles: pathophysiology and clinical implications. *Chest*. 2005; 128:2918–2932. [PubMed: 16236969]
3. Barratt DM, Harch PG, Van Meter K. Decompression illness in divers: a review of the literature. *Neurologist*. 2002; 8:186–202. [PubMed: 12803690]
4. Berger, SA.; Goldsmith, W.; Lewis, ER. Introduction to bioengineering. Oxford, Eng. ; New York: Oxford University Press; 1996. p. xiv, 526 p.
5. Bilek A, Dee K, Gaver D III. Mechanisms of surface-tension-induced epithelial cell damage in a model of pulmonary airway reopening. *Journal of Applied Physiology*. 2003; 94:770. [PubMed: 12433851]
6. Boussuges A, Blanc P, Molenat F, Bergmann E, Sainty JM. Haemoconcentration in neurological decompression illness. *Int J Sports Med*. 1996; 17:351–355. [PubMed: 8858406]
7. Butler PJ, Norwich G, Weinbaum S, Chien S. Shear stress induces a time- and position-dependent increase in endothelial cell membrane fluidity. *Am J Physiol Cell Physiol*. 2001; 280:C962–C969. [PubMed: 11245613]
8. Cavanagh DP, Eckmann DM. The effects of a soluble surfactant on the interfacial dynamics of stationary bubbles in inclined tubes. *Journal of Fluid Mechanics*. 2002; 469:369–400.
9. Chien S. Effects of disturbed flow on endothelial cells. *Ann Biomed Eng*. 2008; 36:554–562. [PubMed: 18172767]
10. Conkin J, Kumar KV, Powell MR, Foster PP, Waligora JM. A probabilistic model of hypobaric decompression sickness based on 66 chamber tests. *Aviat Space Environ Med*. 1996; 67:176–183. [PubMed: 8834946]
11. Dailey HL, Ricles LM, Yalcin HC, Ghadiali SN. Image-based finite element modeling of alveolar epithelial cell injury during airway reopening. *J Appl Physiol*. 2009; 106:221–232. [PubMed: 19008489]
12. Eckmann DM, Armstead SC, Mardini F. Surfactant reduces platelet-bubble and platelet-platelet binding induced by in vitro air embolism. *Anesthesiology*. 2005; 103:1204–1210. [PubMed: 16306733]
13. Eckmann DM, Diamond SL. Surfactants attenuate gas embolism-induced thrombin production. *Anesthesiology*. 2004; 100:77–84. [PubMed: 14695727]
14. Eckmann DM, Lomivorotov VN. Microvascular gas embolization clearance following perfluorocarbon administration. *J Appl Physiol*. 2003; 94:860–868. [PubMed: 12571123]
15. Fahlman A, Dromsky DM. Dehydration effects on the risk of severe decompression sickness in a swine model. *Aviat Space Environ Med*. 2006; 77:102–106. [PubMed: 16491576]
16. Gempp E, Blatteau JE, Pontier JM, Balestra C, Louge P. Preventive effect of pre-dive hydration on bubble formation in divers. *Br J Sports Med*. 2009; 43:224–228. [PubMed: 18308884]
17. Haidekker MA, L'Heureux N, Frangos JA. Fluid shear stress increases membrane fluidity in endothelial cells: a study with DCVJ fluorescence. *Am J Physiol Heart Circ Physiol*. 2000; 278:H1401–H1406. [PubMed: 10749738]
18. Huang H, Kamm RD, Lee RT. Cell mechanics and mechanotransduction: pathways, probes, and physiology. *Am J Physiol Cell Physiol*. 2004; 287:C1–C11. [PubMed: 15189819]
19. Jacob AM, Gaver DP. An investigation of the influence of cell topography on epithelial mechanical stresses during pulmonary airway reopening. *Physics of Fluids*. 2005; 17:031502.
20. Kay S, Bilek A, Dee K, Gaver D III. Pressure gradient, not exposure duration, determines the extent of epithelial cell damage in a model of pulmonary airway reopening. *Journal of Applied Physiology*. 2004; 97:269. [PubMed: 15004001]
21. Klinger AJ, Pichette B, Sobolewski P, Eckmann DM. Mechanotransductional basis of endothelial cell response to intravascular bubbles. *Integrated Biology*. 2011
22. Kobayashi S, Crooks SD, Eckmann DM. Microembolism bubble contact and calcium signaling in bovine aortic endothelial cells in vitro. *Undersea and Hyperbaric Medicine*. 2011; 38:27–39. [PubMed: 21384761]

23. Moon RE. Bubbles in the brain: what to do for arterial gas embolism? *Crit Care Med.* 2005; 33:909–910. [PubMed: 15818131]
24. Mukundakrishnan K, Ayyaswamy PS, Eckmann DM. Bubble motion in a blood vessel: shear stress induced endothelial cell injury. *J Biomech Eng.* 2009; 131 074516(074511-074515).
25. Mukundakrishnan K, Ayyaswamy PS, Eckmann DM. Finite-sized gas bubble motion in a blood vessel: non-Newtonian effects. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2008; 78 036303(036301-036315).
26. Mukundakrishnan K, Eckmann DM, Ayyaswamy PS. Bubble motion through a generalized power-law fluid flowing in a vertical tube. *Ann N Y Acad Sci.* 2009; 1161:256–267. [PubMed: 19426324]
27. Mukundakrishnan K, Quan S, Eckmann DM, Ayyaswamy PS. Numerical study of wall effects on buoyant gas-bubble rise in a liquid-filled finite cylinder. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2007; 76 036308(036301-036315).
28. Newton HB, Burkart J, Pearl D, Padilla W. Neurological decompression illness and hematocrit: analysis of a consecutive series of 200 recreational scuba divers. *Undersea Hyperb Med.* 2008; 35:99–106. [PubMed: 18500074]
29. Pries AR, Secomb TW, Gaehtgens P. The endothelial surface layer. *Pflügers Arch.* 2000; 440:653–666. [PubMed: 11007304]
30. Sharan M, Popel AS. A two-phase model for flow of blood in narrow tubes with increased effective viscosity near the wall. *Biorheology.* 2001; 38:415–428. [PubMed: 12016324]
31. Sobolewski P, Kandel J, Klinger AJ, Eckmann DM. Air bubble contact with endothelial cells in vitro induces calcium influx and IP3-dependent release of calcium stores. *American Journal of Physiology-Cell Physiology.* 2011; 301:C679–C686. [PubMed: 21633077]
32. Suzuki A, Armstead SC, Eckmann DM. Surfactant reduction in embolism bubble adhesion and endothelial damage. *Anesthesiology.* 2004; 101:97–103. [PubMed: 15220777]
33. Swaminathan TN, Mukundakrishnan K, Ayyaswamy PS, Eckmann DM. Effect of a soluble surfactant on a finite-sized bubble motion in a blood vessel. *Journal of Fluid Mechanics.* 2010; 642:509–539. [PubMed: 20305744]
34. Voorhees A, Nackman G, Wei T. Experiments show importance of flow-induced pressure on endothelial cell shape and alignment. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Science.* 2007; 463:1409.
35. White CR, Frangos JA. The shear stress of it all: the cell membrane and mechanotransduction. *Philos Trans R Soc Lond B Biol Sci.* 2007; 362:1459–1467. [PubMed: 17569643]
36. Williams ST, Prior FG, Bryson P. Hematocrit change in tropical scuba divers. *Wilderness Environ Med.* 2007; 18:48–53. [PubMed: 17447715]
37. Zhang J, Eckmann DM, Ayyaswamy PS. A front tracking method for a deformable intravascular bubble in a tube with soluble surfactant transport. *Journal of Computational Physics.* 2006; 214:366–396.

Figure 1.
 $Re = 2$, $\lambda = 1$, and $H_D = 0.2$: Velocity vectors and streamlines as observed in: (A) an inertial frame attached to a point P on the vessel wall, (B) a frame moving with the steady state velocity of the bubble, and (C) close-up view of inertial frame streamlines near point P .

Figure 2.

Variation of normalized shear stress as a function of time for a given location on the lumen for (A) $Re = 0.2$, (B) $Re = 2$ and (C) $Re = 200$ with $\lambda = 0.9$ and $H_D = 0.2, 0.45$, and 0.6 . τ_{ref} is basal shear stress for the hematocrit basal state ($H_D = 0.45$) in the absence of a bubble and at steady flow conditions.

Figure 3. Variation of normalized shear stress as a function of time for a given location on the lumen for (A) $Re = 0.2$, (B) $Re = 2$ and (C) $Re = 200$ with $\lambda = 1$ and $H_D = 0.2, 0.45$, and 0.6 . τ_{ref} is basal shear stress for the hematocrit basal state ($H_D = 0.45$) in the absence of a bubble and at steady flow conditions.

Figure 4.

Variations of the magnitude of the maximum jump in shear stress value, maximum value of temporal shear stress gradient, and film thickness (minimum separation distance between the bubble interface and wall) normalized with respect to a representative endothelial glycocalyx surface layer thickness ($\approx 0.5 \mu\text{m}$) as a function of Ca for $Re = 200$, $H_D = 0.45$ and $\lambda = 1$.

Table I

Calculated values of H_C , δ , β , and μ_{layer} for various values of H_D and blood vessel sizes d .

Blood vessel	d (μm)	H_D	δ	H_C	β	μ_{layer} (cP)
Small arteriole	40	0.2	0.33	0.3	1.17	1.4
	40	0.45	0.2	0.55	1.4	1.74
	40	0.6	0.14	0.68	1.54	1.85
Large arteriole	100	0.2	0.12	0.21	1.16	1.4
	100	0.45	0.08	0.47	1.45	1.74
	100	0.6	0.06	0.62	1.64	1.97
Small artery	2000	0.2	0.004	0.2	1	1.2
	2000	0.45	0.004	0.45	1	1.2
	2000	0.6	0.004	0.6	1	1.2

Table II

Estimated values of non-dimensional parameters

The vessel sizes and the centerline velocities are obtained from (4).

D (μm)	U_{max} (cm s^{-1})	Re	Ca	We	Fr	Bi ($H_D = 0.45$)
40	1.75	0.2	2×10^{-2}	4×10^{-3}	0.88	0.0107
100	7.0	2	2.45×10^{-2}	4.9×10^{-3}	2.24	0.0035
2000	35.0	200	2.45×10^{-2}	4.9	2.5	0.012

Calculated non-dimensional values of shear stress jumps, temporal gradients, and film thicknesses for various values of H_D and blood vessels for the case of $\lambda = 0.9$ and 1.0.

Table III

Blood vessel	H_D	$\Delta\tau^* = \tau_{\max}^* - \tau_{\min}^*$				$\frac{\Delta\tau^*}{\Delta t^*} = \frac{\tau_{\max}^* - \tau_{\min}^*}{t_2^* - t_1^*}$				Film Thickness	
		$\lambda = 0.9$	$\lambda = 1$	$\lambda = 0.9$	$\lambda = 1$	$\lambda = 0.9$	$\lambda = 1$	$\lambda = 0.9$	$\lambda = 1$	$\lambda = 0.9$	$\lambda = 1$
Small arteriole ($Re = 0.2$)	0.2	2.2	8.2	8.8	50.4	3.4	0.9				
	0.45	2.8	8.2	11.9	56.6	3.7	0.95				
	0.6	3.1	8.2	21.0	47.4	3.8	1.0				
Large arteriole ($Re = 2$)	0.2	1.6	4.5	5.0	25.1	9.4	2.5				
	0.45	2.0	5.2	5.8	24.4	9.5	3.0				
	0.6	2.6	5.5	7.5	21.3	10.0	3.0				
Small artery ($Re = 200$)	0.2	2.5	4.4	7.4	10.6	33	71				
	0.45	4.6	7.1	16.9	27.5	158	111				
	0.6	6.8	9.4	22.1	33.9	200	168				