Theoretical and experimental intravascular gas embolism absorption dynamics

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Branger, Annette B., and David M. Eckmann. Theoretical and experimental intravascular gas embolism absorption dynamics. J. Appl. Physiol. 87(4): 1287–1295, 1999.—Multifocal cerebrovascular gas embolism occurs frequently during cardiopulmonary bypass and is thought to cause postoperative neurological dysfunction in large numbers of patients. We developed a mathematical model to predict the absorption time of intravascular gas embolism, accounting for the bubble geometry observed in vivo. We modeled bubbles as cylinders with hemispherical end caps and solved the resulting governing equations numerically. We validated the model using data obtained from video-microscopy measurements of bubbles in the intact cremaster microcirculation of anesthetized male Wistar rats. The theoretical model with the use of in vivo geometry closely predicted actual absorption times for experimental intravascular gas embolisms and was more accurate than a model based on spherical shape. We computed absorption times for cerebrovascular gas embolism assuming a range of bubble geometries, initial volumes, and parameters relevant to brain blood flow. Results of the simulations demonstrated absorption time maxima and minima based on initial geometry, with several configurations taking as much as 50% longer to be absorbed than would a comparable spherical bubble.

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and the tissue, leaving N₂ as the principal inert gas for diffusion. This assumption was made on the basis that these metabolic gases constitute a small fraction of the air embolism volume and have a much higher tissue and blood permeability than does the inert gas. The simultaneous exchange of multiple gases in the theoretical model of a spherical bubble has previously been addressed by Burkard and Van Liew (5). The initial rapid efflux of N₂ into the tissue, at the instant of bubble entrapment, was neglected. In addition, capillary perfusion was assumed to carry away the inert gas in the tissue, preventing buildup and causing a decrease in partial pressure of N₂ away from the bubble interface.

The initial configuration of the air embolism is modeled as a cylinder with hemispherical end caps, based on in vivo observations from preliminary experiments (Fig. 1, A and B). In vivo experiments also demonstrated that, once the bubble became lodged in the smaller arterioles of the microcirculation, the diameter of the vessels remained essentially constant over the time course of gas absorption. Vasocostriction occurred immediately on arrival of the bubble in the vessel and persisted for the duration of the embolism resorption. After the initial instant of entrapment, vasocostriction had no additional effect on lodged bubble geometry. The mathematical equations presented below incorporate these additional in vivo findings by dictating that, as the gas diffuses out of the IGE, the cylindrical portion of the bubble decreases in length, while the radius of the end caps remains fixed (Fig. 1C). The cylindrical portion eventually disappears, the remaining end caps fuse to form a sphere, and the bubble shrinks as such (Fig. 1D).

At the time of initial bubble entrapment, the bubble dimension in the radial direction is bounded by the vessel wall, whereas the bubble remains free to lengthen, creating an elongated cylinder with hemispherical end caps. The difference between the pressure inside and outside the bubble is balanced by the product of the surface tension and the curvature at the gas-liquid interface. This pressure difference (ΔP) is defined by Laplace's Law as ΔP = 2πR₀, where Rₐ is the bubble radius and  is the value for surface tension. Because vessel radius showed little or no change during absorption, interfacial shape of the end caps is assumed to remain fixed during collapse of the cylindrical section, and the internal pressure within the bubble also remains constant. Any increase in internal pressure would merely cause the bubble to elongate further. A constant internal pressure creates a uniform driving force for gas diffusion out of the bubble. It is not until the bubble is spherical that the internal pressure changes. As gas diffuses out from the sphere, the bubble radius decreases, causing an increase in bubble internal pressure, an increased driving force for gas diffusion, and, eventually, rapid bubble collapse.

Mathematically, this sequence can be represented in the following manner. At the initial time point when the bubble lodges, t = 0, the length of the cylindrical section of the bubble, l(t), is l(0) = l₀ (Fig. 1B). At t = T₁, the cylindrical portion of the bubble has completely disappeared, i.e., l(T₁) = 0, and the bubble becomes a sphere. During the time period 0 ≤ t ≤ T₁, the radius of the hemispherical caps, R(t), remains fixed at R(t) = R₀. For t > T₁, R(t) decreases until time T, when the bubble has completely collapsed, R(T) = 0.

The absorption process can, therefore, be described for two discrete increments in time: a cylindrical phase (0 ≤ t ≤ T₁) and a spherical phase (T₁ ≤ t ≤ T). Each portion is solved independently. The cylindrical model was solved by using Fick's Law

\[ \frac{\partial V_{bN₂}(t)}{\partial t} = -\frac{P_{bN₂}[R(t)]}{P_b} \ \frac{dV(t)}{dt} = -D\nabla C \cdot A \] (1)

in which V₁(t) is the volume of the inert gas at standard conditions, P₁(t) is the pressure inside the bubble, P₀ is the barometric pressure, and V(t) is the total volume of gas in the bubble at ambient pressure. Following earlier models (17), we equated the gas flux at the bubble interface at standard pressure to the change in total bubble volume at ambient pressure, denoted in Eq. 1. The diffusivity of N₂ in tissue is represented by D, C is the concentration of the inert gas in the tissue, and A is the surface area of the bubble. Substituting in the appropriate A for our geometry and with the expression \( \nabla C = \alpha_{t} \nabla P \), in which the product of the solubility and the pressure of the inert gas in the tissue, \( \alpha_{t} \) and P, respectively, replacing the concentration, we get

\[ \frac{dV(t)}{dt} = \frac{D \alpha_{t}}{P_{bN₂}[R(t)]} \left( \frac{P_b}{2\pi R_0[2R_0 + l(t)]} \right) \frac{dP}{dr} \mid_{r=R_0} \] (2)

The volume of the bubble is given by V(t) = 4πR³/3 + πR³/3(t). Because only the length of the cylinder changes as a function of time during the cylindrical phase, dV(t)/dt = πR³/3(t). The time rate of change of the length of the cylindrical portion is, therefore, expressed as

\[ \frac{dl(t)}{dt} = 2D \frac{\alpha_{t} P_b}{R_0 P_{bN₂}[R(t)]} \left( \frac{2R_0 + l(t)}{R_0 + l(t)} \right) \frac{dP}{dr} \mid_{r=R_0} \] (3)

The pressure inside the bubble, P₁(t), is defined as P₁(t) during the time 0 ≤ t ≤ T₁.

Fig. 1. In vivo and model intravascular gas bubble geometries. A: microscopic view of air bubble entrapped in rat cremaster arteriole. Bubble dimensions are length at time 0 (l₀) = 368 µm and radius at time 0 (R₀) = 33 µm. B: model bubble entrapment geometry at time 0. C: model bubble shape for 0 < t < T₁, where T₁ is time taken for collapse of cylindrical portion, after partial gas absorption. D: model air embolism configuration at t = T₁.
Determination of $P_{bN_2}(R_0)$ requires some simplifying assumptions. We assume the elastic force exerted by the vessel wall on the IGE is very small and can be ignored. We also neglect the effect of the hydrostatic head of blood pressure on the bubble, because it is very small in comparison to the value of $P_b$. Finally, we assume the amount of O$_2$ and CO$_2$ delivered to the tissue during bubble absorption maintains a steady tissue partial pressure of these gases. With the use of Laplace's Law, the expression for $P_{bN_2}(R(t))$ simplifies to

$$ P_{bN_2}(R(t)) = P_T + \frac{2\sigma}{R(t)} \tag{4} $$

The external pressure on the bubble, $P_T$, is the difference between $P_b$ working to collapse the bubble and $P_{bN_2}$, and $P_{tH_2O}$, the partial pressures of O$_2$, CO$_2$, and H$_2$O, respectively, in the tissue. During the cylindrical phase of gas absorption, the radius of the hemispherical end caps does not change, and $P_{bN_2}(R(t))$ is written as $P_{bN_2}(R_0) = P_T + 2\sigma/R_0$.

The driving force for collapse, $dP/dr$ at $r = R_0$, must be solved by using the diffusion equation. To solve for this term in Eq. 3, we begin with

$$ \frac{\partial C}{\partial t} = -D\nabla^2 C \tag{5} $$

First we substitute $C = \alpha_0 P'$, in which $P' = P - P_{bN_2}$, where $P$ is the partial pressure of N$_2$ in the shell around the bubble and $P_{bN_2}$ is the partial pressure of N$_2$ in the incoming arterial blood in locally perfused tissue. Assuming $\partial P'/\partial t = 0$ gives $\nabla^2 P' - 2\beta^2 P' = 0$. In this expression, $\beta$ represents the general elmination of N$_2$ from the tissue and is defined by $\beta = (Q_{\alpha0}/2D_{\alpha0})^{1/2}$, where the solubility of N$_2$ in blood is $\alpha_0$ and $Q$ is tissue perfusion. Accounting for the flux of N$_2$ across the entire surface area of the bubble, this expression becomes

$$ 2\frac{d^2P'}{dr^2} + \frac{3}{r}\frac{dP'}{dr} - 2\beta^2 P' = 0 \tag{6} $$

The boundary conditions for $P'(r)$ are

$$ P'(\infty) = 0 \tag{7} $$

and

$$ P'(R_0) = P_{bN_2}(R_0) - P_{aN_2} \tag{8} $$

The first boundary condition indicates that there is no gradient in N$_2$ far from the bubble. Equation 8 defines the magnitude of the N$_2$ gradient at the gas-liquid interface. Subject to these boundary conditions, the exact solution to Eq. 6 is

$$ P(r) = P_{aN_2} + \frac{[P_{bN_2}(R_0) - P_{aN_2}]0.25}{[K_{0.25}(\beta R_0)]0.25} \frac{K_{0.25}(\beta r)}{[K_{0.25}(\beta R_0)]0.25} \tag{9} $$

in which $K_i(n)$ represents a modified Bessel function of the second kind of order i. Equation 9 can be readily differentiated to evaluate the term needed to solve Eq. 3

$$ \frac{dP}{dr} \bigg|_{r = R_0} = -\beta[P_{bN_2}(R_0) - P_{aN_2}] \frac{K_{1.25}(\beta R_0)}{K_{1.25}(\beta R_0)} \tag{10} $$

Solving Eq. 3 for $l(t)$ gives

$$ l(t) = [2R_0 + l_0] e^{\lambda t} - 2R_0 \tag{11} $$

with

$$ \Phi = -2D_{\alpha_0} P_b \beta \frac{1}{R_0} \frac{[P_{aN_2}]0.25}{[K_{0.25}(\beta R_0)]0.25} \frac{K_{1.25}(\beta R_0)}{[K_{0.25}(\beta R_0)]0.25} \tag{12} $$

Equation 11 was solved numerically for Fortran (Lahey Computer Systems) on a 486–66 PC (Gateway 2000).

Once the IGE geometry becomes spherical, the transport equations are simpler to solve. The governing equations for $T_1 \leq t \leq T$ are, again, Fick's Law and the diffusion equation, and they yield the time rate of change of the radius, previously defined in Ref. 27 as

$$ \frac{dR(t)}{dt} = D_{\alpha_0} P_b \left\{ 1 - \frac{P_{aN_2}}{P_{bN_2}(R(t))} \right\} \left[ \frac{1}{R(t)} + \sqrt{2} \right] \tag{13} $$

With the use of the fourth-order Runga-Kutta method, Eq. 13 was also solved numerically with Fortran. The time to complete bubble absorption, $T$, defined at $R(T) = 0$, was calculated to within 0.01 min. Values for the physiological parameters simulating air bubbles in the cerebral circulation were obtained from the literature (11). We used $D = 6.22 \times 10^{-4}$ cm$^2$/min, $\alpha_0 = 2.092 \times 10^{-5}$ ml·cm$^3$ brain$^{-1}$·mmHg$^{-1}$, $\alpha_b = 1.855 \times 10^{-5}$ ml·ml·blood$^{-1}$·mmHg$^{-1}$, $Q = 0.525$ ml·blood$^{-1}$·min$^{-1}$, $\sigma = 0.0355$ mmHg/cm, $P_a = 760$ Torr, $P_{aN_2} = 428$ Torr, $P_{tO_2} = 40$ Torr, $P_{tCO_2} = 44$ Torr, and $P_{tiH_2O} = 47$ Torr. Our code was verified by running our model for the spherical case ($l_0 = 0$) and comparing the results to those previously published. Our predicted values were within $\pm 3\%$ of the values computed by Dexter and Hindman (11).

Model predictions for cerebrovascular embolism. We used the computer model and the same physiological parameters listed above to predict the absorption time for cerebrovascular bubbles with identical initial volumes but varying initial geometries by using a range of $l_0$ and $R_0$ to define an aspect ratio, $X = l_0/R_0$. The total time for bubble absorption, $T$, is $T = T_1 + T_2$, with $T_1$ and $T_2$ defined as the time taken for the collapse of the cylindrical and spherical portions, respectively. The values for $T_1$ and $T_2$ are calculated from Eqs. 11 and 13 to be

$$ T_1 = \frac{\lambda R_0}{\Phi} \ln \left( \frac{2}{2 + \lambda R_0} \right) \tag{14} $$

and

$$ T_2 = \frac{\lambda R_0}{\Phi} \ln \left( 1 + \frac{\lambda R_0}{\Phi} \right) \tag{15} $$

in which $\lambda = (2)^{1/2}\beta$. Formally, $P_{bN_2}(R^*)$, the pressure inside the bubble based on the time-averaged mean of the radius of the sphere, $R^*$, replaces the expression $P_{bN_2}(R(t))$, which behaves in a nonlinear time-dependent fashion. Initially, with larger values of $R$, $P_{bN_2}(R(t))$ is small; however, as the radius becomes very small, $P_{bN_2}(R(t))$ becomes extremely large. The nonlinear rise of internal pressure does not lend to easy calculation of $T_2$; therefore, we have made the approximation that $R \approx R^*$. We calculated the value of $R^*$ as a fraction, $n$, of the initial radius: $R^* = nR_0$. To find the value of $n$, we used the
expression

$$nR_0 = \frac{1}{T_2} \int_0^{T_2} R(t) \, dt = \frac{1}{T_2} \int_0^{R_0} T'(R') \, dR'$$  \hspace{1cm}(16)$$

Because each of the integrals in Eq. 16 equivalently represents the area under the radius-time curve, we evaluate the latter expression, because we can write $T'(R')$ explicitly as $T(R') = T_2(R_0) - T_2(R')$, giving

$$nR_0 = \frac{1}{T_2} \int_0^{R_0} \left[ \frac{1}{1 - \frac{P_{in}}{P_{a} + 2\pi\ln R_0}} \right] R_0 \, dR_0$$

Using Eqs. 15 and 17, we obtain the following expression for $n$

$$n = \frac{1}{R_0} \left[ \lambda R_0^2 - \ln (1 + \lambda R_0) - \lambda R_0' + \ln (1 + \lambda R_0') \right]$$

This result, however, did not consider a wide range of initial geometries, $X$, and bubble volumes.

All computer simulations used to obtain absorption times were run under very specific conditions. The embolism was assumed to be an air bubble, at 37°C, in a patient breathing a common postoperative CPB ventilation mixture (inspired O$_2$ fraction ($F_{I,O_2}$) = 0.4), at atmospheric pressure. Any changes in this set of conditions, such as a different ventilation gas mixture, an increase in external pressure, or hypothermic conditions, would change one or more of the given variables in the governing equation and provide a different set of results.

Animal model. Adult male Wistar rats ($n = 5$), weighing 200–425 g, were handled according to specifications set forth by the Animal Care and Use Committee and the University of Pennsylvania, in conformance with National Institutes of Health guidelines. Anesthesia was induced by inhalation of halothane (3%) in an air-O$_2$ mixture (0.30 ≤ $F_{I,O_2}$ ≤ 0.36). Blood pressure and heart rate were monitored with a catheter (PE 50) in the right carotid artery. The ventilation rate and $F_{I,O_2}$ were adjusted to keep arterial PO$_2$ ~ 100 Torr and arterial PCO$_2$ ~ 35 Torr, based on arterial blood-gas analysis (Corning pH Blood Gas System 168). A PE 50 catheter was also placed in the left jugular vein for intravenous (iv) administrations of the muscle relaxant pancuronium bromide (1 mg/kg iv), if needed. Additional catheters (PE 10) were inserted into the femoral artery of each leg for injection of air bubbles directly into the cremaster circulation. Body temperature was monitored with a rectal thermometer and maintained at 37°C with a heating pad.

The cremaster muscle was prepared as previously described (3, 19). Briefly, the cremaster muscle was exposed and separated from the surrounding tissue and organ through a midline incision, first in the scrotum and then the muscle itself. Loose connective tissue was carefully dissected away with forceps. The cremaster was then spread over a transparent pedestal built into the Plexiglas tray. Sutures were attached in five locations to keep the muscle flat on the platform. The cremaster was superfused at 2 l/min with a warmed (34°C), gassed (95% N$_2$-5% CO$_2$) Kreb’s buffer containing (in mmol/l) 132 NaCl, 25 NaHCO$_3$, 5 KCl, 1.2 MgCl$_2$, and 2 CaCl$_2$. The cremaster muscle was given 30 min to equilibrate before any experimentation was begun.

The cremaster circulation was visualized at a videomicroscopy workstation consisting of a compound microscope (Leitz Wetzlar), high-resolution television camera (Microimage Video CA2063), video image analyzer (Boeckeler VIA-150), monitor (Sony PVM-1343MD), and videocassette recorder (Panasonic AG1970). The components of this system enable visualization of arterioles 200–10 µm in diameter, determination of vessel dimensions with a video micrometer, observation of erythrocyte motion, and a videotaped recording of the experiment.

An initial record of baseline perfusion was made in the cremaster circulation after the equilibration period to determine control conditions of blood flow. To demonstrate the preservation of vascular responses during the preparation, a 0.75 ml bolus of 10⁻⁴ mol/l ACh, diluted in Kreb’s buffer, was added topically to the muscle, and vasodilation was verified. A discrete series of bubbles, ranging in number from two to eight, and in volume from 50 to 500 nl, was created in the femoral artery catheter and injected with a small (∼0.5 ml) bolus of 0.9% NaCl, a minimum of 10 min after the application of ACh. The large range of bubble volumes is permissible because individual bubbles break up before reaching the cremaster circulation. After injection, the entrapped bubble was located in the embolized artery and videotaped over time. In the event the entrapped bubble became dislodged, movements into the periphery were continuously tracked and recorded. The bubble was under constant observation until visualization was no longer possible because of either complete absorption or movement to a less favorable viewing area. Occasionally, the bubble failed to enter the cremaster circulation or lodges where visualization was difficult, in which case the procedure of bubble injection was repeated.

Bubble dimensions were measured every 20 s from the videotape by using the video micrometer. The volume of the IGE was calculated assuming a representative geometry (a cylinder with a hemispherical cap on each end) and axisymmetry in the vessel. Only bubbles with volumes between 1.0 and 6.0 nl were examined. Bubbles that lodged where no tissue perfusion from collateral vessels was evident were omitted from the study. Similarly, those bubbles that did not show the cylindrical geometry with hemispherical end caps were also excluded. This included bubbles in direct contact with one another, thereby not exhibiting the hemispherical end caps, or bubbles trapped in vessels with highly nonuniform diameters. Bubbles that continually changed their conformation because of constant dislodgment and reentrapment were also ignored, although occasional movement was permissible.

Validation of theory by experiment. The absorption times of bubbles from different experiments could not be compared with one another because of the dependence of the absorption time on initial bubble volume and the parameters of $I_0$ and $R_0$. No two bubbles in vivo had these same characteristics; therefore, the absorption times for the experimental bubbles were compared with both the theoretical model calculated specifically for the initial geometry in each case and a spherical bubble of the same volume, as shown in Table 1. The theoretical model was used to simulate each in vivo bubble by inserting the measured values of $I_0$ and $R_0$ and the physiological parameters corresponding to the experimental conditions into the Fortran code. The values for the parameters for this case were estimated to be $D = 6.14 \times 10^{-4}$ cm²/min (2, 29);
although this situation occasionally occurred in vivo. Peter was not accounted for in the mathematical model, for simplicity, bubble dislodgment to a vessel of different diameter was not calculated. For this initial radius, the computer simulation program calculated the bubble volume and derived a circulation. From the dimensions of initial bubble geometry, we remain the same as those previously defined for the cerebral circulation. From the dimensions of initial bubble geometry, the program calculated the bubble volume and derived a corresponding initial radius for a spherical bubble of the same volume. With this initial radius, the computer simulation then calculated the absorption time for the sphere. For simplicity, bubble dislodgment to a vessel of different diameter was not accounted for in the mathematical model, although this situation occasionally occurred in vivo.

### RESULTS

Preliminary observations. The air emboli observed in the rat cremaster circulation generally ranged in volume from 0.2 to 6.0 nl. All bubbles lodged having initial radii between 30 and 55 µm and initial lengths from 180 to 550 µm. These dimensions corresponded to an aspect ratio, \( X \), ranging in value from 4.3 to 11.2. An example of a bubble lodged inside a cremaster arteriole is shown in Fig. 1A.

In no case were the bubbles observed to pass through the capillaries and travel into the venous circulation. If the bubble did travel further downstream after initially lodging in a vessel, bubble movement could usually be described as “stick and slip.” Stick and slip refers to the fact that the bubbles travel at very inconsistent speeds, often becoming reentrapped and dislodging several more times in a vessel of fairly uniform diameter.

Validation of theory by experiment. To validate our theoretical model, we compared the experimentally measured absorption times with our theoretical predictions using the corresponding physiological values and initial bubble volume for both the in vivo and spherical bubble geometry. The theoretical model calculated longer absorption times for bubbles with the in vivo geometry than for spherical bubbles. The predicted differences in absorption times between the two geometries, in vivo and spherical, however, proved to be quite variable, depending on the initial configuration of the experimental bubble being simulated. In the majority of cases, our model using the in vivo geometry predicted the experimentally measured absorption times more closely than when the model assumed a purely spherical bubble. An example of the various measured and calculated absorption times is presented in Fig. 2. Both geometric models tracked the initial minutes (~4 min) of experimental bubble absorption well, but as the bubble volume became small (<0.5 nl), the in vivo configuration predicted the measured time more closely than did the spherical geometry. The absorption time of the experimental bubble was 22.0 min, and the accompanying theoretical predictions were 21.1 min with the use of the in vivo configuration and 16.4 min assuming a spherical shape. In the five cases examined, the predicted values for absorption times differed overall from the experimental absorption times by 12.1 ± 4.9 (SD)% for the in vivo geometry and by 20.1 ± 12.1% for the spherical configuration. Results from the predictive model were significantly different for the two geometries (Student's t-test, \( P < 0.01 \)).

Model predictions for cerebrovascular embolism. Our theoretical model was used to calculate the time rate of change of bubble volume for a cerebrovascular bubble of a given initial volume under different initial geometric configurations. The bubble volume was constrained at 2.5 nl, and the total absorption time was found for \( X = 0, 2.5, 10, \) and 20. The results of the computer simulations are presented in Fig. 3. Each bubble geometry gives a unique absorption curve based on initial geometry. The spherical bubble, \( X = 0 \), and the highly elongated bubble, \( X = 20 \), are predicted to have absorption times of 9.3 and 9.4 min, respectively, whereas a bubble of the same volume with \( X = 2.5 \) is predicted to take 13.3 min to be absorbed. The relationship between absorption times and \( X \) is, therefore, complex, neither

### Table 1. Measured and predicted embolism bubble absorption times

<table>
<thead>
<tr>
<th>Bubble Volume, nl</th>
<th>Aspect Ratio, X</th>
<th>Measured Time, min</th>
<th>Predicted Time, In vivo geometry, min</th>
<th>Predicted Time, Spherical geometry, min</th>
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<td>13.1</td>
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</tr>
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<td>4.4</td>
<td>9.0</td>
<td>11.4</td>
<td>8.9</td>
</tr>
</tbody>
</table>

\( \alpha = 2.103 \times 10^{-5} \text{ml} \cdot \text{cm}^3 \cdot \text{muscle}^{-1} \cdot \text{mmHg}^{-1} \) (2, 29); \( Q = 0.042 \text{ml blood} \cdot \text{cm}^3 \cdot \text{muscle}^{-1} \cdot \text{min}^{-1} \) (14); and 456 Torr \( \leq P_{\text{atm}} \leq 500 \text{Torr} \) (11). Those values not listed were assumed to remain the same as those previously defined for the cerebral circulation.

![Fig. 2. Measured and predicted absorption times for bubble having initial volume of 2.8 nl. In vivo measurement (large dotted line), prediction using initial in vivo bubble dimensions (dashed line), and prediction assuming spherical bubble of same initial volume (small dotted line) are shown.](Image)

![Fig. 3. Bubble volume during absorption for different initial aspect ratios (\( X = I_0/R_0 \)). All curves are for an initial volume of 2.5 nl. Aspect ratios shown are spherical bubble \( X = 0 \) (solid line), \( X = 2.5 \) (long dashed line), \( X = 10 \) (short dashed line), and \( X = 20 \) (dotted line).](Image)
monotonically increasing nor decreasing. The point of discontinuity in the slope in each of the three curves, $X = 2.5, 10,$ and $20$, represents the transition between the cylindrical and spherical solutions, which is missing, of course, in the purely spherical case.

Calculations of absorption times were also made at fixed initial bubble volumes ($0.5, 2.5,$ and $10$ nl) for varying initial geometries (Fig. 4). A maximum absorption time, $T_{\text{max}}$, exists on each curve of initial bubble volume clustered around $X = 2.6$. At $X = 0$, the absorption time corresponds to the time required for an initially spherical bubble to be absorbed, $T_{\text{sphere}}$. The predicted $T_{\text{sphere}}$ for a 10-nl bubble is 22.2 min, whereas $T_{\text{max}}$ for the same volume is predicted to be 33.6 min, an increase of 51% from $T_{\text{sphere}}$.

The time required for a spherical bubble to be absorbed is considered the minimum physiologically realistic absorption time possible. Although shorter absorption times are predicted, they are for $X \gg 20$. With this aspect ratio, bubbles would have a diameter smaller than a capillary, a geometry we consider to be physiologically irrelevant. Solid lines at $X < 0.3$ and $13.1$ in Fig. 4 indicate the range of aspect ratios in which bubble absorption time is within 80% of $T_{\text{max}}$. Of note, all of the in vivo experimental bubble configurations fell within this range of aspect ratios.

The computer model was used to calculate $T_{X}$, the time required for a bubble of initial volume, $V_{0}$, to be absorbed as a function of initial surface area, $A_{0}(X)$, over the range $0 \leq X \leq 25$. The resulting iso-initial volume curves, presented in Fig. 5, demonstrate the influence of initial surface area on absorption time. Presenting the data in the surface area domain resulted in similar trends, as were previously noted in Fig. 4. This representation of the data uniquely demonstrates that absorption time is a linear function of initial surface area for a given value of $X$ over a range of initial bubble volumes. Each curve shown has a unique maximum absorption time as well as a point at the far left corresponding to $T_{\text{sphere}}$. The maximum absorption time for each curve occurs at $X = 2.6$. These maxima form a locus of points linear in $A_{0}(X)$ with a slope of $m_{X} = 130.9$ mm$^2$/min ($R^2 = 0.9988$). The values of $T_{\text{sphere}}$ on each curve also fall along a straight line having a slope of $m_{0} = 97.5$ mm$^2$/min ($R^2 = 0.9940$). The slopes of these two lines were determined by linear regression by using the points illustrated in Fig. 5 and forcing the result through the origin. These two slopes were significantly different ($P < 0.001$, Student’s $t$-test to evaluate the difference in regressions).

By using the equation included in Fig. 5, $T_{X} = m_{X}A_{0}(X)$, the following simple expression can be used to determine $T_{X}$ based only on initial bubble volume, $V_{0}$, and the aspect ratio, $X$.

$$T_{X} = 2m_{X}A_{0}(X)(2 + X)(4/3 + X)^{-1/3}$$  \(19\)

in which $m_{X}$ is the slope of the line for a given value of $X$. Equation 19, with the values of $m_{2.6}$ and $m_{0}$ given above, yields predicted absorption times for $T_{\text{max}}$ and $T_{\text{sphere}}$ very close to those found by using the computer simulation based on Eqs. 14 and 15. A comparison of the two methods can be found in Table 2. This simplified approach with the use of the predicted slope accurately estimates the absorption times calculated by the computer model, with an average error <4% for $T_{\text{max}}$ and <6% for $T_{\text{sphere}}$.

**DISCUSSION**

Validation of theory by experiment. IGE is unfortunately a frequent and not completely avoidable complication of CPB surgery that can lead to serious neurological injury or death. To address areas of potential treatments for emboli, one must first understand the
behavior of gas bubbles in the vasculature as it relates to the bubble’s in vivo configuration (Fig. 1A).

Air emboli always remained in the arterial circulation until complete absorption, although they would occasionally dislodge and flow downstream. Transcapillary bubble passage has been reported (13, 26); however, we did not observe bubbles lodged in the venous circulation. This is because, at volumes small enough to fit into the capillaries, bubbles collapsed at a rate faster than they could physically move to the venules.

We have only applied our model to arterial air embolism absorption; however, bubbles have also been shown to enter the venous circulation (8), and they have frequently been observed intraoperatively by one of the authors (D. M. Eckmann) in the cephalic vein of surgical patients undergoing placement of a permanent central venous catheter. Those instances have been limited to patients having a distal peripheral iv catheter in the ipsilateral upper extremity, indicating air introduction through the iv catheter.

Our model, however, can easily be adapted to consider venous gas embolism, if desired. In the absence of external or interfacial stresses, surface tension dictates that bubbles would most prefer to assume a spherical shape, to minimize the surface area for a given volume. The increased distensibility of the venous vessels may initially allow bubbles to lodge more closely to their spherical configuration than if entrapped in the arteries. The inability of veins to vasoconstrict to the same degree as arteries makes it less likely that bubble dimensions, and therefore internal pressure, will change after entrapment.

The stick-and-slip movement observed by bubbles throughout the arterial vasculature has tribological implications of interfacial interactions between various physiological components. A layer of denatured proteins has been seen at the bubble-blood interface in vivo (21, 30). This network of denatured proteins may have some complex adhesive interactions with the glycoplyx or the endothelial cell membrane (10, 31). In addition, there may be other types of interactions present at the air-blood-vessel interface that affect interfacial mechanics such as contact-angle hysteresis with wetting and dewetting phenomena (4, 7).

The present theoretical model, taking the specific geometry of the in vivo IGE into account, was validated by using data from our animal experiments. Comparing the absorption times predicted by the theory to the measured absorption times demonstrated that using the in vivo configuration ($X = 0$) in the model led to predicted times that were significantly different from times calculated assuming a spherical shape ($X = 0$) and that more accurately matched the experimental data (Table 1).

Despite the improved accuracy, our model still underestimated the time of absorption in a majority of cases, compared with the animal data. This discrepancy may be due to the fact that the blood-borne matter that absorbs to the bubble interface potentially inhibits gas diffusion and prolongs bubble absorption (6, 28) but has not yet been taken into account in our mathematical model.

Model predictions for cerebrovascular embolism. The initial aspect ratio is an extremely important factor in determining the absorption time of an intravascular bubble, as seen from Eq. 14. The direct effect of the aspect ratio on the time rate of change of bubble volume is demonstrated in Fig. 3, in which a 2.5-nl bubble has markedly different absorption curves depending on initial geometry. The theoretical model, simulating cerebral IGEs, predicts that there exists a value of $X = l_0/R_0 ≈ 2.6$, which results in a maximum absorption time that is as much as 51% greater than if absorption is calculated for a spherical bubble with the same initial volume. All of the experimental IGEs lodged with initial geometries that were near the peaks of the curves shown in Figs. 4 and 5, suggesting that the in vivo bubbles lodge in configurations associated with longer absorption times.

The nonlinearity of absorption times as a function of aspect ratio, seen in Fig. 4, cannot be explained purely as an increase in initial bubble surface area leading to decreased absorption time (Fig. 5). This demonstrates that additional competing mechanisms are at work, such as constant internal bubble pressure. Both the maximum absorption time and the absorption time for a spherical bubble are linear functions of initial surface area over a range of bubble volumes, and the slopes of each of these lines are significantly different from one another. The results of these linear approximations can be used to construct an accurate simplified estimate of absorption time, as shown in Table 2. It is apparent that there is little difference in the bubble absorption times calculated by the full computer model and those times estimated with Eq. 19. Using Eq. 19 and a value of the aspect ratio at 2.6 or 0, therefore, provides a very simple, accurate means of predicting the maximum and minimum time of bubble absorption, respectively, given the initial volume. This slope equation could be useful in trying to estimate the bounds of residence time of bubbles found entrapped in the cerebral circulation, say by computed tomography or magnetic resonance imaging, and deciding whether or not to invoke a therapy such as hyperbaria.

The theoretical model lends considerable insight into the role of bubble geometry on the residence time of IGEs. In a clinical context, one would desire to minimize this or eliminate gas bubbles from the circulation altogether. Present methods of treatment include hyperbaric therapy and ventilation with gases containing lower concentrations of $N_2$. One avenue that still remains largely unexplored is manipulating bubble geometry, perhaps with the help of surface active agents. Inducing the bubbles to break up (25), or lodge with an elongated shape ($X > 15$), could potentially minimize the time for bubble absorption and until tissue blood flow is resumed. There are several additional issues associated with bubble geometry that must also be considered when assessing the potential adverse effects of a particular IGE conformation.
Whereas highly elongated (large X) bubbles are predicted to have a shorter residence time in the embolized vessel, a longer initial bubble length increases the contact area between the bubble and the endothelium. Endothelial cells are very susceptible to damage caused by contact with air and have been shown to release from the basement membrane or form gaps after being exposed to bubbles (1, 31). A larger surface area may also potentiate the activation of thromboinflammatory pathways. This induces additional responses, including platelet aggregation and local neutrophil sequestration (1, 21).

Bubbles lodging as spheres may minimize absorption time and endothelial contact area but may have other associated negative effects. Bubbles remaining close to the spherical shape after lodging would have the largest initial radius possible for a given volume. The embolized vessel in this case would be of larger diameter than if the bubble were elongated. Occluding a vessel of larger diameter could block blood flow and O₂ delivery to a larger vascular territory. The area of tissue ischemia and severity of neurological damage, therefore, would potentially be increased.

Clearly, physics and physiology related to IGEs are extremely complex. The theoretical model presented, based on in vivo bubble geometry, now allows some new issues heretofore ignored to be addressed. We have shown the importance of incorporating bubble geometry when the residence times of intravascular bubbles are predicted. With this theoretical model, we accurately predict the actual bubble absorption times measured in vivo. It is important to stress that these results apply to only one specific set of conditions: cerebral air embolism in a patient with normal blood gases at sea level and 37°C. Situations arise that would change these results and would have to be accounted for in the computer model. These situations include ventilating patients with different gas mixtures such as He and O₂, placing patients in a hyperbaric chamber, which increases the external pressure, or cooling or warming patients during CPB. By altering different parameters to simulate clinical situations, use of this model can be extended to predict the effects of various therapeutic maneuvers on their ability to accelerate IGE absorption. Such computer simulations may help form a better understanding of the factors influencing the deposition and absorption of cerebrovascular gas bubbles and lead the way for the development of more effective and innovative strategies in dealing with this important clinical problem.

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