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.

Methods

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.
The ventilated lung compartment (or pocket) represents dependent areas of lung, the airway to which doses at induction of anesthesia. The ventilated 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 lungs 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 equal to the alveolar partial pressures at the end of the preinduction phase. Alveolar volume in the ventilated lung compartment (i.e., VA) 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., VL,ti) is reduced so that the ratio of lung tissue volume to alveolar volume in this compartment 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 E). VAI 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 D), 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 O2 and a single inert gas, either N2 or N2O. A range of FIO2 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 60 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
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 FIO2 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 FIO2 was 1.0 postinduction. Both with and without preoxygenation, the higher the FIO2, after induction, the faster the rate of collapse. Without preoxygenation, the time to collapse was largely independent of whether N2 or N2O was breathed after induction. With preoxygenation for 3 min, breathing N2 rather than N2O 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 FIO2 after induction plays an important though lesser role, and that whether N2 or N2O 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 CO2 in the pocket (PpCO2) equilibrated rapidly with the mixed venous partial pressure of CO2 (PvCO2). The partial pressure of O2 in the pocket (PpO2) always equilibrated with the mixed venous partial pressure of O2 (PvO2) before the pocket had collapsed, but if preoxygenation had been performed and then high FIO2 breathed, equilibration was not reached until late in the time course of pocket collapse.

With no preoxygenation, equilibration of PpO2 with PvO2 took ~2 min.

If N2O was breathed after induction (see Fig. 4A) the mixed venous partial pressure of N2 (PvN2) fell and the mixed venous partial pressure of N2O (PvN2O) rose, favoring movement of N2 out of the pocket and N2O into it. Because of its higher solubility, N2O moved in faster than N2 moved out, so the pocket expanded. The partial pressure of N2O in the pocket (PpN2O) followed PvN2O closely, except that the PpN2O-PvN2O gradient often widened during rapid fluxes of O2 and CO2. The partial pressure of N2 in the pocket (PpN2) never approached equilibration with PvN2. After the early rapid gas fluxes, gas left the pocket at a relatively rapid rate. Volume fell slightly as O2 and CO2 equilibrated with mixed venous blood, rose as N2O entered the pocket, then fell as a gradient for both N2 and N2O to leave the pocket was established.

If N2 was breathed after induction (see Fig. 4B), volume fell rapidly as O2 and CO2 equilibrated with mixed venous blood. A state of constant composition was soon reached, where PpN2 substantially exceeded PvN2, and gas left the pocket at a relatively slow rate, determined mainly by the PpN2-PvN2 gradient and the relatively low solubility of N2.

If N2O was breathed after induction (see Fig. 4C), PvN2O rose, causing influx of N2O into the pocket, and PpN2O roughly followed PpN2O-PvN2 fell slowly with N2 washout from the tissue compartment. PpN2 rose initially as N2 was concentrated by uptake of other gases, then fell slowly. Volume fell rapidly until PpO2 equilibrated with PvO2, then fell more slowly.

If N2 was breathed after induction (see Fig. 4D), PpN2 was maintained or rose, depending on the FIO2. In both cases, PpN2 was at first higher than PpN2O, so N2 moved into the pocket; PpN2 rose because of influx of other gases, then fell slowly. Volume fell rapidly until PpO2 equilibrated with PpO2, then fell more slowly at a constant rate determined mainly by the PpN2-PvN2 gradient and the relatively low solubility of N2.

For the same FIO2, which inert gas was breathed after induction did not greatly affect the PpN2-PvN2 gradient after the rapid early gas fluxes.

With preoxygenation for 3 min, the pocket initially contained mainly O2, so despite rapid initial uptake from the pocket, equilibration of PpO2 with PvO2 took 5–7 min.

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 FIO2 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 to the PpN2-PvN2 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 FIO2 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 = 0.1 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 FIO2. 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...
Fig. 5. Effect of varying duration of preoxygenation. Time to collapse for a range of preoxygenation times (middle; min) when a mixture of N$_2$O and O$_2$ (FIO$_2$ = 0.21–1.0) was breathed postinduction (left) and when a mixture of N$_2$ and O$_2$ 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.

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 O$_2$ and N$_2$O with an FIO$_2$ 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 N$_2$O and O$_2$ with an FIO$_2$ of 0.4 after induction, and the other received a mixture of N$_2$ and O$_2$ with an FIO$_2$ 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 FIO$_2$ on critical V˙A/Q˙ with a theoretical model. He found that, when a mixture of O$_2$ and an inert gas with an FIO$_2$ of 0.4 is breathed, critical V˙A/Q˙ was 20 times greater when the inert gas was N$_2$O than when it was N$_2$. This suggests that more extensive atelectasis should develop when N$_2$O instead of N$_2$ is breathed. Joyce et al. (11) calculated the time that an area of lung takes to collapse, when the airway to it becomes occluded. If the same gas mixture was breathed before and after the occlusion, the calculated times for collapse were 214 min (11) for 30% O$_2$–70% N$_2$ and 8 min (11) for 30% O$_2$–70% N$_2$O. Webb and Nunn (30) calculated that, if air was breathed before the occlusion and 30% O$_2$–70% N$_2$O afterward, complete absorption took just over 100 min. This suggests that atelectasis develops more rapidly when N$_2$O is breathed instead of N$_2$ 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 N$_2$O 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). Our model (HPV not incorporated) predicts that if there is no preoxygenation, and a mixture of O$_2$ and an inert gas with an FIO$_2$ of 0.4 is breathed after induction of anesthesia, complete collapse will take 87.6 min if the inert gas is N$_2$ and 84.1 min if it is N$_2$O. The predictions are in agreement with the findings of Gunnarson et al. of progressive development of atelectasis over 90 min, with no difference between the N$_2$O and N$_2$ groups.

Rothen et al. (22) examined the amount of atelectasis visible on CT scans 20 min after induction of anesthesia.

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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Values are the time to collapse (min). FIO$_2$, inspired O$_2$ fraction. Predictions are given both with hypoxic pulmonary vasoconstriction (HPV) incorporated and without, with preoxygenation for 3 min (PreO$_2$) and without, and with the inert gas in the inspired gas mixture after induction being N$_2$ or N$_2$O.
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 Pvo2. 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% changed 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-PVNO2 gradient. For the same postinduction FIO2, which inert gas was breathed postinduction made little difference in the time to collapse or in the PPN2-PVNO2 gradient.

This may be explained by the following argument. After the early rapid gas fluxes, PpO2 and PpCO2 have equilibrated with PVo2 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 - PVo2 - PVco2, which is constant for a given FIO2, regardless of which inspired gas mixture is breathed. When no N2O is breathed, PPN2 = Pb - PH2O - PVo2 - PVco2. When N2O is breathed, PPN2 closely approxi-
mates $P_{vN_2}$, so $P_{pN_2} = P_B - P_{H_2O} - P_{vO_2} - P_{vCO_2} - P_{vN_2}$. Thus when $N_2O$ instead of $N_2$ is breathed, $P_{pN_2}$ is reduced by an amount approximately equal to $P_{vN_2}$. Therefore, the $P_{pN_2}$-$P_{vN_2}$ gradient is the same whether $N_2O$ or $N_2$ is breathed postinduction, provided that any change in $P_{vN_2}$ is matched by an opposite change in $P_{vN_2}$. Consider the two extremes, "induction" and "equilibration of tissue gas exchange." At induction, only air has been breathed, so $P_{vN_2}$ 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); $P_B = P_{H_2O} + P_{ACO_2} + P_{AO_2} + P_{vN_2} + P_{vN_2}$. At a given $F_{I_{O_2}}$, $P_{H_2O}$, $P_{ACO_2}$, and $P_{AO_2}$ are not affected by which inert gas is breathed postinduction; thus any difference in $P_{vN_2}$ between breathing $N_2$ or $N_2O$ postinduction must be matched by an opposite change in $P_{vN_2}$. Therefore, at these two extremes, the $P_{pN_2}$-$P_{vN_2}$ gradient will be the same regardless of which inert gas is breathed, providing the $F_{I_{O_2}}$ is the same. Between these points, the $P_{pN_2}$-$P_{vN_2}$ gradient will be the same only if the time course of changes 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)

$$\text{half-life (min)} = \frac{1}{K}$$

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 $F_{I_{O_2}}$, the initial rapid equilibration of $P_{pN_2}$ and $P_{pCO_2}$ with mixed venous blood has occurred, the $P_{pN_2}$-$P_{vN_2}$ 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 $P_{pO_2}$ always exceeded alveolar partial pressure of $N_2$. Blood from the pocket and the ventilated lung compartment combines to form arterial blood. At induction, $P_{vN_2}$ rise, reducing the $P_{pN_2}$-$P_{vN_2}$ gradient, so collapse takes longer. This general pattern does not apply to all scenarios, because gas fluxes before equilibration of $P_{pO_2}$ with $P_{vO_2}$ 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 $F_{I_{O_2}}$ is set to 0.21, inspired $N_2$ fraction ($F_{I_{N_2}}$) to 0.79, and the inspired $N_2O$ fraction ($F_{I_{N_2O}}$) to 0. The inspired partial pressures ($P_{I_{O_2}}$, $P_{I_{N_2}}$, and $P_{I_{N_2O}}$) are calculated by

$$P_{I_{O_2}} = F_{I_{O_2}} \cdot (P_B - P_{H_2O})$$
$$P_{I_{N_2}} = F_{I_{N_2}} \cdot (P_B - P_{H_2O})$$
$$P_{I_{N_2O}} = F_{I_{N_2O}} \cdot (P_B - P_{H_2O})$$

$P_{ACO_2}$ 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

$$P_{AO_2} = P_{I_{O_2}} - (P_{ACO_2}/RQ) \cdot (1 - F_{I_{O_2}} \cdot (1 - RQ))$$

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

$$V_{AE} = V_{CO_2} \cdot CF \cdot (P_B - P_{H_2O})/P_{ACO_2}$$

where $CF$ is the STPD-to-BTPS correction factor.
Because at equilibration the only gas exchange is O₂ and CO₂
\[ \dot{V}_{AI} = V_{AE} + CF \cdot (\dot{V}_{O2} - \dot{V}_{CO2}) \]

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

Because there is no inert gas exchange
\[ P_{AN2} = P_{IN2} \cdot \dot{V}_{AI}/\dot{V}_{AE} \]
and
\[ P_{AN2O} = P_{IN2O} \cdot \dot{V}_{AI}/\dot{V}_{AE} \]

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

Because at equilibration the only gas exchange is O₂ and CO₂
\[ C_{\dot{V}O2} = C_{\dot{V}CO2} = \dot{V}_{O2}/\dot{Q} \]

and
\[ C_{\dot{V}CO2} = C_{\dot{V}CO2} = \dot{V}_{CO2}/\dot{Q} \]

Venous partial pressures of inert gas are calculated by
\[ PV_{N2} = (\dot{Q}_{VPRG} \cdot PV_{RGN2} + \dot{Q}_{MG} \cdot PM_{GN2} + \dot{Q}_{FG} \cdot PF_{GN2} + \dot{Q}_{VG} \cdot PV_{PGN2})/\dot{Q}_{tot} \]

and
\[ PV_{N2O} = (\dot{Q}_{VPRG} \cdot PV_{RGN2O} + \dot{Q}_{MG} \cdot PM_{GN2O} + \dot{Q}_{FG} \cdot PF_{GN2O} + \dot{Q}_{VG} \cdot PV_{PGN2O})/\dot{Q}_{tot} \]

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

Differential equations governing gas uptake from the lung compartment.

\[
\begin{align*}
\frac{dP_{AO2}}{dt} &= [\dot{V}_{AI} \cdot P_{IN2} - V_{AE} \cdot P_{AO2} + CF \cdot \dot{Q} \cdot (C_{\dot{V}O2} - C_{\dot{V}CO2}) \cdot (P_{B} - P_{H2O})] / (V_{A} + V_{L,ti} \cdot \lambda \cdot t_{i} \cdot t_{i2}) \quad (B1) \\
\frac{dP_{AO2}}{dt} &= [\dot{V}_{AI} \cdot P_{IN2} - V_{AE} \cdot P_{AO2} + \dot{Q} \cdot P_{B} \cdot (P_{V} - P_{H2O})] / (V_{A} + V_{L,ti} \cdot \lambda \cdot t_{i} \cdot t_{i2}) \quad (B2) \\
\frac{dP_{AN2}}{dt} &= [\dot{V}_{AI} \cdot P_{IN2} - V_{AE} \cdot P_{AN2} + \dot{Q} \cdot P_{B} \cdot (P_{V} - P_{H2O})] / (V_{A} + V_{L,ti} \cdot \lambda \cdot t_{i} \cdot t_{i2}) \quad (B3) \\
\frac{dP_{AN2O}}{dt} &= [\dot{V}_{AI} \cdot P_{IN2O} - V_{AE} \cdot P_{AN2O} + \dot{Q} \cdot P_{B} \cdot (P_{V} - P_{H2O})] / (V_{A} + V_{L,ti} \cdot \lambda \cdot t_{i} \cdot t_{i2}) \quad (B4)
\end{align*}
\]

Because equilibration is present and an ideal lung model is used
\[ P_{AO2} = P_{AO2} \]
\[ P_{AO2} = P_{AO2} \]

where \( P_{AO2} \) and \( P_{ACO2} \) are the arterial partial pressures of O₂ and CO₂ respectively.

Arterial O₂ and CO₂ content (\( C_{AO2} \) and \( C_{ACO2} \)) respectively are calculated by using West’s modifications (31) of Kelman’s subroutines (13–15)
\[ C_{\dot{V}O2} = C_{\dot{V}O2} = \dot{V}_{O2}/\dot{Q} \]
\[ C_{\dot{V}CO2} = C_{\dot{V}CO2} = \dot{V}_{CO2}/\dot{Q} \]

where \( C_{\dot{V}O2} \) and \( C_{\dot{V}CO2} \) are the mixed venous O₂ and CO₂ content, respectively.

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. \( P_{AO2} \), \( P_{ACO2} \), \( P_{AN2} \), and \( P_{AN2O} \) are known. Arterial partial pressures \( P_{AO2} \) and \( P_{ACO2} \) are set equal to alveolar partial pressures. \( C_{AO2} \) and \( C_{ACO2} \) are calculated from \( P_{AO2} \) and \( P_{ACO2} \).

\[ C_{\dot{V}O2} = C_{\dot{V}O2} = \dot{V}_{O2}/\dot{Q} \]
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 partial pressures at the end of the preinduction phase. Call the alveolar volume of the lung compartment prior to induction VL,tiPre, and the lung tissue volume of the lung compartment prior to induction VL,tiPre.

The operator sets the ratio (f), where f = Vp/VL,tiPre

\[ Vp = f \cdot VL,tiPre \]

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

\[ VpO_2 = Vp \cdot PAO_2/(Pb - PH_2O) \]
\[ VpCO_2 = Vp \cdot PCO_2/(Pb - PH_2O) \]
\[ VpN_2 = Vp \cdot PN_2/(Pb - PH_2O) \]
\[ VpN_2O = Vp \cdot PN_2O/(Pb - PH_2O) \]

VA is maintained constant at the preinduction value

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

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 = VpO_2 + VpCO_2 + VpN_2 + VpN_2O

The partial pressures of each gas in the pocket are calculated

\[ PP_{O_2} = (Pb - PH_2O) \cdot VpO_2/pocket volume \]
\[ PP_{CO_2} = (Pb - PH_2O) \cdot VpCO_2/pocket volume \]
\[ PP_{N_2} = (Pb - PH_2O) \cdot VpN_2/pocket volume \]
\[ PP_{N_2O} = (Pb - PH_2O) \cdot VpN_2O/pocket volume \]

If HPV is not incorporated, \( \dot{Q}_p = 1.5 \dot{Q}_t \cdot f \), and \( \dot{Q}_L = \dot{Q}_t \cdot (1 - f) \) respectively.

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

\( PA_{O_2}, PA_{CO_2}, PB_{O_2}, PB_{CO_2} \) are known. The O2 and CO2 contents in blood leaving the ventilated lung compartment (CAO_2 and CAPCO_2) are calculated from PAO_2 and PACO_2. The O2 and CO2 contents in blood leaving the unventilated lung compartment (CAO_2 and CAPCO_2) are calculated from PAO_2 and PACO_2.

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)

\[ P_{SO_2} = \frac{P_{TV_2}^{0.41} \cdot PA_{O_2}^{0.59}}{100 \cdot P_{SO_2}^{0.2616}/(6.683 \times 10^{-5} + P_{SO_2}^{0.2616})} \]

\[ rPVR = 1 + \frac{rPVR_{max} \cdot (rPVR_{max} - 1)}{100} \]

Using the PAO_2 in the ventilated lung compartment in these calculations will give rPVRV, the rPVR pertaining to the ventilated lung compartment. If P_{SO_2} is used instead of PAO_2, 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
\[ \dot{Q}_p = 1.5 \dot{Q}_{tot} f \]
and
\[ \dot{Q}_L = \dot{Q}_{tot} - \dot{Q}_p \]
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 \( P_T \), \( P_A \), and \( P_O \), of interest
\[ \dot{Q}_p = \dot{Q}_{tot} / \left[ (1 - 1.5 f) / 1.5 f \right] \cdot \left( rPVR_p / rPVRA \right) + 1 \]
\[ \dot{Q}_L = \dot{Q}_{tot} - \dot{Q}_p \]

At the time these calculations are made, \( P_T \), \( P_A \), and \( PAO_2 \) are known, but not \( P_V \), \( P_VO_2 \), and \( PQ_2 \), dependent on \( Q_p \) and \( Q_L \), and vice versa, so an iterative method of solution is required. The solution for \( P_T \), \( Q_L \), and \( Q_p \) could be found by using the binary search method, but, in practice, convergence with this method was prohibitively slow. The following method was attempted, with test data over the range of \( P_T \) and \( P_A \) used in the calculations of the program, and it was found to produce values of \( Q_L \) and \( Q_p \) within 0.2% of the values produced by the binary search method: 1) \( P_V \) was calculated as if arterial blood were composed entirely of blood draining from the ventilated lung compartment; 2) this value of \( P_V \) used with \( P_A \) and \( P_VO_2 \), used to calculate \( Q_L \) and \( Q_p \); 3) these estimates of \( Q_L \) and \( Q_p \) were used to calculate a new estimate of \( P_V \); and 4) this new estimate of \( P_V \), used with \( P_A \) and \( P_VO_2 \), was used to calculate final values of \( Q_L \) and \( Q_p \).

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