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Theoretical Assessment of Normobaric Oxygen Therapy to Treat Pneumocephalus: Recommendations for Dose and Duration of Treatment

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Abstract

Background: Pneumocephalus has been linked to several clinical conditions, including headache, lethargy, and even brain herniation or death. The effects of different normobaric oxygen concentrations and durations of therapy on the rate of air absorption were examined.

Methods: An existing mathematical model of inert gas absorption was used. The model accounts for the major phenomena that determine absorption of bubbles, including surface tension, pressure dependence of bubble size, and removal of gases to the surrounding tissue. Sensitivity analysis tested reliability of our results.

Results: Times for a 50-ml air collection to have been absorbed were 5.8, 1.9, and 0.6 weeks at an FI_{O2} of 0.21, 0.4, and 1.0, respectively. Thirty percent and 72% of the air was absorbed in 2 days at an FI_{O2} of 0.4 and 1.0, respectively. The percent decrease in time for absorption achieved by increasing the FI_{O2} from 0.21 was nearly identical for different volumes of air. The benefit of increasing the FI_{O2} decreased with progressive increases in the FI_{O2}. Increasing the FI_{O2} from 0.21 to 0.4 caused the time to total air absorption to decrease by 67%. In

Graphics

contrast, increasing the FI_{O2} from 0.8 to 1.0 caused the time to total air absorption to decrease by an additional 3%.

Conclusions: Based on mathematical model predictions, an FI_{O2} of 0.4 or 1.0 for at least 1 week or 2 days, respectively, will significantly decrease the time for absorption of a pneumocephalus.

Key words: Bubble absorption. Computer simulation. Mathematical modeling. Pneumocephalus. Sensitivity analysis.

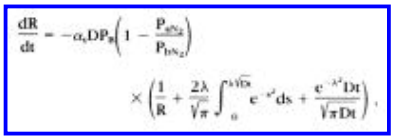
PNEUMOCEPHALUS is a common consequence of intracranial surgery. Reasoner et al. found, by retrospective review of head computed tomography (CT) scans, that 100% of patients have pneumocephalus in the first 3 days after craniotomy. [1] Although usually asymptomatic, postoperative pneumocephalus has been linked to a variety of clinical conditions, most commonly headache and lethargy. More serious sequelae include brain herniation or death. [2-7] To speed reabsorption of intracranial air, a therapy recommended by neurosurgical textbooks, and practiced at our institution, is the routine delivery of supplemental oxygen to patients after they have undergone craniotomy. [2] The proposed benefit of this therapy is to replace nitrogen with oxygen, which speeds absorption of intracranial air by increasing the diffusion gradient for nitrogen between the air collection and the surrounding cerebral tissue. Standefer et al. reported that they successfully treated symptomatic pneumocephalus after posterior-fossa procedures using conservative therapy with 100% $Oxygen_2$. [3] Normobaric oxygen therapy has also been claimed to reduce intracranial gas volume within 1 h. [2] In contrast, head CT data show that, in most patients (i.e., probably receiving nasal cannulae oxygen), more than 1 week is required for the air to be absorbed. [1] Therefore, supplemental oxygen therapy may increase the rate of absorption of pneumocephalus. However, neither the concentration of oxygen that should be delivered nor the necessary duration of therapy is known. The goal of this study was to assess the technique of using normobaric oxygen for treatment of pneumocephalus. In particular, we examined the effects of different oxygen concentrations and durations of therapy on the rate of air absorption.

Because of the syndrome of decompression sickness, the physics of air and bubble absorption have been studied in detail. A mathematical model of gas absorption has been developed. [8] It was validated by comparing its predictions with the absorption of inert gas bubbles in water, tissue, and subcutaneous gas pockets. [8,9] For example, rates of exit of argon from subcutaneous gas pockets were measured in rats. The model predicted the volumes and partial pressures of the collections of the inert gas as functions of time. The mathematical model accounts for the major phenomena that determine growth and absorption of air collections. These phenomena include surface tension, the pressure dependence of bubble size, and removal or addition of gases to the surrounding tissue. In this study, we applied this experimentally validated mathematical model to examine the dynamics of pneumocephalus absorption and the effect of oxygen therapy.

Methods

Predicting Size of the Air Collection

We consider a bubble of radius R (cm) at time t (min) surrounded by cerebral tissue. P_{bN2} represents the partial pressure of nitrogen in the bubble (mmHg). P_{aN2} (mmHg) represents partial pressure of nitrogen in arterial blood. P_B (mmHg) represents absolute gas pressure surrounding the body. The physical coefficients are the diffusivity of nitrogen in cerebral tissue (D, cm^2 *symbol* min sup -1), solubility of nitrogen in blood ($alpha_{bl}$, ml *symbol* ml sup -1 blood *symbol* mmHg sup -1), solubility of nitrogen in brain tissue (alpha sub t, ml *symbol* ml sup -1 brain *symbol* mmHg sup -1), brain density (rho_t, g brain *symbol* ml sup -1 brain), and regional cerebral blood flow (Q, ml blood *symbol* g sup -1 brain *symbol* min sup -1). From Fick's law for diffusion in a spherical geometry, [8] Equation 1 where Equation 2.



Equation 1

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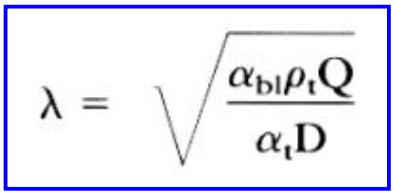

Equation 2

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The first term (1/R) in the right-hand most parentheses represents diffusion of nitrogen away from the bubble. The second and third terms represent effect of blood flow on transport of nitrogen out of the brain.

The pressures tending to collapse the bubble (P_B, pressure due to surface tension and pressure due to tissue elastic forces) balance the sum of the partial pressures of all gases (nitrogen, oxygen, carbon dioxide, and water) inside the bubble [9,10]: Equation 3, where gamma and K represent surface tension (mmHg *symbol* cm) and tissue elastic modulus (mmHg *symbol* ml sup -1 gas) coefficients, respectively. P_H sub 2 O represents water vapor pressure. The right-most term gives the pressure due to elastic forces (i.e., the increase in intracranial pressure from the bubble). This term is small compared to barometric pressure, even in the setting of profound intracranial hypertension (e.g., 40 vs. 760 mmHg). We henceforth exclude it from the analysis. Implications of this analysis are considered in the discussion section. Rearranging terms and assuming equilibrium of metabolic gases between bubble and tissue, [9,10] Equation 4 where P_{tO2} and P_{tCO2} represent the tissue partial pressures of oxygen and carbon dioxide, respectively.

$$P_{bN_2} + P_{bO_2} + P_{bCO_2} + P_{H_2O} = P_B + \frac{2\gamma}{R} + K\left(\frac{4}{3}\pi R^3\right).$$

Equation 3

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$$P_{bN_2} \approx P_B + \frac{2\gamma}{R} - (P_{bO_2} + P_{bCO_2} + P_{H_2O}).$$

Equation 4

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Physical Constants and Physiologic Parameters

A numeric value was obtained or calculated for each physical constant and physiologic parameter in the model. We used P_B = 760 mmHg and P sub H_2 O = 47 mmHg. Surface tension gamma [nearly equal] 0.03545 mmHg *symbol* cm sup -1. [11] Solubility of nitrogen in blood $alpha_{bl}$ [nearly equal] 1.855 *symbol* 10 sup -5 ml *symbol* ml sup -1 blood *symbol* mmHg sup -1. [12] Solubility of nitrogen in cerebral tissue $alpha_t$ [nearly equal] 2.092 *symbol* 10 sup -5 ml *symbol* ml sup -1 blood *symbol* mmHg sup -1. [12] Diffusivity of nitrogen in whole brain D [nearly equal] 6.22 *symbol* 10 sup -4 cm^2 *symbol* min sup -1. [13,14] Brain density rho_t = 1.05 g *symbol* ml sup -1. [15] Tissue partial pressures P_{tO2} [nearly equal] 40 mmHg, and P_{tCO2} [nearly equal] 44 mmHg. Cerebral blood flow for adult patients Q [nearly equal] 0.50 ml *symbol* g sup -1 brain *symbol* min sup -1. [16] We simulated the effect of varying the fraction of inspired oxygen (FI_O sub 2) on P_{aN2} with the use of the alveolar gas equation: Equation 5.

$$P_{aN_2} \approx (P_B - P_{H_2O}) \cdot (1 - FI_{O_2}).$$

Equation 5

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Numeric Methods

We calculated, to within 10 min, the time required for the air collection to be absorbed. This condition was arbitrarily considered to have been satisfied when the bubble's radius R had decreased to less than 1 micro meter. Equation 1 was numerically solved using IMSL FORTRAN's implementation of the Runge-Kutta-Verner fifth and sixth-orders method (Visual Numerics, Houston, TX). Adaptive stepsize control maintained the absolute error in the radius R to less than 1.0 micro meter. Simulations were started at time t = 0.001 min to avoid time t = 0.0 min, at which equation 1 is undefined.

Results

Simulations

We simulated absorption of pneumocephalus for different fractional inspired concentrations of oxygen (FI_{O2}). Times for a 50-ml

air collection to be absorbed to a volume of 1 ml (as visible on head CT) were 5.8 weeks, 1.9 weeks, and 0.6 weeks at an FI_{O2} of 0.21, 0.4, and 1.0, respectively (Figure 1). Most of the air was absorbed initially. For example, treatment with FI_{O2} of 0.4 or 1.0 for 1 day caused 16% or 44% of the air to be absorbed, respectively. After 2 days, 30% or 72% of the air was absorbed, respectively. At an FI_{O2} of 0.4, 79% of the air was absorbed within 1 week. There was a progressive decrease in the rate of decrease of volume (Figure 1). Larger volumes of air did not take much longer to be fully absorbed, especially at high FI sub O_2 (Figure 1). Once a large volume of air had decreased to a smaller volume, the remaining time to absorption was nearly identical to that of air collections that were originally of the smaller volume (not shown). The percent decrease in time for absorption achieved by increasing the FI_{O2} from 0.21 was nearly identical for different volumes of air (Figure 2). Hence, the relative effect of increasing the FI_{O} sub 2 did not depend on the starting volume of air. The benefit of increasing the FI_{O2} decreased with progressive increases in the FI_{O2} (Figure 2). For example, increasing the FI_{O2} from 0.21 to 0.4 caused the time to total air absorption to decrease by 67%. In contrast, increasing the FI_{O2} from 0.8 to 1.0 caused the time to total air absorption to decrease by an additional 3%.

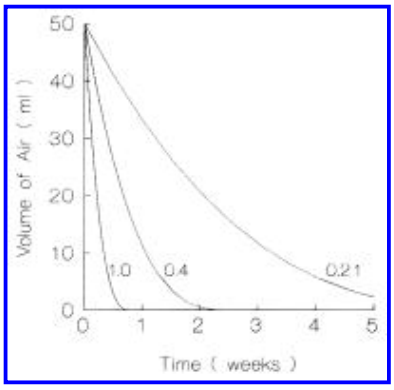

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Figure 1. Change in volume of pneumocephalus over time. Volume of the air collection is plotted as a function of time for an FI_{O2} of 0.21 (room air), 0.40, and 1.0.

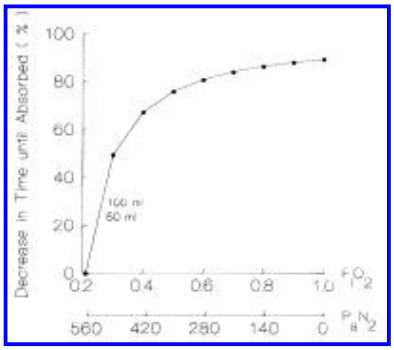

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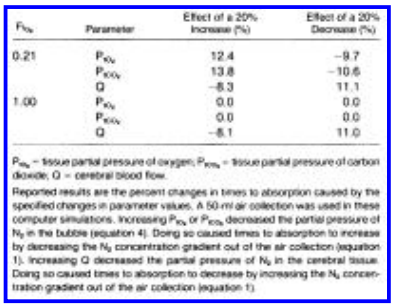
Figure 2. Effect of increasing the FI_{O2} from room air (0.21) on time to complete absorption of the pneumocephalus. Results were nearly identical for 50- and 100-ml collections of air. An FI_{O2} (unitless) and the corresponding partial pressure of nitrogen in arterial blood (P_{aN2}, mmHg) are given.

Sensitivity Analysis

The dependence of time to absorption on FI_{O2} may depend on our choice of the physiologic parameters: tissue partial pressure

of oxygen, tissue partial pressure of carbon dioxide, and cerebral blood flow. We repeated the simulations for 50 ml of air after increasing or decreasing these three parameters by 20% (Table 1). The precise values for the tissue partial pressures of oxygen and carbon dioxide had little effect on simulation results at an FI_{O2} of 0.21, because they had effects only relative to barometric pressure (Equation 4). Increasing or decreasing them by 20% changed the times to absorption by less than 14%. At higher FI_{O2}, the effects of changing these parameters were even smaller. Increasing or decreasing cerebral blood flow by 20% changed the times to absorption by less than 11%. Therefore, our results did not substantively depend on the numeric values we chose for the physiologic parameters.*.



$F_{I_{O_2}}$	Parameter	Effect of a 20% Increase (%)	Effect of a 20% Decrease (%)
0.21	$P_{t_{O_2}}$	12.4	−9.7
	$P_{t_{CO_2}}$	13.8	−10.6
	Q	−8.3	11.1
1.00	$P_{t_{O_2}}$	0.0	0.0
	$P_{t_{CO_2}}$	0.0	0.0
	Q	−8.1	11.0

$P_{t_{O_2}}$ = tissue partial pressure of oxygen; $P_{t_{CO_2}}$ = tissue partial pressure of carbon dioxide; Q = cerebral blood flow.

Reported results are the percent changes in times to absorption caused by the specified changes in parameter values. A 50-ml air collection was used in these computer simulations. Increasing $P_{t_{O_2}}$ or $P_{t_{CO_2}}$ decreased the partial pressure of N_2 in the bubble (equation 4). Doing so caused times to absorption to increase by decreasing the N_2 concentration gradient out of the air collection (equation 1). Increasing Q decreased the partial pressure of N_2 in the cerebral tissue. Doing so caused times to absorption to decrease by increasing the N_2 concentration gradient out of the air collection (equation 1).

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Table 1. Effect of Changing Values of Physiologic Variables on Results

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Discussion

Clinical Implications

Our model predicts the time course of intracranial air absorption. For example, treatment with FI_{O2} of 0.4 or 1.0 for 2 days causes 30% or 72% of the air to be absorbed, respectively. Greater than 90% of intracranial gas is absorbed in 2-4 weeks in typical postoperative patients (FI_{O2} of 0.21-0.4; Figure 1). Consistent with this prediction, Reasoner et al., using retrospective head CT data, observed that the incidence of detectable pneumocephalus decreases from 100% on postoperative day 1 to approximately 10% by the middle of the 4th postoperative week. [1].

The mathematical model also predicts that the rate of pneumocephalus absorption decreases with size of the air collection (Figure 1). Therefore, at all levels of oxygen therapy, most intracranial air is absorbed in the initial periods of oxygen therapy. This result is consistent with the head CT data. The percentage of patients with moderate or large air collections decreased faster over time than the percentage of patients with any amounts of intracranial air. [1].

The rate of air absorption varies greatly within the clinical range of supplemental oxygen concentrations (Figure 1 and Figure 2). An inspired oxygen concentration of 40% would decrease the time to total pneumocephalus absorption by 80% compared to room air (Figure 1 and Figure 2). Additional increases in the inspired oxygen concentration would cause additional decreases in the time required for pneumocephalus absorption, but to a lesser degree. The plateau of the gas absorption curve is reached at about an FI_{O2} of 0.4. An FI_{O2} of 0.4 is easily administered by a tight-fitting face mask. In addition, significant oxygen toxicity does not occur at an FI_{O2} of 0.50 or less. [17,18] Thus, an FI_{O2} of 0.4 seems to be reasonable to achieve a near maximal rate of absorption with minimal risk.

Our analysis addresses the duration of normobaric oxygen therapy that should be used to treat pneumocephalus. Standard clinical practice of many institutions is to administer supplemental oxygen to neurosurgical patients for the first 1 or 2 days after surgery. Oxygen therapy often is stopped when the patient is ambulatory and doing well from a pulmonary standpoint. However, the duration of oxygen therapy that our mathematical model predicts is necessary for complete pneumocephalus absorption of a 50-ml air collection varies from less than 1 week for an FI_{O2} of 1.0 to more than 5 weeks for an FI_{O2} of 0.21 (Figure 1). Therefore, when the decision is made to treat pneumocephalus, the duration of oxygen therapy probably should extend at least 1 week or 2 days with an FI_{O2} of 0.4 or 1.0, respectively. These required durations of therapy seem long to us. Therefore, when pneumocephalus is life-threatening, hyperbaric oxygen therapy is probably more appropriate than normobaric oxygen therapy. Furthermore, times to absorption will vary among patients (Table 1). When treating the pneumocephalus is considered important, response to therapy should be monitored (e.g., with CT).

An unresolved clinical question is whether complete absorption of pneumocephalus is important. Is it sufficient to reduce the air collection by a third or a half, or should the therapeutic goal be near or complete absorption of the pneumocephalus? Because intracranial air occupies space, the air can contribute to decreased intracranial compliance in patients with cerebral edema or space occupying lesions. Most concerning is the case of tension pneumocephalus, in which even a small amount of intracranial air can cause rapid neurologic deterioration. [2,4] However, some small pneumocephalus in a patient with normal intracranial pressure is of unclear significance. Markham attributed postoperative headaches to pneumocephalus in 40% of neurosurgical patients. [5] Pneumocephalus has been linked to severe headache, nausea, and vomiting after attempted treatment of spinal headaches with epidural blood patches or saline infusion. [6,7] In the latter case, the volume of air detected by CT was only 12-15 ml. Despite these reports, most cases of small (a few milliliters) pneumocephalus are probably asymptomatic. We know this to be true, because all patients have some pneumocephalus after craniotomy.

Mechanistic Implications

The predicted benefit of oxygen therapy for pneumocephalus is not from a higher FI_{O2} per se but from the decrease in inspired nitrogen (Equation 1). The composition of the pneumocephalus would be expected to be that of room air ([nearly equal] 79% N_2). The partial pressure of nitrogen in brain tissue reflects that of the blood, and in turn, the concentration of inspired nitrogen. Replacing nitrogen in the inspired gas mixture with oxygen increases the nitrogen concentration gradient. This increase speeds the diffusion of nitrogen from the air collection to the surrounding tissue and, in turn, to the bloodstream. Increasing the FI_{O2} per se does not significantly change bubble size, because oxygen rapidly equilibrates between bubble and tissue, and increasing the FI_{O2} does not significantly increase cerebral oxygen delivery and, therefore, the partial pressure of oxygen in brain tissue.

The model predicts that intracranial hypertension does not significantly increase the rate of pneumocephalus absorption (Equation 3). Therefore, although pneumocephalus can cause intracranial hypertension, the increase in intracranial pressure does not decrease the size of the air collection in a feedback manner. We show the reason for this result in Equation 3. The increase in intracranial pressure from the air collection would only significantly affect the rate of pneumocephalus absorption if the increase in intracranial pressure were large compared with barometric pressure. Even in the setting of profound intracranial hypertension (e.g., 40 vs. 760 mmHg), this condition does not occur.

Once a large volume of air has decreased, the remaining time to absorption is nearly identical to that of air collections that are originally of the smaller volume. This result is not obvious. A large air collection that decreases to the size of a smaller air collection is the same as the smaller air collection. However, nitrogen diffuses from the air collection into the surrounding tissue. Therefore, the air collection changes the partial pressure of nitrogen in the surrounding cerebral tissue. The mathematical model shows that nitrogen has a solubility and diffusivity in cerebral tissue sufficiently high that the time course of changes in the spatial distribution of nitrogen partial pressure in the surrounding brain is much quicker than the time course of absorption of the air collection.

Model Assumptions

The major limitation of our mathematical model is the assumption that the geometry of the air collection in the skull is spherical. This assumption probably does not affect our results. Pneumocephalus can take many shapes, as air fills the skull. Compressing the air collection will increase the surface area-to-volume ratio. Therefore, the rate of absorption will increase. On the other hand, the air is not entirely surrounded by well perfused brain. The cerebral ventricles and dura are relatively avascular. Therefore, the rate of absorption will decrease. In combination, these model underestimates and overestimates may cancel, but to an unknown extent. Furthermore, the sensitivity analysis (Table 1) shows that clinically relevant variations in the physiologic parameters of the mathematical model have no substantive effects on the clinical or mechanistic implications of our analyses.

We applied a mathematical model of air absorption to predict the effect of supplemental oxygen therapy on absorption of pneumocephalus. Indications for oxygen therapy to treat pneumocephalus are controversial. Nevertheless, based on mathematical model predictions, we can recommend how to rationally use normobaric oxygen therapy to treat pneumocephalus when the decision is made to do so. An FI_{O2} of 0.4 for at least 1 week will significantly decrease the time required for absorption of pneumocephalus. A higher FI_{O2} (e.g., 1.0) would be necessary to achieve significant air absorption within a couple of days.

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