Computer simulation of microscopic cerebral air emboli absorption during cardiac surgery

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Dexter F, Hindman BJ. Computer simulation of microscopic cerebral air emboli absorption during cardiac surgery. Undersea Hyper Med 1998; 25(1):43–50.—Microscopic cerebral arterial air emboli (MCAAE) cause neurologic injury during cardiac surgery. We used a mathematical model of gas absorption to gain a preliminary assessment of what physical or physiologic parameters affect MCAAE absorption in the setting of cardiac surgery with its unique set of normal values. Simulated MCAAE of radii 50 and 200 μm have absorption times of 2 and 32 min, respectively. Predicted absorption times depend dramatically on Pa_{N_2}. MCAAE are predicted to be absorbed twice as quickly at a Pa_{N_2} of 0 vs. 380 mmHg ($Fi_{O_2} \approx 0.50$). Moderate hypothermia (27°C) is predicted to cause only small decreases in absorption time. Changes in cerebral blood flow (for example, as affected by hemoglobin concentration, Pa_{CO_2}, Pa_{O_2}, collateral circulation, anesthetics, or cerebral metabolism) probably have only small effects on absorption time. Intravascular perfluorocarbons are predicted to cause small-to-moderate decreases in absorption time. In conclusion, there is probably only one important determinant of MCAAE absorption time during normothermic or moderately hypothermic CPB: arterial nitrogen partial pressure.

cardiac surgery, cardiopulmonary bypass, cerebral arterial air embolism, computer simulation, mathematical modeling

Microscopic cerebral arterial air emboli (MCAAE) are an important problem during cardiac surgery and cardiopulmonary bypass (CPB). Microbubbles (radius 25–150 μm) produced by bubble oxygenators (1,2) impair postoperative neuropsychologic performance (3). MCAAE can also originate from the operative field. Echocardiographic studies have shown that microbubbles are present in the left ventricle and/or ascending aorta of virtually all patients undergoing open-chamber procedures (4–6). Even in closed-chamber procedures, 15–50% of patients have intracavitary microbubbles (4,6). With removal of the aortic cross-clamp and resumption of left ventricular ejection, cardiac microbubbles enter the systemic and cerebral circulations. Accordingly, whenever embolic signals are detected in the heart or aorta by transesophageal echocardiography, emboli are detected in the cerebral circulation by transcranial Doppler (6,7). Thus, virtually all patients undergoing cardiac surgery are at risk of microscopic cerebral arterial air embolism at some point during the operation.

We have developed an animal model of cerebral arterial air embolism on and off CPB (8). Our studies suggest that inflammatory processes are important in the injury produced by MCAAE (9). However, inflammation is but one component of the pathophysiology of cerebral air embolism. Experimental studies of MCAAE show that air bubbles lodge in the vasculature, interrupting cerebral blood flow until the bubbles have been absorbed or pass downstream (10). Hence, the pathophysiology of MCAAE involves a form of transient cerebral ischemia. The kinetics and dynamics of MCAAE absorption may affect this injury. There is currently insufficient data to know: a) how long it takes for MCAAE of various sizes to be absorbed (seconds, minutes, or hours); and b) what experimental parameters have the greatest effect on absorption of MCAAE.

We considered using pial vessel preparations to answer these questions. However, they are not well suited to study MCAAE absorption. First, intravascular microbubbles do not remain totally stationary, but tend to migrate distally as they are absorbed (11,12). Second, pial vessel preparations can only examine short segments of single microvessels. As a result, pial vessel preparations cannot differentiate bubble absorption from downstream migration. Third, clinically and experimentally, MCAAE often occur in boluses consisting of numerous individual emboli of varying size. Thus, the distribution of MCAAE within the field of view of a pial vessel preparation is variable and unpredictable.

Mathematical modeling is an alternative approach for

gaining a preliminary assessment for determinants of MCAAE absorption. Because of the syndrome of decompression sickness, the physics of air absorption has been studied in detail (13,14). Mathematical models of gas absorption from blood and tissue have been developed (13,14). Hlastala and Van Liew's model of bubble absorption from tissue (14) applies to MCAAE lodging in the cerebral vasculature. Their model accounts for all major physical and physiologic processes controlling absorption of air collections and has been validated experimentally (15,16). In this paper, we use their model to gain a preliminary assessment of what physical or physiologic parameters affect MCAAE absorption in the setting of CPB, with its unique set of normal values.

METHODS

Since bubbles do not move in bulk from the vessel via the blood–brain barrier into the parenchyma (11,12), bubble absorption occurs by diffusion of nitrogen into the brain. Small spherical bubbles (MCAAE) are approximately spherical because of the strong effect of surface tension (17). From Ficks law for diffusion in the specified geometry (14), and using the coefficients defined in Table 1,

$$\frac{dR}{dt} = -\alpha_t D P_B \left(1 - \frac{P_{a_{N_2}}}{P_{b_{N_2}}}\right) \times \left(\frac{1}{R} + \lambda erf[\lambda (Dt)^{0.5}] + \frac{e^{-\lambda^2 Dt}}{(\pi Dt)^{0.5}}\right) \quad (1)$$

where

$$\lambda = \left(\frac{\alpha_{bl}\rho_t Q}{\alpha_t Q}\right)^{0.5} \quad (2)$$

and erf[ ] is the error function.

The pressures tending to collapse the bubble balance the sum of the partial pressures of all gases inside the bubble (16,18):

$$P_{b_{N_2}} + P_{b_{O_2}} + P_{b_{CO_2}} + P_{H_2O} = P_B + \frac{2\gamma}{R} + K\left(\frac{4}{3}\pi R^3\right) \quad (3)$$

The far-right term gives the pressure due to elastic force (i.e., the increase in intracranial pressure from the bubble). In normal brain, this term is very small compared to barometric pressure (e.g., < 2 mmHg ÷ 760 mmHg = 0.3%). We henceforth exclude it from the analysis. We have assumed that the bubble is surrounded by cerebral tissue. However, the bubble is delivered by the blood. A hydrostatic head of blood pressure may be present behind the bubble. This would act as an additional pressure on the right side of *Eq. 3* to cause the bubble to shrink. However, like intracranial pressure, this force (≤ arteriolar pressure) would be insignificant compared with the absolute gas pressure surrounding the body. Thus, this additional pressure can be neglected.

Equilibrium of metabolic gases (O_2 and CO_2) between bubble and surrounding tissue occurs in only a few seconds (16). Rearranging terms in *Eq. 3* and assuming equilibrium of metabolic gases between bubble and tissue (17,18),

$$P_{b_{N_2}} = P_B + \frac{2\gamma}{R} - \left(P_{t_{O_2}} + P_{t_{CO_2}} + P_{H_2O}\right) \quad (4)$$

Equation 4 assumes that the bubble does not deliver sufficient O_2 or CO_2 to the brain to increase Pt_{O_2} or Pt_{CO_2}. Since the volume of O_2 in MCAAE is small relative to cerebral O_2 delivery, this assumption is reasonable. Likewise, MCAAE contain a tiny volume of CO_2 vs. the volume cleared by the blood.

A numeric value was obtained or calculated for each physiologic parameter in the model (Table 2). Some comments are necessary. First, using a Pt_{CO_2} independent of temperature is strictly appropriate only for pH-stat blood gas management. However, the precise values for Pt_{O_2} and Pt_{CO_2} have no significant effect on the simulation results, because they have an effect only relative to P_B (*Eq. 4*). Second, we consider moderately hypothermic temperatures (27°C) but not profoundly hypothermic temperatures (17°C), because insufficient data are available for α_{bl} (*see* Table 3 of reference 19). Third, a small blood interface may exist behind the bubble. Since that blood will not be flowing, the interface could decrease regionally α_t by 16% to α_{bl} (Table 2). From *Eq. 2*, this change would decrease absorption time much less than the 50% decrease in Q considered in Results. By similar arguments, other interfaces (e.g., bubble to endothelium to basement membrane, etc.) are unlikely to have effects as large as those considered in Results.

We calculated, to within 0.01 min, the time required for the bubble (MCAAE) to be absorbed. This condition was arbitrarily considered to have been satisfied when the bubbles radius had decreased to less than 1 μm. *Equations 2* and *4* and numeric values for coefficients (Table 2) were substituted into *Eq. 1*. Then *Eq. 1* was numerically solved using Microsoft Fortran and IMSL FORTRAN implementation of the Runge-Kutta-Verner fifth- and sixth-orders method (Visual Numerics, Inc., Houston, TX). Adaptive stepsize control maintained the absolute error to less than 0.01 μm. Simulations were started at time 0.001 min, to avoid time 0.0 min at which *Eq. 1* is undefined. Computer

Table 1: Symbols, Definitions, and Units

Symbol	Definition	Unit
α_{bl}	solubility of N_2 in hemodilute blood	ml · ml^{-1} blood · mmHg^{-1}
α_t	solubility of N_2 in brain	ml · ml^{-1} blood · mmHg^{-1}
D	diffusivity of N_2 in cerebral tissue	cm^2 · min^{-1}
γ	surface tension	mmHg · cm
K	tissue elastic modulus	mmHg · ml^{-1} gas
Pa_{N_2}	partial pressure of N_2 in arterial blood	mmHg
Pb_{CO_2}	partial pressure of CO_2 in the bubble	mmHg
Pb_{N_2}	partial pressure of N_2 in the bubble	mmHg
Pb_{O_2}	partial pressure of O_2 in the bubble	mmHg
P_B	absolute gas pressure surrounding body	mmHg
P_{H_2O}	water vapor pressure	mmHg
Pt_{CO_2}	tissue partial pressure of CO_2	mmHg
Pt_{O_2}	tissue partial pressure of O_2	mmHg
Q	regional cerebral blood flow	ml blood · g^{-1} brain · min^{-1}
ρ_t	brain density	g brain · ml^{-1} brain
R	radius of spherical bubble	cm
t	time	min

Table 2: Numerical Values of Coefficients[a]

Symbol	Value	Temperature, °C	References and Comments
α_{bl}	1.89×10^{-5}	37	refer to note below table
	2.12×10^{-5}	27	from 37°C value using Table 4 of (19)
α_t	2.20×10^{-5}	37	refer to note below table
	2.47×10^{-5}	27	from 37°C value using Table 4 of (19)
D	6.22×10^{-4}	37	whole adult dog brain (25,26)
	4.72×10^{-4}	27	from 37°C value using Table 1 of (19)
γ	0.0355	37	quadratic interpolation of data from (27)
	0.0367	27	quadratic interpolation of data from (27)
Pa_{N_2}	360		
P_B	760		
P_{H_2O}	47.1	37	(28)
	26.7	27	(28)
Pt_{CO_2}	44		
Pt_{O_2}	40		
Q	0.51	37	adults undergoing bypass (29)
	0.30	27	adults undergoing bypass (29)
ρ_t	1.05		(30)

[a] Since $\alpha_{plasma} = 0.945 \times \alpha_{blood}$ at 37.3°C (31), and hemodilution for CPB halves the hemoglobin concentration, $\alpha_{bl} \cong [(1 + 0.945)/2] \times \alpha_{blood} = 0.972 \times (1.95 \times 10^{-5})$ from (32). Likewise, since $\alpha_t = 1.13 \times \alpha_{blood}$ at 37°C in rabbits (33), $\alpha_t \cong 1.13 \times (1.95 \times 10^{-5})$.

code was checked by comparing our calculations to those reviously reported (14)

We performed several simulations while one parameter was varied over a clinically relevant range, keeping all other variables constant at their normal values. By doing so, we determined which physiologic and physical parameters are predicted to have the greatest effect on MCAAE absorption. This approach permitted a quantitative assessment of the extent to which different interventions affect predicted MCAAE absorption time. For presentation purposes, we describe reductions in predicted absorption time caused by clinically attainable interventions as small (< 20%), moderate (20–50%), or dramatic (>50%).

RESULTS

Effect of emboli size on absorption time

Microscopic cerebral arterial air emboli occur with release of the aortic cross clamp and/ or with resumption of ejection (6,7,20). Even when surgery is done under hypothermic conditions (e.g., 17°– 33°C), the patient will have been rewarmed to near normothermia at this point in the operation. Thus, we chose to first model absorption of MCAAE under conditions that typify normothermic (37°C) CPB (Table 2). Absorption was simulated for MCAAE starting at radii of 50 or 200 μm. Such sizes are reasonable because MCAAE temporarily plug and then pass through the pial vessels, which have external radii of 25–150 μm (10). Predicted absorption times equal 2.3 and 32 min for MCAAE of radii 50 and 200 μm, respectively (Table 3). Once a MCAAE has decreased to a lesser volume, the remaining absorption time is nearly the same as that of a MCAAE starting at that smaller volume (not shown). As the MCAAE approach the size of erythrocytes (radii 2–4 μm) they can pass through capillary beds. Thus, model estimates for absorption times may slightly overestimate times emboli would remain in the brain.

Effect of arterial nitrogen partial pressure on absorption time

As shown in Table 3, the absorption time of MCAAE depends dramatically on arterial nitrogen partial pressure. We assume MCAAE have the composition of air (79% N_2, 21% O_2). The partial pressure of nitrogen in brain tissue is close to that of arterial blood. Consequently, brain nitrogen partial pressure is close to the fractional concentration of N_2 in the oxygenator or inspired gases. Replacing N_2 with O_2 in the inspired gas mixture increases the bubble–brain N_2 concentration gradient. This increase speeds the diffusion of N_2 from an air embolus to the surrounding tissue and, in turn, to the bloodstream. MCAAE are absorbed more than twice as quickly at an arterial nitrogen partial pressure of 0 mmHg than at 360 mmHg (Table 3). An arterial nitrogen partial pressure of ≅0 mmHg would be achieved by using 100% O_2 in the oxygenator, as performed at some clinical centers (21). An arterial nitrogen partial pressure of 360 mmHg would then be achieved by using a fractional concentration of O_2 of ≅0.50 in the oxygenator, as is also a common clinical practice.

Effect of temperature on absorption time

A wide range of temperatures is commonly used during CPB (e.g., 15°–39°C). Decreasing temperature could either decrease absorption time (by increasing solubility) or increase absorption time (by decreasing cerebral blood flow and diffusion). The computer simulations predict that decreasing temperature from 37° to 27°C causes a small increase in absorption time (Table 4).

Effect of regional cerebral blood flow on absorption time

Microscopic cerebral arterial air emboli decrease regional cerebral blood flow in two phases. First, a MCAAE obstructs flow by occluding a vessel. Once the MCAAE have been sufficiently absorbed, flow is restored. However, experimental studies show that cerebral blood flow subsequently declines (10). Decreases in cerebral blood flow caused by MCAAE would be expected to increase absorption times of remaining MCAAE. We studied the magnitude of this interaction. Fifty percent decreases in cerebral blood flow cause only slight increases in absorption time (Table 4). Decreases in cerebral blood flow to extremely low levels can cause moderate increases in absorption time for larger MCAAE (Table 4). However, this does not hold for smaller MCAAE. Even in the absence of cerebral blood flow, MCAAE absorption continues to occur by the process of N_2 diffusion. Overall, in the absence of severe reductions, the effect of cerebral blood flow is small. Thus, heterogeneity of perfusion (at both the regional and microcirculatory levels) is unlikely to have an important effect on absorption time. Likewise, changes in cerebral blood flow caused by hemoglobin concentration, arterial carbon dioxide partial pressure, arterial oxygen partial pressure, collateral circulation, volatile anesthetics, cerebral metabolism, or vasodilators such as nitroprusside are unlikely to have important effects on absorption time

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Effect of perfluorocarbons (blood nitrogen solubility) on absorption time

Intravascular perfluorocarbon emulsions are undergoing clinical evaluation for use during CPB. Hemodilution with perfluorocarbons increases blood N_2 solubility (22). Rabbits hemodiluted with perfluorocarbons have a greater

Table 3: Absorption Times for Cerebral Arterial Air Embolism During Normobaric CPB[a]

		Starting Radii 50 μm		Starting Radii 200 μm	
Pa_{N_2}, mmHg	Fi_{O_2}	absorption time, min	change, %	absorption time, min	change, %
360	0.5	2.3		32	
500	0.3	4.6	90	66	100
430	0.4	3.1	30	44	30
360	0.5	2.3	0	32	0
280	0.6	1.8	−22	25	−23
210	0.7	1.5	−35	21	−36
140	0.8	1.3	−44	18	−45
70	0.9	1.1	−51	16	−52
0	1.0	1.0	−57	14	−57

[a]Values for Fi_{O_2} in the second column were estimated from Pa_{N_2} using the relationship appropriate for cardiopulmonary bypass: $Pa_{N_2} = (P_B - P_{H_2O}) \times (1 - Fi_{O_2})$.

Table 4: Effect of Temperature and Regional Cerebral Blood Flow on Absorption Time[a]

		Starting Radii 50 μm		Starting Radii 200 μm	
Temperature, °C	Cerebral Blood Flow	absorption time, min	change, %	absorption time, min	change, %
37	0.51	2.3	0	32	0
27	0.30	2.6	13	38	16
37	0.60	2.3	0	32	−2
	0.51	2.3	0	32	0
	0.25	2.4	1	35	8
	0.10	2.4	2	37	15
	0	2.4	3	40	23
27	0.40	2.6	−1	36	−3
	0.30	2.6	0	38	0
	0.15	2.7	1	40	7
	0.10	2.7	1	41	10
	0	2.7	2	45	19

[a]Normal values for regional cerebral blood flow Q at 37° and 27°C equal 0.51 and 0.30 ml blood · g^{-1} brain · min^{-1} (Tables 1 and 2). Absorption times in the second row (27°C) are compared to those of the first row (37°C). Otherwise, results are reported relative to absorption times achieved using cerebral blood flows normal for CPB at 37° or 27°C.

Table 5: Effect of Blood N_2 Solubility on Absorption Time

		Starting Radii 50 μm		Starting Radii 200 μm	
α_{bl}	α_{bl}, % Increase	absorption time, min	change, %	absorption time, min	change, %
1.89×10^{-5}	0	2.3	0	32	0
3.78×10^{-5}	100	2.3	−2	30	−9
5.67×10^{-5}	200	2.2	−4	28	−15
7.56×10^{-5}	300	2.2	−6	26	−19
9.45×10^{-5}	400	2.2	−7	25	−23

rate of survival after cerebral arterial air embolism than do control rabbits (22). Likewise, rats given perfluorocarbons require injection of more intracarotid air to achieve complete flattening of the electrocorticogram than do saline-treated rats. Perfluorocarbons could be used during CPB to speed absorption of MCAAE. We therefore examined effect of changing blood N_2 solubility on absorption time. Blood N_2 solubility can be increased up to 400% with perfluorocarbon (23). Such changes in blood solubility are predicted to cause small to moderate decreases in absorption time for 50 or 200 μm MCAAE, respectively (Table 5).

DISCUSSION

Model validation

The terms in the mathematical model are physical (e.g., solubility of N_2 in cerebral tissue). The mathematical model that we used (14) has been validated experimentally (15,16). Thus, the results are probably reliable. The greatest potential problem with our study relates to how heterogeneity of perfusion (at both the regional and microcirculatory levels) might affect MCAAE absorption. Yet, the computer simulations show clearly that variation in cerebral blood flow does *not* have important effects on our results.

We would have liked to compare model predictions to experimental data. However, appropriate experimental data do not exist for effects of clinical maneuvers on absorption times. When air enters the cerebral circulation, large bubbles rapidly fractionate into smaller MCAAE. Thus, the sizes of MCAAE entering the cerebral circulation change and are not currently measurable or predictable. This experimental limitation is one reason why we addressed the questions in this study using mathematical modeling, instead of using our animal model of cerebral air embolism (8,9).

Some experimental data exist for bubble absorption times in the absence of intervention. The predicted time courses of MCAAE absorption are about the same as those observed experimentally. The model predicts absorption times of 2–32 min for MCAAE of radii 50–200 μm (Table 3). MCAAE can be seen microscopically when trapped in the pial vasculature. These vessels have radii of 25–150 μm (10). Fritz and Hossmann (24) found that MCAAE are cleared from the brain within 3–15 min of injection. Similarly, Helps et al. (10) found that air passes from pial arterioles within 1–6 min. Nevertheless, as considered in the Introduction, we were initially skeptical about the suitability of pial vessel preparations for the study of MCAAE absorption. The fact that our model predictions match these experimental values probably can be considered only weak support for our model. On the other hand, our model results may explain why absorption times match between pial vessel preparations and our simulation results. Our simulations predict that MCAAE of radii < 25 μm are absorbed within seconds. Thus, once MCAAE are small enough to clear pial arterioles, their remaining lifetimes are probably insignificantly short.

Application to experimental design

A dose-response relationship exists between the volume of air entering the cerebral circulation and neurologic outcome (9). The value of our modeling study is that it provides estimates for times required for absorption of MCAAE once entrapped in the brain. For bubbles smaller than 50 μm in radius, predicted absorption times are sufficiently short (≤2 min) that primary ischemic injury to the brain seems unlikely. In contrast, larger MCAAE are more likely to cause vessel occlusion of sufficient duration to cause primary ischemic injury. Hence, for MCAAE larger than 50 μm, interventions that substantively reduce absorption times may affect neurologic outcome, and thus should be controlled for in experimental studies.

The results of our simulation studies are clear. First, the model predicts that absorption time depends dramatically on arterial nitrogen partial pressure (Table 3). Eliminating N_2 from the blood is predicted to speed absorption by greater than 50%. Experimental studies of MCAAE must control for arterial nitrogen partial pressure. Second, the simulations predict that moderate decreases in temperature cause only small changes in absorption time (Table 4). Thus, experimental protocols probably do not need to tightly control temperature. Third, even marked changes in cerebral blood flow are predicted to have only small effects on absorption time (Table 4). Hence, many of the experimental variables that modify cerebral blood flow probably have little effect on MCAAE absorption. These include hemoglobin concentration, arterial carbon dioxide partial pressure, arterial oxygen partial pressure, collateral circulation, volatile anesthetics, cerebral metabolism, and vasodilators.

We have determined the physical parameter most likely to affect MCAAE absorption during cardiac surgery (arterial nitrogen partial pressure). However, the pathophysiology of MCAAE is complex and involves more than simple vessel occlusion. MCAAE damage cerebral endothelium, initiating a complex thrombo-inflammatory response that causes secondary injury (9). This secondary injury, mediated in part by leukocytes, occurs after MCAAE have been absorbed or cleared. Our study cannot address whether decreasing absorption times proportionately reduces the severity of endothelial injury and ensuing secondary processes. However, the implications of our studies are that when inflammatory processes that follow

MCAAE are considered, arterial nitrogen partial pressure needs to be tightly controlled.

Application to clinical studies

Usually, 60–90 min elapse from aortic clamp removal to the end of cardiac surgery. This interval exceeds the 32 min needed for absorption of a 200–μm MCAAE (Table 3). It is likely that MCAAE are present for most of the time patients remain in the operating room after CPB. Thus, clinical trials that change arterial nitrogen partial pressure have the potential to affect bubble absorption.

Some investigators are studying ways to rapidly extubate patients after cardiac surgery. One way to achieve rapid awakening of patients after CPB is to use nitrous oxide, a short-acting anesthetic. Our simulations show that MCAAE are probably present for the majority of the time patients remain in the operating room after CPB (Table 3). Nitrous oxide rapidly diffuses into air collections, such as MCAAE, and will dramatically increase their size. Thus, our simulations suggest that the use of nitrous oxide in the post-CPB period prolongs MCAAE absorption time.

Manuscript received June 1997; accepted September 1997.

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