Kinetics of absorption atelectasis during anesthesia: a mathematical model

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Joyce, C. J., and A. B. Williams. Kinetics of absorption atelectasis during anesthesia: a mathematical model. J. Appl. Physiol. 86(4): 1116–1125, 1999.—Recent computed tomography studies show that inspired gas composition affects the development of anesthesia-related atelectasis. This suggests that gas absorption plays an important role in the genesis of the atelectasis. A mathematical model was developed that combined models of gas exchange from an ideal lung compartment, peripheral gas exchange, and gas uptake from a closed collapsible cavity. It was assumed that, initially, the lung functioned as an ideal lung compartment but that, with induction of anesthesia, the Airways to dependent areas of lung closed and these areas of lung behaved as a closed collapsible cavity. The main parameter of interest was the time the unventilated area of lung took to collapse; the effects of preoxygenation and of different inspired gas mixtures during anesthesia were examined. Preoxygenation increased the rate of gas uptake from the unventilated area of lung and was the most important determinant of the time to collapse. Increasing the inspired O2 fraction during anesthesia reduced the time to collapse. Which inert gas (N2 or N2O) was breathed during anesthesia had minimal effect on the time to collapse.

Atelectasis develops with the induction of anesthesia. It is visible on computed tomography (CT) scans in 90% of healthy subjects as dependent lung densities (1, 6–10, 24–27). Clinical studies indicate that absorption atelectasis plays a key role in the genesis of anesthesia-related atelectasis (22).

Theoretical studies examining the effect of inspired gases on absorption atelectasis have suggested atelectasis is promoted by using N2O instead of N2 in the inspired gas mixture; critical ventilation-perfusion (VA/Q) is higher (3, 31), and, if complete airway occlusion occurs, then the time to collapse is shorter (11, 30). In contrast, the limited data available from clinical studies suggest that whether N2 or N2O is breathed during anesthesia has little effect on the amount of atelectasis (5). The theoretical studies assume that mixed venous inert gas concentrations are constant. This is valid at “steady state” but not during the induction of anesthesia, when inert gas concentrations in mixed venous blood change rapidly, particularly if N2O is administered.

This paper presents a theoretical mathematical model of the kinetics of absorption atelectasis during anesthesia that incorporates a model of peripheral inert gas exchange. This enables the kinetics to be studied during the early stages of anesthesia.

Methods

General description of the model. The model consists of two major compartments, lung and tissue. Before the induction of anesthesia, the lungs were modeled as an ideal lung, with normal ventilation. At the induction of anesthesia, the lung compartment is divided into two subcompartments, one of which continues to ventilate whereas the other is unventilated (see Fig. 1). The ventilated lung compartment is modeled as an ideal lung, whereas the unventilated lung is modeled as a closed collapsible cavity (11). The tissue compartment models peripheral inert gas exchange, tissue O2 extraction, and CO2 production. It consists of four peripheral tissue subcompartments as described by Wagner (29).

Initial conditions are set according to the scenario to be modeled. Gas exchange from each compartment is described by a series of differential equations. Integration with respect to time allows the gas contents of the various compartments to be plotted against time; of particular interest are the changes in volume within the unventilated lung compartment.

Preinduction phase. The preinduction phase allows the effects of preoxygenation to be examined. Anesthesia has not been induced, so airway closure has not occurred. The lungs were modeled as an ideal lung, consisting of two subcompartments, the alveolar compartment and the lung tissue compartment (see Fig. 2). The volume of the alveolar compartment (VA; 3,000 ml STPD) and that of the lung tissue compartment (VL,t,i, 600 ml) were maintained constant. Instantaneous equilibration of the gases between these two compartments is assumed. Gases dissolve in the lung tissue compartment according to their individual Ostwald solubility coefficients (κL,i). Inspired gas reaches the lung compartment at a rate VAI, and alveolar gas leaves at a rate VAE, where V is ventilation. Mixed venous blood perfuses the lung compartment, and perfusion limitation of gas uptake is assumed. Blood flow to the lung compartment and to the peripheral tissues was maintained constant at 6 l/min, giving a blood flow-to-alveolar volume ratio of 2:1. The tissue compartment consists of four peripheral tissue subcompartments (see Fig. 1): vessel-rich group (VRG), muscle group (MG), fat group (FG), and vessel-poor group (VPG) as described by Wagner (29). Each has its individual blood flow, volume, and solubility for each inert gas. Perfusion-limited gas transfer of inert gases between blood and the tissue compartments is assumed. The partial pressures of the inert gases in mixed venous blood are determined by the mixing of blood leaving the four tissue subcompartments. The tissue compartment extracts 250 ml O2 STPD/min and produces 200 ml CO2 STPD/min.

Initial conditions are set assuming that air has been breathed until equilibration has been reached (see Appendix A). The alveolar partial pressure of CO2 (PACO2) is set at 40 Torr, and other alveolar partial pressures are calculated by the ideal alveolar gas equation. The inspired ventilation to the lung compartment (i.e., VAI) that satisfies these initial conditions is calculated and then maintained constant (4.376 l/min STPD in the standard version of the model). Inert gas partial pressures in arterial and venous blood, and in the tissue compartments, are then set equal to alveolar values. At
The unventilated lung compartment (or pocket) represents dependent areas of lung, the airway to which doses at induction of anesthesia. The unventilated lung compartment is modeled as a closed collapsible cavity, where gas composition and volume vary with gas uptake but total pressure is maintained constant at barometric pressure (11). A lung tissue subcompartment was not included, because of previous work showing that including such a compartment makes minimal difference to the time the unventilated lung takes to collapse (11). Mixed venous blood perfuses the pocket, and perfusion limitation of gas exchange is assumed. The ventilated lung compartment and the peripheral tissue compartments are modeled in a similar manner as before induction of anesthesia.

Initial conditions for the postinduction phase depend on the scenario to be modeled (see Appendix C). The initial partial pressures of gases in the pocket and the ventilated lung compartment are set equal to the alveolar partial pressures at the end of the preinduction phase. Alveolar volume in the ventilated lung compartment (i.e., $V_A$) is reduced by the initial volume of the pocket (300 ml, which is 10% of preinduction alveolar volume in the standard version of the model), then maintained constant. Lung tissue volume in the ventilated lung compartment (i.e., $V_{L,ti}$) is reduced so that the ratio of lung tissue volume to alveolar volume is unchanged. The initial partial pressures of gases in the four tissue compartments are set equal to the pressures in the corresponding compartments at the end of the preinduction phase. Total lung blood flow is maintained constant at 6 l/min, but the blood flow per unit volume to the nonventilated lung is initially set at 1.5 times that of the lung as a whole. This gives a blood flow-to-alveolar volume ratio for the nonventilated lung compartment of 3:1 and that for the lung compartment (ventilated + nonventilated) of 2:1. This blood flow is then maintained constant, except where hypoxic pulmonary vasoconstriction (HPV) is incorporated into the model (see Appendix D). $V_{AI}$ is maintained constant at the preinduction value. Once initial conditions are set, the model is an initial-value problem, with 16 differential equations (see Appendix E), which is solved with Gill’s modification of the Runge-Kutta method (23).

Scenarios modeled. The changes in volume and composition within the pocket were examined for a variety of inspired gas mixtures during anesthesia. Each gas mixture consisted of $O_2$ and a single inert gas, either $N_2$ or $N_2O$. A range of $F_{I,O_2}$ from 0.21 to 1.0 was modeled, both with and without preoxygenation for 3 min. The effects of including or not including HPV in the model, varying the initial volume of the pocket from 1 to 30% of preinduction alveolar volume, and varying the duration of preoxygenation from 0 to 30 min were also examined. The program was written by using Think Pascal (Symantec) and run on a Macintosh LC with a Motorola 68882 math coprocessor.

**RESULTS**

Unless stated otherwise, the results presented in Figs. 3–5 and Table 1, and described in the following paragraphs are for the standard version of the model, with the initial volume of the pocket set at 10% of the preinduction alveolar volume, HPV incorporated, and with a preinduction time of 3 min. The pattern of results described here was consistent over all versions of the model.

The main result centered on the time that the pocket took to collapse. Preoxygenation for 3 min increased the
Fig. 3. Time to collapse of unventilated lung compartment. PreO$_2$, 3 min of preoxygenation. N$_2$ or N$_2$O is inert gas breathed after induction. Collapse occurred faster with preoxygenation than without. The higher the inspired O$_2$ fraction (FIO$_2$) after induction, the faster the collapse. Time to collapse is largely independent of whether inspired gas mixture after induction contains N$_2$ or N$_2$O.

rate of collapse substantially. For any given inspired gas composition after induction, collapse was at least four times faster with preoxygenation for 3 min than without. With preoxygenation for 3 min, collapse was complete in ~0.5 h even when air was breathed postinduction; when FIO$_2$ was 1.0 postinduction, collapse was complete in <10 min. In contrast, without preoxygenation, collapse took >4 h when air was breathed; collapse took >0.5 h when FIO$_2$ was 1.0 postinduction. Both with and without preoxygenation, the higher the FIO$_2$, after induction, the faster the rate of collapse. Without preoxygenation, the time to collapse was largely independent of whether N$_2$ or N$_2$O was breathed after induction. With preoxygenation for 3 min, breathing N$_2$O rather than N$_2$ after induction reduced the time to collapse by no more than 31%. Including HPV in the model prolonged the time to collapse, and this effect was greater without preoxygenation. These findings suggest that the presence or absence of preoxygenation is the most important determinant of the kinetics of absorption atelectasis during anesthesia, that the FIO$_2$ after induction plays an important though lesser role, and that whether N$_2$ or N$_2$O is breathed after induction is unimportant.

The second result of interest was the changes in composition and volume of the pocket (see Fig. 4, A-D). In all scenarios, the partial pressure of CO$_2$ in the pocket (PpCO$_2$) equilibrated rapidly with the mixed venous partial pressure of CO$_2$ (PvCO$_2$). The partial pressure of O$_2$ in the pocket (PpO$_2$) always equilibrated with the mixed venous partial pressure of O$_2$ (PvO$_2$) before the pocket had collapsed, but if preoxygenation had been performed and then high FIO$_2$ breathed, equilibration was not reached until late in the time course of pocket collapse.

With no preoxygenation, equilibration of PpO$_2$ with PvO$_2$ took ~2 min.

If N$_2$O was breathed after induction (see Fig. 4A) the mixed venous partial pressure of N$_2$ (PvN$_2$) fell and the mixed venous partial pressure of N$_2$O (PvN$_{2O}$) rose, favoring movement of N$_2$ out of the pocket and N$_2$O into it. Because of its higher solubility, N$_2$O moved in faster than N$_2$ moved out, so the pocket expanded. The partial pressure of N$_2$O in the pocket (PpN$_{2O}$) followed PvN$_{2O}$ closely, except that the PpN$_{2O}$-PvN$_{2O}$ gradient sometimes widened during rapid fluxes of O$_2$ and CO$_2$. The partial pressure of N$_2$ in the pocket (PpN$_2$) never approached equilibration with PvN$_2$. After the early rapid gas fluxes, gas left the pocket at a relatively rapid rate. Volume fell slightly as O$_2$ and CO$_2$ equilibrated with mixed venous blood, rose as N$_2$O entered the pocket, then fell as a gradient for both N$_2$ and N$_2$O to leave the pocket was established.

If N$_2$ was breathed after induction (see Fig. 4B), volume fell rapidly as O$_2$ and CO$_2$ equilibrated with mixed venous blood. A state of constant composition was soon reached, where PpN$_2$ substantially exceeded PpN$_{2O}$, and gas left the pocket at a relatively slow rate, determined mainly by the PpN$_2$-PvN$_2$ gradient and the relatively low solubility of N$_2$.

For the same FIO$_2$, which inert gas was breathed after induction did not greatly affect the PpN$_2$-PvN$_2$ gradient after the rapid early gas fluxes.

With preoxygenation for 3 min, the pocket initially contained mainly O$_2$, so despite rapid initial uptake from the pocket, equilibration of PpO$_2$ with PvO$_2$ took 5–7 min.

If N$_2$O was breathed after induction (see Fig. 4C), PpN$_{2O}$ rose, causing influx of N$_2$O into the pocket, and PpN$_2$ roughly followed PpN$_{2O}$-PvN$_{2O}$ fell slowly with N$_2$ washout from the tissue compartment. PpN$_2$ rose initially as N$_2$ was concentrated by uptake of other gases, then fell slowly. Volume fell rapidly until PpO$_2$ equilibrated with PvO$_2$, then fell more slowly.

If N$_2$ was breathed after induction (see Fig. 4D), PpN$_2$ was maintained or rose, depending on the FIO$_2$. In both cases, PpN$_2$ was at first higher than PpN$_{2O}$, so N$_2$ moved into the pocket; PpN$_2$ rose because of flux into the pocket and the concentration of N$_2$ in the pocket by O$_2$ uptake; when PpN$_2$ rose above PpN$_{2O}$, N$_2$ flux out of the pocket began. Volume fell rapidly until PpO$_2$ equilibrated with PvO$_2$, then fell more slowly.

For the same FIO$_2$, which inert gas was breathed after induction made little difference to the PpN$_2$-PvN$_2$ gradient after the rapid early gas fluxes.

The initial volume of the pocket varied from 1 to 30% of preinduction alveolar volume (f = 0.01–0.3) and compared with the standard model (f = 0.1). The overall pattern of results was similar: preoxygenation for 3 min substantially increased the rate of collapse; breathing high FIO$_2$, postinduction increased the rate of collapse, but this effect was smaller than that of preoxygenation; and which inert gas was breathed after induction made little difference. However, the size of the initial volume of the pocket did affect the absolute time to collapse. For most scenarios, as the size of the pocket increased, so did the time to collapse, but there were some exceptions. If the difference between the time to collapse at f = 0.01 and the time to collapse at the f of interest are expressed as a percentage of the time to
collapse at \( f = 0.1 \), then the maximum difference was 
-12% at \( f = 0.01 \), -7% at \( f = 0.05 \), 19% at \( f = 0.20 \), and 49% at \( f = 0.3 \).

The duration of preoxygenation varied from 0–60 min (see Fig. 5). Longer preoxygenation decreased the time to collapse. This effect was greater at low postinduction \( F_{iO_2} \). Most of the effect occurred as the preoxygenation time was increased from 0 to 3 min; longer preoxygenation produced relatively small reductions in the time to collapse.

**DISCUSSION**

With the induction of anesthesia, functional residual capacity (FRC) falls by 20%, and atelectasis is visible on CT scans as dependent lung densities. The amount by which FRC is reduced, and the size of the area of atelectasis, is independent of whether intravenous or inhalational anesthesia or muscle relaxation is used, intermittent positive pressure ventilation is used, or spontaneous ventilation is maintained (7). The average
amount of atelectasis seen on CT scans after induction corresponds to 8–10% of the whole lung (21), so not all the decrease in volume is due to atelectasis.

Atelectasis during anesthesia could be caused by three basic mechanisms (20): compression atelectasis, loss of surfactant atelectasis, or absorption atelectasis. Initially, it was thought that compression atelectasis was the major mechanism (1), but more recent work has shown that very little atelectasis develops during anesthesia if preoxygenation is avoided and O2 and N2 with an FIO2 of 0.3 is breathed after induction (22). This argues strongly for gas absorption being the main mechanism. Absorption atelectasis can occur by either complete airway occlusion (16, 19) or by reduction of the inspired V˙A/Q˙ to below a critical level (3).

With the induction of anesthesia, diaphragmatic tone is reduced and FRC falls (27). If FRC is reduced below closing capacity, airway closure will occur. Beyond the site of airway closure, gas will be trapped during at least part of the respiratory cycle, with a predisposition to absorption atelectasis. The importance of muscle tone and changes in FRC in the genesis of atelectasis is illustrated by ketamine anesthesia. With ketamine anesthesia, muscle tone is maintained, FRC does not change, and atelectasis does not develop; only if muscle paralysis is added do FRC fall and atelectasis develop (27).

Theoretical and clinical studies. Gunnarson et al. (5) examined the amount of atelectasis that developed on CT scans after induction of anesthesia and muscle paralysis. Two groups were examined: one breathed a mixture of N2O and O2 with an FIO2 of 0.4 after induction, and the other received a mixture of N2 and O2 with an FIO2 of 0.4. Atelectasis was present on scans 10 min after induction and progressively increased on subsequent scans, with no difference between the two groups. Dantzker et al. (3) calculated the effect of inert gas solubility and FIO2 on critical V˙A/Q˙ with a theoretical model. He found that, when a mixture of O2 and an inert gas with an FIO2 of 0.4 is breathed, critical V˙A/Q˙ was 20 times greater when the inert gas was N2O than when it was N2. This suggests that more extensive atelectasis should develop when N2O instead of N2 is breathed. Joyce et al. (11) calculated the time that an area of lung takes to collapse, when the airway comes occluded. If the same gas mixture was breathed before and after the occlusion, the calculated times for collapse were 214 min (11) for 30% O2–70% N2 and 8 min (11) for 30% O2–70% N2O. Webb and Nunn (30) calculated that, if air was breathed before the occlusion and 30% O2–70% N2O afterward, complete absorption took just over 100 min. This suggests that atelectasis develops more rapidly when N2O is breathed instead of N2 and is consistent with the results from an experimental dog model (2, 12). However, neither the calculations nor the experimental models were designed to mimic the gas fluxes during the early phases of N2O uptake during anesthesia, as they assume that mixed venous gas partial pressures remain constant. This explains the difference between the results of these studies and the results of Gunnarson et al. (5).

Fig. 5. Effect of varying duration of preoxygenation. Time to collapse for a range of preoxygenation times (middle; min) when a mixture of N2O and O2 (FIO2 = 0.21–1.0) was breathed postinduction (left) and when a mixture of N2 and O2 was breathed postinduction (right) is shown. Longer preoxygenation decreased time to collapse, with most of this effect occurring as preoxygenation time was increased from 0 to 3 min.

Table 1. Prediction by the model of the time after induction of anesthesia that the unventilated area of lung takes to collapse

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<th>FIO2</th>
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<th>HPV</th>
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<tbody>
<tr>
<td>N2</td>
<td>N2O</td>
<td>N2</td>
</tr>
<tr>
<td>PreO2</td>
<td>PreO2</td>
<td>PreO2</td>
</tr>
<tr>
<td>0.21</td>
<td>29.7</td>
<td>267.9</td>
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<tr>
<td>0.25</td>
<td>23.2</td>
<td>184.3</td>
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<tr>
<td>0.3</td>
<td>18.7</td>
<td>133.6</td>
</tr>
<tr>
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<td>14.0</td>
<td>87.6</td>
</tr>
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<td>11.6</td>
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</tr>
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<td>10.2</td>
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<tr>
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<td>8.7</td>
<td>39.1</td>
</tr>
<tr>
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<td>8.2</td>
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<table>
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<th>N2</th>
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<tbody>
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<tr>
<td>0.1</td>
<td>29.7</td>
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</table>

Values are the time to collapse (min). FIO2, inspired O2 fraction. Predictions are given both with hypoxic pulmonary vasoconstriction (HPV) incorporated and without, with preoxygenation for 3 min (PreO2) and without, and with the inert gas in the inspired gas mixture after induction being N2 or N2O.
and muscle paralysis. One group (high-FIO₂ group) was ventilated with an FIO₂ of 1.0 during induction, then subsequently with N₂ and O₂ with an FIO₂ of 0.4. The other group (low-FIO₂ group) was ventilated with N₂ and O₂ with an FIO₂ of 0.3 during and after induction. In the high-FIO₂ group, there was more atelectasis on the 20-min scan than on a control scan before induction, whereas atelectasis was minimal on both scans in the low-FIO₂ group. Some of the low-FIO₂ group were also scanned at 70 min, and there was more atelectasis than earlier. Our model predicts that with preoxygenation and breathing of O₂ and N₂ with an FIO₂ of 0.4, complete collapse will take <20 min, whereas without preoxygenation and breathing O₂ and N₂ with an FIO₂ of 0.3, complete collapse will take >2 h. If ventilation with an FIO₂ of 1.0 during induction of anesthesia is analogous to preoxygenation in our model, then our predictions agree with the findings of Rothen et al.

Limitations of the model. The model assumes that atelectasis develops because of complete airway closure at induction of anesthesia, with subsequent absorption of trapped gas. With complete airway closure, atelectasis is inevitable; altering inspired gas composition can only affect time to collapse. With ventilation at a low Vₐ/Q, altering inspired gas composition affects not only time to collapse but also critical Vₐ/Q, which may determine whether atelectasis develops.

The timing of airway closure during anesthesia has not been well defined by experimental studies. If airway closure does not occur until several minutes after induction, then gas in the alveoli at induction will be largely replaced by gas breathed subsequently. The gas breathed before induction would have little effect on gas uptake from unventilated lung. There is evidence that airway closure occurs very early during anesthesia. First, the gas breathed during induction is critical in determining the amount of atelectasis that develops (22). This argues that airway closure occurs before washout of alveoli with the postinduction inspired gas. Second, atelectasis can be demonstrated on CT scans at 10 min after induction. Even with complete denitrogenation by prolonged breathing of an FIO₂ of 1.0 before airway closure, a lung unit will take ~8 min to collapse when an FIO₂ of 1.0 is breathed after airway closure (11). This suggests that airway closure must have occurred very early, to allow sufficient time for collapse to occur.

Perfusion limitation of inert gas uptake from the lung is assumed, but this is widely accepted in the physiological literature (28). Although equilibration of O₂ and CO₂ between gas in the unventilated area of lung and the blood perfusing it may not be complete under some circumstances, this should not introduce significant error into calculations of gas uptake (11). Before induction, the lung has been modeled as an ideal lung, and after induction the ventilated lung compartment has been modeled as an ideal compartment. This is unlikely to result in significant error if the lungs are normal.

The model assumes that cardiac output, O₂ consumption, CO₂ production, and inspired alveolar ventilation remain constant. Many anesthetic agents reduce cardiac contractility, and cardiac output often falls with the induction of anesthesia. O₂ consumption and CO₂ production usually fall by ~10%. Most anesthetic agents depress respiratory drive, and minute ventilation falls in the spontaneously breathing subject. In the mechanically ventilated subject, minute ventilation will be maintained. The model does not incorporate the tidal nature of ventilation or the pulsatile nature of cardiac output.

The distribution of blood flow between the ventilated and unventilated lung compartments will vary with the vascular resistances of the two compartments. Because of HPV, these resistances will vary with the alveolar partial pressure of O₂ (PAO₂), PDo₂, and PVBar. The adjustment for HPV is given in Appendix E and is based on data from Marshall et al. (18). N₂O obtunds the HPV response (4). There are insufficient data to quantify the effect of HPV in the presence of N₂O, but the effect should lie between the extremes of normal HPV and no HPV. The results for these extremes are presented in this study.

If a circulation time delay between peripheral tissues and the lung is not included in models of inert gas uptake, significant errors are only present in the first 2 min of uptake or elimination (17). The lack of such a time delay in our model is unlikely to introduce significant error, because the shortest time to collapse found by the model was over 7 min. Varying the volume of any of the four peripheral tissue subcompartments by ±20% did not change the time to collapse by <4%.

In normal lung, diffusion equilibrium exists between the lung tissue and gas in the alveoli, but this is not necessarily the case as an area of lung collapses. An analysis of gas uptake from unventilated lung has shown that this does not result in >10% error in predicted times to collapse of an area of unventilated lung (11).

Explanation of the findings of the model. First, we consider the standard version of the model when air is breathed before induction. Because of the low solubility of N₂, the limiting factor determining how long the pocket takes to collapse is N₂ uptake. When the airway closes, the amount of trapped N₂ is the same regardless of what is breathed afterward. Uptake of N₂ is determined by N₂ solubility and the PPn₂-PV₂ gradient. For the same postinduction FIO₂, which inert gas was breathed postinduction made little difference in the time to collapse or in the PPn₂-PV₂ gradient.

This may be explained by the following argument. After the early rapid gas fluxes, PpO₂ and PpcO₂ have equilibrated with PV₂ and PVCO₂, whereas barometric pressure (Pb) and the saturated vapor pressure of water (PH₂O) are constant; the sum of the partial pressures of inert gases in the pocket equals Pb - PH₂O - PV₂ - PVCO₂, which is constant for a given FIO₂, regardless of which inspired gas mixture is breathed. When no N₂O is breathed, PPn₂ = Pb - PH₂O - PV₂ - PVCO₂. When N₂O is breathed, PPn₂ closely approxi-
mates $P_{N_2}^{\text{eq}}$, so $Pp_{N_2} = P_B - PH_2O - PV_{O_2} - PV_{CO_2} - PV_{N_2}^{\text{eq}}$. Thus when $N_2O$ instead of $N_2$ is breathed, $Pp_{N_2}$ is reduced by an amount approximately equal to $PV_{N_2}^{\text{eq}}$. Therefore, the $Pp_{N_2} - PV_{N_2}^{\text{eq}}$ gradient is the same whether $N_2O$ or $N_2$ is breathed postinduction, provided that any change in $PV_{N_2}^{\text{eq}}$ is matched by an opposite change in $PV_{N_2}^{\text{eq}}$. Consider the two extremes, “induction” and “equilibration of tissue gas exchange.” At induction, only air has been breathed, so $PV_{N_2}^{\text{eq}}$ is independent of whether $N_2O$ or $N_2$ will be breathed later. At equilibration of tissue gas exchange, the inert gas partial pressures in the tissues, mixed venous blood, and the ventilated lung compartment are equal (ignoring the small effect of blood perfusing the pocket); $P_B = PH_2O + PACO_2 + PAO_2 + PV_{N_2}^{\text{eq}} + PV_{N_2}^{\text{eq}}$; at a given $FIO_2$, $PH_2O$, $PACO_2$, and $PAO_2$ are not affected by which inert gas is breathed postinduction; thus any difference in $PV_{N_2}^{\text{eq}}$ between breathing $N_2$ or $N_2O$ postinduction must be matched by an opposite change in $PV_{N_2}^{\text{eq}}$. Therefore, at these two extremes, the $Pp_{N_2} - PV_{N_2}^{\text{eq}}$ gradient will be the same regardless of which inert gas is breathed, providing the $FIO_2$ is the same. Between these points, the $Pp_{N_2} - PV_{N_2}^{\text{eq}}$ gradient will be the same only if the time course of gas uptake in the partial pressures of $N_2$ and $N_2O$ are similar in the various compartments. Wash-in of gas into the ventilated lung compartment, and equilibration of the vessel-rich compartment with the ventilated lung compartment, is rapid for both $N_2$ and $N_2O$, largely complete within 5 min. The half-life (min) for changes in $N_2$ in the tissue groups are VRG (1.02), MG (22.7), FG (169), and VPG (113) and for $N_2O$ are VRG (0.74), MG (26.1), FG (75), and VPG (113) (29). The only major difference between the two gases is in the FG, which receives only 5% of cardiac output. Thus for a given $FIO_2$, once the initial rapid equilibration of $PP_{O_2}$ and $PP_{CO_2}$ with mixed venous blood has occurred, the $Pp_{N_2} - PV_{N_2}^{\text{eq}}$ gradient, and therefore the time to collapse, will be similar whether $N_2O$ or $N_2$ is breathed postinduction.

Second, consider the standard version of the model when preoxygenation is performed. Most of the gas in the pocket is $O_2$, which is rapidly taken up until $Pp_{O_2}$ is maintained or rises, depending on the $FIO_2$; there is a greater flux of $N_2$ into the pocket during the rapid phase of gas uptake than if $N_2O$ was breathed, so the amount of $N_2$ in the pocket at the start of the slow uptake phase is greater and time to collapse is slightly longer.

Finally, consider the effect of variations from the standard model. The main effect of preoxygenation is to wash $N_2$ out of the lung compartment, reducing the initial amount of $N_2$ in the pocket. This washout is virtually complete within 3 min. Further preoxygenation will wash $N_2$ out of other compartments, reducing $PV_{N_2}$, and hence time to collapse, but this effect is much smaller.

Once $PP_{O_2}$ equilibrated with $PV_{O_2}$, it was lower than $PP_{O_2}$ in the ventilated lung compartment. If HPV was included in the model, blood flow was then diverted away from the pocket, so collapse took longer than without HPV. With preoxygenation, the equilibration of $PP_{O_2}$ with $PV_{O_2}$ did not occur until most of the gas had left the pocket, so the effect of HPV was relatively small.

Most of the $N_2$ uptake from the pocket occurred after equilibration of $PP_{O_2}$ with $PV_{O_2}$. After this equilibration, $PP_{O_2}$ always exceeded alveolar partial pressure of $N_2$. Blood from the pocket and the ventilated lung compartment combines to form arterial blood. As the pocket size increases, the fraction of cardiac output passing to it increases; alveolar partial pressure of $N_2$ and, hence, $PV_{N_2}$ rise, reducing the $Pp_{N_2} - PV_{N_2}^{\text{eq}}$ gradient, so collapse takes longer. This general pattern does not apply to all scenarios, because gas fluxes before equilibration of $PP_{O_2}$ with $PV_{O_2}$ may override this effect.

Conclusion. Preoxygenation before the induction of anesthesia will promote atelectasis. After induction, addition of $N_2$ or $N_2O$ to the inspired gas mixture will retard atelectasis. Our model predicts that whether the inert gas is $N_2O$ or $N_2$ will have little effect on the development of atelectasis. This prediction is quite the opposite of what has been predicted previously on theoretical grounds, but it is entirely in keeping with the limited experimental evidence to date. Further experimental studies addressing this question are awaited with interest.

APPENDIX A

Calculation of Initial Conditions for the Preinduction Phase

The $FIO_2$ is set to 0.21, inspired $N_2$ fraction ($FIO_2$) to 0.79, and the inspired $N_2O$ fraction ($FIO_2$) to 0. The inspired partial pressures ($P_{O_2}$, $P_{N_2}$, and $P_{N_2O}$) are calculated by

$P_{O_2} = FIO_2 (PB - PH_2O)$

$P_{N_2} = FIO_2 (PB - PH_2O)$

$P_{N_2O} = FIO_2 (PB - PH_2O)$

$P_{CO_2}$ is set at 40 Torr. Equilibration with air is assumed, so the ideal alveolar gas equation applies. The respiratory quotient (RQ) is 0.8, so

$PAO_2 = P_{O_2} - (PAO_2/RQ) [1 - FIO_2 (1 - RQ)]$

Because the $CO_2$ efflux in the expired alveolar ventilation must equal $CO_2$ production ($V_{CO_2}$) at BTPS

$\dot{V}_{AE} = \dot{V}_{CO_2} \cdot CF \cdot (PB - PH_2O) / PAO_2$

where $CF$ is the STPD-to-BTPS correction factor.
Because at equilibration the only gas exchange is O2 and CO2:

\[
V_{AI} = V_{AE} + CF \cdot (\dot{V}O_2 - \dot{V}CO_2)
\]

where \(\dot{V}O_2\) is O2 uptake, this value of \(V_{AI}\) is maintained constant throughout the program.

Because there is no inert gas exchange

\[
P_{AN2} = P_{IN2} \cdot V_{AI}/V_{AE}
\]

and

\[
P_{AN2O} = P_{IN2O} \cdot V_{AI}/V_{AE}
\]

where \(P_{AN2}\) and \(P_{AN2O}\) are the alveolar partial pressures of N2 and N2O, respectively.

---

\[
\frac{dPAO_2}{dt} = [\dot{V}_{AI} \cdot P_{O_2} - \dot{V}_{AE} \cdot PAO_2 + CF \cdot \dot{Q} \cdot (C\dot{V}O_2 - CAO_2) \cdot (Pb - PH_2O)]/(VA + Vl,ti \cdot \lambda_l,ti_0) \tag{B1}
\]

\[
\frac{dPA_{N2}}{dt} = [\dot{V}_{AI} \cdot P_{N2} - \dot{V}_{AE} \cdot PAN2 + \dot{Q} \cdot \beta_{N2} \cdot (P\tau_{N2} - P_{AN2}) \cdot (Pb - PH_2O)]/(VA + Vl,ti \cdot \lambda_l,ti_0) \tag{B2}
\]

\[
\frac{dPA_{N2O}}{dt} = [\dot{V}_{AI} \cdot P_{N2O} - \dot{V}_{AE} \cdot PAN2O + \dot{Q} \cdot \beta_{N2O} \cdot (P\tau_{N2O} - P_{AN2O}) \cdot (Pb - PH_2O)]/(VA + Vl,ti \cdot \lambda_l,ti_{N2O}) \tag{B3}
\]

\[
\frac{dPA_{CO_2}}{dt} = [-\dot{V}_{AE} \cdot PA_{CO_2} + CF \cdot \dot{Q} \cdot (C\dot{V}CO_2 - CA_{CO_2}) \cdot (Pb - PH_2O)]/(VA + Vl,ti \cdot \lambda_l,ti_0) \tag{B4}
\]

where \(\beta\) is the solubility of inert gas in blood expressed as milliliters BTPS of gas per deciliter of blood per millimeters Hg at 37°C, and CF is defined as in Appendix A.

\[
\frac{dPAO_2}{dt} + \frac{dPA_{CO_2}}{dt} + \frac{dPA_{N2}}{dt} + \frac{dPA_{N2O}}{dt} = 0
\]

so there are five equations with five unknowns, which are initially solved for \(V_{AE}\) by using the false-position method, then Eqs. B1–B4 are solved by substitution.

Differential equations governing gas exchange in the peripheral tissues.

\[
\frac{dPV_{RGN1}}{dt} = (P_{N2} - P_{VPG1}) \cdot \dot{Q}_{VPG}/(\lambda V_{PG1} \cdot V_{PG}) \tag{B5}
\]

\[
\frac{dPM_{G1}}{dt} = (P_{N2} - P_{MG1}) \cdot \dot{Q}_{MG}/(\lambda V_{MG1} \cdot V_{MG}) \tag{B6}
\]

\[
\frac{dPF_{G1}}{dt} = (P_{N2} - P_{FG1}) \cdot \dot{Q}_{FG}/(\lambda V_{FG1} \cdot V_{FG}) \tag{B7}
\]

\[
\frac{dPV_{PG1}}{dt} = (P_{N2} - P_{VPG1}) \cdot \dot{Q}_{VPG}/(\lambda V_{PG1} \cdot V_{PG}) \tag{B8}
\]

\[
\frac{dPV_{RGN2}}{dt} = (P_{N2} - P_{VPG2}) \cdot \dot{Q}_{VPG}/(\lambda V_{PG2} \cdot V_{PG}) \tag{B9}
\]

\[
\frac{dPM_{G2}}{dt} = (P_{N2} - P_{MG2}) \cdot \dot{Q}_{MG}/(\lambda V_{MG2} \cdot V_{MG}) \tag{B10}
\]

\[
\frac{dPF_{G2}}{dt} = (P_{N2} - P_{FG2}) \cdot \dot{Q}_{FG}/(\lambda V_{FG2} \cdot V_{FG}) \tag{B11}
\]

\[
\frac{dPV_{PG2}}{dt} = (P_{N2} - P_{VPG2}) \cdot \dot{Q}_{VPG}/(\lambda V_{PG2} \cdot V_{PG}) \tag{B12}
\]

APPENDIX B

Procedure Followed by the Program To Solve the Differential Equations Used in the Runge-Kutta Method During the Preinduction Phase

Calculation of arterial and venous partial pressures. \(PAO_2\), \(PA_{CO_2}\), \(PA_{N2}\), and \(PA_{N2O}\) are known. Arterial partial pressures \(PAO_2\) and \(PA_{CO_2}\) are set equal to alveolar partial pressures. \(CAO_2\) and \(CA_{CO_2}\) are calculated from \(PAO_2\) and \(PA_{CO_2}\).

\[
C\dot{V}O_2 = CAO_2 - \dot{V}O_2/\dot{Q}
\]

and

\[
C\dot{V}CO_2 = CA_{CO_2} - \dot{V}CO_2/\dot{Q}
\]

Venous partial pressures of inert gas are calculated by

\[
P\tau_{N2} = (Q_{VRG} \cdot PV_{RGN2} + Q_{MG} \cdot PM_{G2} + Q_{FG} \cdot PF_{G2}) + Q_{VPG} \cdot PV_{PG2}/\dot{Q}_{tot}
\]

and

\[
P\tau_{N2O} = (Q_{VRG} \cdot PV_{RGN2O} + Q_{MG} \cdot PM_{G2O} + Q_{FG} \cdot PF_{G2O}) + Q_{VPG} \cdot PV_{PG2O}/\dot{Q}_{tot}
\]

where \(\dot{Q}_{tot}\) is total \(\dot{Q}\).

Differential equations governing gas uptake from the lung compartment.
APPENDIX C

Initial Conditions in the Postinduction Phase

At induction, the lung compartment is divided into an unventilated lung compartment (pocket volume \( Vp \)) and a ventilated lung compartment (alveolar volume \( VA \) and lung tissue volume \( Vl, ti \)). Partial pressures in the ventilated and unventilated lung compartments are set equal to alveolar partial pressures at the end of the preinduction phase. Partial pressures in the four tissue compartments are set equal to the pressures in the corresponding compartments at the end of the preinduction phase. Call the alveolar volume of the lung compartment before induction \( VAPre \), and the lung tissue volume of the lung compartment prior to induction \( Vl, tiPre \).

The operator sets the ratio \( f \), where \( f = Vp/VAPre \)

\[
Vp = f \cdot VAPre
\]

The volumes in the pocket corresponding to each gas (BTPS) are calculated

\[
VpO2 = Vp \cdot PAO2/(PB - PH2O)
\]
\[
VpCO2 = Vp \cdot PACO2/(PB - PH2O)
\]
\[
VpN2 = Vp \cdot PpN2/(PB - PH2O)
\]
\[
VpN2O = Vp \cdot PpN2O/(PB - PH2O)
\]

\( VAI \) is maintained constant at the preinduction value

\[
VA = (1 - f) \cdot VAPre
\]
\[
Vl, ti = (1 - f) \cdot Vl, tiPre
\]

APPENDIX D

Procedure Followed by the Program to Solve the Differential Equations Used in the Runge-Kutta Method During the Postinduction Phase

Calculation of arterial and venous partial pressures. Call the volume of the unventilated lung compartment “pocket volume”

Pocket volume = \( VpO2 + VpCO2 + VpN2 + VpN2O \)

The partial pressures of each gas in the pocket are calculated

\[
PP02 = (PB - PH2O) \cdot VpO2/pocket volume
\]
\[
PPCO2 = (PB - PH2O) \cdot VpCO2/pocket volume
\]
\[
PPN2 = (PB - PH2O) \cdot VpN2/pocket volume
\]
\[
PPN2O = (PB - PH2O) \cdot VpN2O/pocket volume
\]

If HPV is not incorporated, \( \dot{Q}p = 1.5 \dot{Q}tot \cdot f \), and \( \dot{QL} = \dot{Q}tot - \dot{Q}p \), where \( \dot{Q}p \) and \( \dot{QL} \) are \( Q \) of the pocket and lung, respectively.

If HPV is incorporated, \( \dot{Q}p \) and \( \dot{QL} \) are set as described in APPENDIX E.

\( PAO2, PACO2, PpO2, \) and \( PpCO2 \) are known. The \( O2 \) and \( CO2 \) contents in blood leaving the ventilated lung compartment (\( CAO2 \) and \( CA CO2 \)) are calculated from \( PAO2 \) and \( PACO2 \). The \( O2 \) and \( CO2 \) contents in blood leaving the unventilated lung compartment (\( CaO2 \) and \( Ca CO2 \)) are calculated from \( PpO2 \) and \( PpCO2 \)

\[
CaO2 = (\dot{Q}l \cdot CAO2 + \dot{Q}p \cdot CP O2)/\dot{Q}tot
\]
\[
CaCO2 = (\dot{Q}l \cdot CA CO2 + \dot{Q}p \cdot CP CO2)/\dot{Q}tot
\]
\[
CaO2 = CaO2 - (Vl, ti/\dot{Q}tot)
\]
\[
CaCO2 = CaCO2 + (Vl, ti/\dot{Q}tot)
\]
\[
PpO2 = (\dot{Q}p \cdot PpN2 + \dot{Q}l \cdot PpN2)/\dot{Q}tot
\]
\[
PpCO2 = (\dot{Q}p \cdot PpN2O + \dot{Q}l \cdot PpN2O)/\dot{Q}tot
\]
\[
VaV = (\dot{Q}VRG \cdot PVRGN2 + \dot{Q}MG \cdot PMGN2
\]
\[
+ \dot{Q}FG \cdot PFGN2 + \dot{Q}VPG \cdot PVPGN2)/\dot{Q}tot
\]
\[
PvV = (\dot{Q}VRG \cdot PVRGN2O + \dot{Q}MG \cdot PMGN2O
\]
\[
+ \dot{Q}FG \cdot PFGN2O + \dot{Q}VPG \cdot PVPGN2O)/\dot{Q}tot
\]

Differential equations governing gas uptake from the ventilated lung compartment. Gas uptake from the ventilated lung compartment is calculated by using the same method as during the preinduction phase (by using Eqs. B1–B4).

Differential equations governing gas exchange in the peripheral tissues. Gas exchange in the peripheral tissues is calculated by using the same method as during the preinduction phase (by using Eqs. B5–B12).

Differential equations governing gas exchange from the unventilated lung compartment.

\[
dVpO2/dt = CF \cdot \dot{Q} \cdot \left( \dot{Q}vO2 - CP O2 \right)
\]
\[
dVpCO2/dt = CF \cdot \dot{Q} \cdot \left( \dot{Q}vCO2 - CP CO2 \right)
\]
\[
dVpN2/dt = \dot{Q} \cdot \left( PpN2 - PpN2 \right)
\]
\[
dVpN2O/dt = \dot{Q} \cdot \left( PpN2O - PpN2O \right)
\]

APPENDIX E

Calculation of Blood Flow Incorporating HPV

The ability to incorporate HPV was built into the postinduction phase of the model. Because there was only one lung compartment in the preinduction phase, incorporation of HPV into that phase was unnecessary.

The ratio of actual pulmonary vascular resistance to pulmonary vascular resistance under hyperoxic conditions [rPVR] may be predicted by the following calculations [by using a value of maximal rPVR (rPVRmax) = 3.15] (18)

\[
PvO2 = PVV0.41 \cdot PAO20.59
\]
\[
r\%PVRmax = 100 \cdot PVV0.41/3.15 \cdot (6.683 \times 10^{-5} + PVV0.59)
\]

Using the \( PVV \) in the ventilated lung compartment in these calculations will give \( rPVR \), the rPVR pertaining to the ventilated lung compartment. If \( PVV \) is used instead of \( PAO2 \), these calculations will give \( rPVRp \), the rPVR pertaining to the unventilated lung compartment.

To allow calculation of the blood flow to the ventilated and unventilated lung compartments, it was considered that
under hyperoxic conditions blood flow was distributed according to
\[
\dot{Q}_p = 1.5 \dot{Q}_{\text{tot}} f
\]
and
\[
\dot{Q}_L = \dot{Q}_{\text{tot}} - \dot{Q}_p
\]
where \(f\) is the ratio derived in Appendix C.

Given the condition that both vascular beds must have the same perfusion pressure across them, it can be calculated that at the \(P_{\text{PAO}_2}, P_{\text{PAO}_2}\) and \(P_{\text{PAO}_2}\) of interest
\[
\begin{align*}
\dot{Q}_p &= \dot{Q}_{\text{tot}}/[1 + \gamma (1 - 1.5 f)/1.5 f] \\
\dot{Q}_L &= \dot{Q}_{\text{tot}} - \dot{Q}_p
\end{align*}
\]

At the time these calculations are made, \(P_{\text{PAO}_2}\), \(P_{\text{PAO}_2}\), and \(P_{\text{PAO}_2}\) are known, but not \(P_{\text{PAO}_2}\), \(P_{\text{PAO}_2}\), and \(P_{\text{PAO}_2}\); therefore, these estimates of \(\dot{Q}_L\) and \(\dot{Q}_p\) were used to calculate a new estimate of \(P_{\text{PAO}_2}\) as if arterial blood were composed entirely of blood draining from the ventilated lung compartment; 2) this value of \(P_{\text{PAO}_2}\), used with \(P_{\text{PAO}_2}\) and \(P_{\text{PAO}_2}\) was used to calculate \(Q_L\); 3) these estimates of \(Q_L\) and \(Q_p\) were used to calculate a new estimate of \(P_{\text{PAO}_2}\); 4) this new estimate of \(P_{\text{PAO}_2}\) used with \(P_{\text{PAO}_2}\) and \(P_{\text{PAO}_2}\) was used to calculate final values of \(Q_L\) and \(Q_p\).

References

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