Can Mathematical Modeling Explain the Measured Magnitude of the Second Gas Effect?

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ABSTRACT

Background: Recent clinical studies suggest that the magnitude of the second gas effect is considerably greater on arterial blood partial pressures of volatile agents than on end-expired partial pressures, and a significant second gas effect on blood partial pressures of oxygen and volatile agents occurs even at relatively low rates of nitrous oxide uptake. We set out to further investigate the mechanism of this phenomenon with the help of mathematical modeling.

Methods: Log-normal distributions of ventilation and blood flow were generated representing the range of ventilation-perfusion scatter seen in patients during general anesthesia. Mixtures of nominal delivered concentrations of volatile agents (desflurane, isoflurane and diethyl ether) with and without 70% nitrous oxide were mathematically modeled using steady state mass-balance principles, and the magnitude of the second gas effect calculated as an augmentation ratio for the volatile agent, defined as the partial pressure in the presence to that in the absence of nitrous oxide.

Results: Increasing the degree of mismatch increased the second gas effect in blood. Simultaneously, the second gas effect decreased in the gas phase. The increase in blood was greatest for the least soluble gas, desflurane, and least for the most soluble gas, diethyl ether, while opposite results applied in the gas phase.

Conclusions: Modeling of ventilation-perfusion inhomogeneity confirms that the second gas effect is greater in blood than in expired gas. Gas-based minimum alveolar concentration readings may therefore underestimate the depth of anesthesia during nitrous oxide anesthesia with volatile agents. The effect on minimum alveolar concentration is likely to be most pronounced for the less soluble volatile agents in current use. (Anesthesiology 2018; 128:1075-83)

The second gas effect occurs when a soluble first gas such as nitrous oxide is delivered in high inspired concentrations. Alveolar-capillary uptake of the first gas increases the alveolar concentrations of other gases present, accelerating their uptake. The effect was first described by Epstein et al.,1 who believed it was due to extra gas drawn into the lung to replace the nitrous oxide taken up by blood. Subsequently, Stoelting and Eger showed that the second gas effect must involve a concentrating effect as well, i.e., an effect due to volume "shrinkage."1,2 They produced a diagram to explain these two steps, a diagram that then appeared in many anesthetic textbooks. Years later, Korman and Mapleson showed that the effect is primarily one of volume "shrinkage" and produced modifications of the Stoelting-Eger diagram that explained the phenomenon more accurately, including equilibration of the alveolar compartment with blood.3

Several clinical studies involving the measurement of end-expired concentrations of volatile anesthetic agents in patients have confirmed the existence of the second gas effect.4,5 However, in a clinical study prompted by results of computer modeling of gas-exchange in the lung,6–8 Peyton et al. found that the magnitude of the second gas effect is considerably greater where the effect on arterial blood partial pressures is measured instead.9 They explained this by the effect of inhomogeneity or scatter of ventilation and blood flow ratios (ventilation-perfusion [V/Q] ratios) on the distribution of perfusion-driven nitrous oxide uptake throughout the lung, with more powerful concentrating effects generated in lung compartments with higher blood flow and lower V/Q. They suggested furthermore that this could produce a significant second gas effect on blood partial pressures of oxygen and volatile agent even at relatively low "maintenance phase" rates of nitrous oxide uptake,10 a
suggestion that has been questioned, but is supported by clinical studies.\textsuperscript{5,9}

The idea that a phenomenon traditionally believed to be caused by the large reductions in gas volume associated with high rates of nitrous oxide uptake can persist at clinically significant concentrations even when those volume changes fall away is a significant departure from traditional teaching. We set out to further explore the mechanism of this proposed phenomenon with computer modeling of theoretical distributions of \(V/Q\) scatter seen in patients during general anesthesia, across a range of nitrous oxide uptake rates, and the predicted effect on second gases with different solubilities in blood.

Materials and Methods

The minimum number of components in the gas phase necessary for a theoretical study of the second gas effect is as follows:

A first gas. Alveolar-capillary uptake of this gas generates the volume changes responsible for the second gas effect. It must be soluble in blood. The difference in partial pressures between the inspired gas mixture and mixed venous blood must be sufficient to produce the desired volume changes.

A second gas. This is usually a volatile agent used in low concentrations. This gas responds to the volume changes by exhibiting the second gas effect.

The remaining gas. This acts purely as a “vehicle” for delivering the first and second gases, and for the purposes of the analysis is regarded as being completely insoluble in blood.

In clinical practice, the first gas is always nitrous oxide (Ostwald solubility coefficient in blood at 37°C, \(\lambda = 0.47\)). A fractional concentration of 70% in dry gas is assumed in all calculations. This is usually regarded as the highest clinically effective concentration that can be used safely in the general population during anesthesia without producing hypoxia.\textsuperscript{12}

In modern clinical anesthesia, the second gases used are mainly desflurane, sevoflurane, and isoflurane. We will consider diethyl ether as well because it is an example of a volatile anesthetic with a high solubility in blood. We examine the second gas effect as the uptake of the first gas, nitrous oxide, decreases toward zero, as is seen with time in clinical use. This is achieved in our model by increasing the mixed venous pressure of nitrous oxide in a stepwise fashion. The proportion of nitrous oxide washin is expressed as a washin ratio, which mirrors the usual alveolar/inspired concentration ratio, \(i.e.,\) a washin ratio of 0.9 is roughly equivalent to the situation where the alveolar/inspired concentration ratio equals 0.9. We estimate that our steady state equations are reasonably accurate within 10 to 15 min from the start of induction, when nitrous oxide washin is more than 90% complete and its uptake rate has plateaued.\textsuperscript{13}

The second gas effect is expressed as an augmentation ratio, defined as the partial pressure of second gas in the presence of nitrous oxide, divided by that which would have existed in the absence of the nitrous oxide, with all other variables kept constant. With no second gas effect, the augmentation ratio is 1. Once the second gas effect becomes evident, the augmentation ratio exceeds 1. The term “augmentation ratio” was first used by Epstein et al.\textsuperscript{1} Although they only calculated augmentation ratios in end-tidal gas, the ratio may also be calculated for blood.

We have assumed a log-normal distribution of \(V/Q\) ratios in our investigations.\textsuperscript{14} Colburn et al.\textsuperscript{15} have shown that if \(\sigma_v\) is the log SD of ventilation per unit volume and \(\sigma_q\) is the log SD of blood flow per unit volume, then \(\sigma\), the degree of mismatch between ventilation and blood flow, depends only on \(\left|\sigma_v - \sigma_q\right|\), the absolute value of the difference between the two standard deviations. This is illustrated in figure 1. In figure 1A, the ventilation as a fraction of the total alveolar ventilation \((\dot{v})\) has been drawn in blue while the blood flow as a fraction of the total pulmonary blood flow \((\dot{q})\) has been drawn in red. The unit on the x-axis is not log \((V/Q)\) but \((1/\alpha)\log(\dot{v}/\dot{q})\), where \(\alpha = \sigma_v - \sigma_q\). Drawn in this way, the graphs of ventilation and blood flow are exactly the same size and shape, and do not change size or shape as \(\alpha\) is varied. What does change is the distance between the mean for ventilation and the mean for blood flow. These means are situated exactly \(\alpha/2\) units on opposite sides of the y-axis. When \(\alpha = 0\), the curves overlap completely so that matching between ventilation and blood flow is optimal. As \(\alpha\) increases, they overlap less and less and the degree of \(V/Q\) mismatch increases. This is shown further in figure 1B, in which the blood flow as a fraction of the total pulmonary blood flow \((\dot{q})\) has been rotated through 180° degrees about the x-axis. In awake healthy adults, \(\alpha\) varies from 0.25 to 1.0. Worsening of \(V/Q\) matching is known to occur soon after induction of anesthesia and has been well documented experimentally, with typical values for \(\alpha\) of 0.75 to 1.5.\textsuperscript{16–20} Further information regarding this way of presenting a log-normal distribution of ventilation and blood flow is provided in appendix 1.

A general equation for the augmentation ratio (AR) was obtained having the following form in which the difference between inspired alveolar ventilation, \(\dot{V}_i\), and expired alveolar ventilation, \(\dot{V}_A\), appears:

\[
AR = 1 + k \left( \frac{\dot{V}_i - \dot{V}_A}{\dot{V}_i} \right)
\]

Derivation of equation 1 is given in appendix 2. In the absence of nitrous oxide, inspired alveolar ventilation and expired alveolar ventilation are equal, the augmentation ratio equals 1, and there is no augmentation. In the presence of nitrous oxide, inspired alveolar ventilation is greater than expired alveolar ventilation, the augmentation ratio is greater than 1, and the second gas effect appears. Its magnitude is then given by the augmentation ratio. The difference \((\dot{V}_i - \dot{V}_A)\) is equal to the rate of nitrous oxide uptake. The \((\dot{V}_i - \dot{V}_A)/\dot{V}_A\) term is the “concentrating effect” or “shrinkage” factor given...
in classical descriptions of the second gas effect. The $k$ term is positive and includes contributions from the solubility of the second gas, the overall alveolar ventilation-perfusion ratio of the lung, and the degree of mismatch between ventilation and blood flow.

Input variables for each gas were its inspired concentration, mixed venous partial pressure, and solubility in blood. For simplicity, we have assumed trace concentrations of second gas in the inspired gas mixture with mixed venous concentrations of zero. An expired alveolar ventilation of 4 l/min was assumed. The pulmonary blood flow was set at 5 l/min. Equation 1 was first solved for each second gas in a homogenous lung (i.e., $\sigma = 0$), then in a multicompartment lung for a log-normal distribution of ventilation and perfusion with $\sigma$ varying from 0.25 to 2 in increments of 0.25 units. Calculations were performed in both the presence and absence of nitrous oxide. Outputs were calculated from the flow-weighted uptake rates of each compartment. The output variable for each second gas was its augmentation ratio in the blood and gas phases. In each situation, results were obtained for 3 gases representing a wide range of blood solubilities: desflurane (λ = 0.42), isoflurane (λ = 1.4), and diethyl ether (λ = 12.1).

Results

Figure 2 shows the results for the blood and gas phases. The arrow in each diagram of figure 2 indicates the direction in which $\sigma$ is increasing. The x-axis shows the proportion of nitrous oxide washin, and the y-axis shows the augmentation ratio. The most consistent feature of these diagams is the divergence of the lines from the point (1, 1), the point on the x-axis representing complete washin of the nitrous oxide, at which time expired alveolar ventilation becomes equal to inspired alveolar ventilation, so that according to equation 1, the second gas effect disappears completely.

Each augmentation ratio plot appears to be a straight line. The line for $\sigma = 0$, which represents a homogenous lung, is the same for both gas phase and blood phase, as expected for a “single compartment” lung with full equilibration between blood and gas phases. In addition, it is the same for all three gases, i.e., it is independent of the solubility of the second gas in blood.

The effect of increasing $\sigma$ and hence the degree of $\dot{V}/\dot{Q}$ mismatch is seen to be opposite for the blood and gas phases. In blood, an increase in $\sigma$ increases the augmentation ratio, while in the gas phase, the augmentation ratio decreases. Moreover, in blood, this amplification is greatest for the least soluble gas, desflurane, and least for the most soluble gas, diethyl ether, while in the gas phase, the opposite is true.

Discussion

Our mathematical model allows contributions from solubility and $\dot{V}/\dot{Q}$ mismatch to the second gas effect to be assessed separately. The results show that an increase in $\dot{V}/\dot{Q}$ mismatch augments the second gas effect in blood, but reduces the second gas effect in the gas phase. This result is most pronounced for the insoluble gases used in clinical practice today. Although not shown here for brevity, results obtainable for sevoflurane (λ = 0.67) are similar to those shown for desflurane.

The choice of a log-normal distribution is mathematically convenient and has been used previously in simulations of gas exchange in the lung.6-8,14,21 However, the method used to display the distributions of ventilation and blood flow in figure 1 is new, and illustrates clearly how $\sigma$ controls the degree of $\dot{V}/\dot{Q}$ mismatch. A further advantage of this method is that it facilitates equilibration of gas and blood over the whole range of $\dot{V}/\dot{Q}$ values, particularly at the
extremities of each log-normal distribution. Log-normal distributions are not the only distributions seen clinically, but we believe the choice is not particularly relevant to the conclusions reached here, which depend primarily on the application of the Fick principle.

Equation 1 provides an explanation of how the second gas effect can continue, even after nitrous oxide uptake decreases to levels seen in the “maintenance phase.” The term \( k(V - V_A)/V_A \) is responsible for the second gas effect. Here the difference \( V - V_A \) is produced by nitrous oxide. A decrease in this difference as nitrous oxide uptake decreases can be compensated for by a simultaneous increase in \( k \), indicating that “shrinkage” need not be the only factor involved in producing the second gas effect. We have shown that \( k \) is affected by the degree of \( V/Q \) mismatch and that the effect of \( V/Q \) mismatch on \( k \) differs in the gas phase and in blood. With no \( V/Q \) mismatch, \( \sigma = 0 \) and \( k = 1 \) in both phases. This is the situation that corresponds to the classical volume “shrinkage” explanation of the second gas effect. As \( V/Q \) mismatch increases, \( \sigma \) increases. In blood, as \( \sigma \) increases, \( k \) also increases and is greater than 1. In the gas phase, as \( \sigma \) increases, \( k \) decreases and is less than 1. The term \( k \) may be thought of as a scaling factor, controlling the degree to which the volume “shrinkage,” \( (V - V_A)/V_A \), is expressed.
Our findings are consistent with the experimental clinical findings of Peyton et al.,\textsuperscript{10} that the magnitude of the second gas effect on arterial sevoflurane partial pressures was significantly greater than that measured simultaneously on end-tidal partial pressures in patients immediately after induction of anesthesia and for 30 min afterward. However, these authors did not attribute the finding to a concomitant diminution in second gas effect in the gas phase. Our model provides a more precise explanation for their findings. While effects in the gas phase are most easily detected using end-tidal gas concentration monitoring by the infrared analyzers available in most operating theaters today, augmentation in the blood phase is not measured in normal clinical practice but is important because it most directly affects anesthetic partial pressures in blood and therefore depth of anesthesia. An obvious clinical implication of these findings is that minimum alveolar concentration (MAC) calculations based on end-tidal concentration measurements may well underestimate the depth of anesthesia when nitrous oxide is supplemented with a volatile agent. This represents a new factor that should be taken into consideration in addition to other relevant factors\textsuperscript{22–24} when interpreting an end-tidal MAC reading during anesthesia.

Figure 2 illustrates the predicted effects of typical increases in the degree of $V/Q$ scatter on the augmentation ratio. We can treat the line for the homogenous lung, i.e., the line for which $\theta = 0$, as the first line in the series. This line is identical in the upper (gas phase) and lower (blood phase) diagrams in figure 2, as expected for a homogeneous “single compartment” lung. As steady state conditions are approached for the first gas, augmentation in a homogenous lung is independent of the second gas solubility in blood. It depends only on the ratio of the uptake of nitrous oxide to the alveolar ventilation, which is equal to $(V_j - V_a)/V_a$. Once ventilation and perfusion are no longer perfectly matched, solubility becomes the important factor.

It is evident from figure 2 that the second gas effect in blood and its augmentation by increasing $V/Q$ scatter is greater for the least soluble second gas, desflurane. This finding is remarkable, as lung modeling in the absence of nitrous oxide predicts that increasing $V/Q$ scatter, with a reduction in effective alveolar ventilation, impairs alveolar-capillary gas exchange more severely for less soluble gases,\textsuperscript{15} a prediction recently confirmed in an animal study of desflurane or isoflurane anesthesia using methacholine inhalation to induce increased $V/Q$ inhomogeneity.\textsuperscript{25} This would suggest that inclusion of nitrous oxide might maintain the efficiency of the lung in exchanging less soluble modern volatile agents in the face of $V/Q$ scatter induced by anesthesia itself.

Our mathematical modeling suggests, moreover, that the second gas effect in blood for less soluble modern agents is expected to remain significant, although progressively reducing, into the “maintenance phase” of inhalational anesthesia with nitrous oxide, where typical degrees of $V/Q$ scatter exist. This is consistent with most previous clinical and theoretical studies, including those of Peyton et al., who measured the second gas effect on arterial sevoflurane and oxygen partial pressures in anesthetized patients.\textsuperscript{5,10} The augmentation to blood desflurane partial pressures at 20 to 30 min predicted by the model is in the order of 10 to 15% with moderate degrees of $V/Q$ scatter. This compares to a mean 12% increase in arterial sevoflurane partial pressures at this time point in ventilated patients measured by Peyton et al.\textsuperscript{10} The lesser augmentation in gas phase desflurane concentrations predicted here is also broadly consistent with the findings of Täheri and Eger, and those of Hendrickx et al. for end-expired sevoflurane concentrations, in anesthetized patients.\textsuperscript{5,5}

Modeling and predicting the effects on respiratory gases is more complex and was not part of the scope of this study. In their previous studies using multicompartment modeling of lung gas exchange, Peyton et al. modeled oxygen as a second gas,\textsuperscript{6–8} and demonstrated significant elevation of predicted partial pressures of oxygen in arterial blood with moderate degrees of $V/Q$ scatter, at 45 min or more into inhalational anesthesia with 70% nitrous oxide as the first gas. This prediction was confirmed in a subsequent clinical study.\textsuperscript{9} In attempting to mimic oxygen uptake as closely as possible, these authors introduced the nonlinear binding of oxygen to hemoglobin, shunt formation, hypoxic vasoconstriction, absorption atelectasis, carbon dioxide elimination and carriage, and acid-base status. Each of these factors is a potential confounder in interpretation of their findings of the relationship of $V/Q$ scatter to the second gas effect. In contrast, we have chosen to eliminate all but the essential components in this study of the second gas effect, permitting explicit mathematical expression of the underlying features, once a particular mathematical distribution of $V/Q$ ratios has been assumed. It remains to be seen to what degree these other factors affect the predictions made here and should be the subject of further work in the field.

In summary, modeling of ventilation-perfusion inhomogeneity confirms that the second gas effect is greater in blood than in expired gas. As the degree of mismatch increases, the magnitude of the second gas effect increases in blood but decreases in expired gas. The change is most pronounced in blood for the less soluble volatile agents in current use. Clinically, this means that MAC readings may well underestimate the depth of anesthesia when nitrous oxide is supplemented with a volatile agent.

**Research Support**

Supported by an Australian Government Research Training Program Fees Offsets to Dr. Korman and by grant Nos. U01-HL122199 and P01-GM066730 from the National Institutes of Health (Bethesda, Maryland; to Dr. Dash).

**Competing Interests**

The authors declare no competing interests.
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Appendix 1: The Log-normal Distribution
Colburn et al.15 derive the following probability density functions for ventilation and blood flow from first principles:

\[ V = \frac{\dot{V}_a}{\sqrt{2\pi}} e^{-x^2/2} \]  
(1.1)

\[ Q = \frac{\dot{Q}_a}{\sqrt{2\pi}} e^{-(x-\sigma)^2/2} \]  
(1.2)

Here \( \dot{V}_a \) is the alveolar ventilation and \( \dot{Q}_a \) the total pulmonary blood flow. Letting \( v = \dot{V}/\dot{V}_a \) and \( \dot{q} = \dot{Q}/\dot{Q}_a \), the fractional or normalized ventilation and blood flow respectively, we have

\[ \dot{v} = \frac{1}{\sqrt{2\pi}} e^{-x^2/2} \]  
(1.3)

\[ \dot{q} = \frac{1}{\sqrt{2\pi}} e^{-(x-\sigma)^2/2} \]  
(1.4)

Dividing equation 1.3 by equation 1.4:

\[ \dot{v} \dot{q} = e^{[(x-\sigma)^2/2] - [x^2/2]} \]  
(1.5)

\[ \dot{v} \dot{q} = e^{-(\sigma^2-2\sigma x)/2} \]  
(1.6)

Taking natural logarithms of both sides and solving for \( x \), we obtain

\[ x = \frac{\sigma}{2} - \frac{1}{\sigma} \log( \dot{v} \dot{q} ) \]  
(1.7)

Letting \( X = \frac{1}{\sigma} \log( \dot{v} \dot{q} ) \) and substituting in equations 1.3 and 1.4, we obtain

\[ \dot{v} = \frac{1}{\sqrt{2\pi}} e^{\left( x - \frac{\sigma}{2} \right)^2} \]  
(1.8)

Equations 1.8 and 1.9 are of the form of a standard normal distribution and have been used to plot figure 1.

These forms of the density function for the log-normal distributions are very useful in equilibrating gas and blood compartment by compartment, in order to obtain flow-weighted outputs in gas and blood. The x-axis is divided into N compartments of equal width. This involves N+1 points. At least 99.7% of cases26 will always be covered if the subdivision of the x-axis begins at \(-\sigma/2 - 3\) and ends at \(\sigma/2 + 3\). The width of each interval is then \((\sigma + 6)/N\). When calculating the contribution of each point to the output, it is necessary to apply the trapezoidal rule so that the first and last points carry half the weight of the other points.27 If this is not done, an error will be introduced that becomes more significant as the number of compartments is reduced. In determining the weight attached to the expired ventilation from each compartment, it is necessary to multiply \( \dot{v} \) by the expired alveolar ventilation, \( \dot{V}_a \). Similarly, \( \dot{q} \) must be multiplied by \( \dot{Q}_a \).

Appendix 2: Derivation of Equation 1

Washin Ratio

The proportion of nitrous oxide washin completed is expressed as a washin ratio (WR), where \( WR = \frac{1 - V_{N,O}/\dot{V}_a F_{N,O}}{V_{N,O}} \).

This ratio is used as an independent variable on the x-axis. Note that when \( V_{N,O} = 0 \), WR = 1 and nitrous oxide uptake is complete; when \( V_{N,O} = \dot{V}_a F_{N,O} \), its maximum possible value, WR = 0, a situation that can only apply at the commencement of anesthesia (see table A2.1). Since, for simplicity, the equations we use are only applicable in the steady state, we restrict our attention to values of \( V_{N,O} \) for 0.9 ≤ WR ≤ 1.0, i.e., when washin of nitrous oxide is 90 to 100% complete and steady state equations represent a satisfactory approximation. Applying Severinghaus’s equation for the rate of uptake of nitrous oxide,13 this should occur within 10 to 15 min from the start of induction, at which time the rate of change in the uptake of nitrous oxide has declined to less than 5% of its current rate of uptake.

Basic Equations

As the steady state equations governing the exchange of the first gas in a single lung unit,* we take

\[ \dot{V}_a F_I - \dot{V}_A F = \dot{Q} \lambda (F - F_I) \]  
(2.1)

and

\[ (1 - F) \dot{V}_A = (1 - F_I) \dot{V}_I \]  
(2.2)
Substituting for $\dot{V}_I$ in equation 2.1, we may solve this equation for $F$.

$$F = \frac{\dot{V}_A F_I + \lambda Q (1 - F_I) \dot{V}_f}{\dot{V}_A + \lambda Q (1 - F_I)}$$

(2.6)

**Second Gas Effect in Blood Phase.** We denote the uptake of the first gas, nitrous oxide, by the symbol $\dot{V}_{N_2O}$, the uptake of the second gas in the absence of the first gas, by $\dot{V}_{SG}$; and the uptake of the second gas in the presence of first gas, by $\dot{V}_{SG/FG}$. $\dot{V}_{N_2O}$ is given by the left-hand side of equation 2.1; $\dot{V}_{SG}$ is given by the left-hand side of equation 2.3 when inspired alveolar ventilation equals $\dot{V}_A$; and $\dot{V}_{SG/FG}$ is given by the left-hand side of equation 2.3 with inspired alveolar ventilation determined from equation 2.2. Using the superscript hl for a homogenous lung,

$$\dot{V}_{hl}^{bl} = \frac{\lambda \dot{V}_A (F - F_I)}{1 - F_I} + \frac{(\dot{V}_A/\dot{Q})}{\lambda (1 - F)}$$

(2.7)

$$\dot{V}_{hl}^{bl} = \frac{\lambda \dot{V}_A \lambda_{SG} F_{SG}^{hl} / \lambda_{SG} + (\dot{V}_A/\dot{Q})}{1 - F}$$

(2.8)

$$\dot{V}_{hl}^{bl} = \frac{(\dot{V}_A \lambda_{SG} F_{SG}^{hl} / \lambda_{SG} + (\dot{V}_A/\dot{Q}) (1 - F)}{1 - F}$$

(2.9)

Note that equation 2.7 was derived by Colburn et al.\textsuperscript{15} Except for the appearance of the factor $(1 - F)/(1 - F_I)$ and the omission of the Fv term, equation 2.9 is similar to equation 2.7. Because $F_{1SG}$ is much smaller than 1, it has been omitted from the denominator of Eqs. 2.8 and 2.9. From Eqs. 2.8 and 2.9, it is trivial to find that the augmentation ratio in blood, AR(blood) = $\dot{V}_{hl}^{bl}$ / $\dot{V}_{SG}^{bl}$ = $(1 - F)/(1 - F_I)$.

**Second Gas Effect in Gas Phase.** Substituting for inspired alveolar ventilation from equation 2.2 in equation 2.3, we obtain an expression for $F_{SG/FG}$:

$$F_{SG/FG}^{hl} = \frac{(\dot{V}_A / \dot{Q}) F_{SG}^{hl}}{(\dot{V}_A / \dot{Q}) + \lambda_{SG} (1 - F)}$$

(2.10)

When no first gas is present, inspired alveolar ventilation equals expired alveolar ventilation and $(1 - F)/(1 - F_I) = 1$, and hence the expression for $F_{SG}^{hl}$ can be easily derived from equation 2.10. Thus, the augmentation ratio in the gas phase, $AR(gas) = F_{SG}^{hl}$ / $F_{SG}^{hl} = (1 - F)/(1 - F_I)$.

We can conclude that in a homogenous lung with constant outflow, the augmentation ratios in the gas phase and in the blood phase are both equal to $(1 - F)/(1 - F_I)$ so that

$$F_I = \frac{1 - F}{1 - F_I} \dot{V}_A$$

(2.5)
the magnitude of the second gas effect is identical in both phases and, after substituting the solution for \( F \) (obtained from equation 2.1), is given by

\[
AR(\text{gas}) = AR(\text{blood}) = \frac{(\dot{V} / \dot{Q}) + \lambda(1 - F_v)}{(\dot{V} / \dot{Q}) + \lambda(1 - F)}
\]  
(2.11)

Nonhomogenous Lung

Consider now a nonhomogenous lung model, denoted by the superscript \( nhl \), composed of \( n \) functional units. Let \( \dot{V}_j \) and \( \dot{Q}_j \) be the alveolar ventilation and blood flow, respectively, to the \( j \)th compartment for \( 1 \leq j \leq n \). Set \( \dot{V}_0 = \dot{V}_1 + \ldots + \dot{V}_n \) and \( \dot{Q}_0 = \dot{Q}_1 + \ldots + \dot{Q}_n \).

Second Gas Effect in Blood Phase. By analogy with equation 2.9, the net uptake of the second gas in the presence of the first gas in the nonhomogeneous lung, \( V_{SG}^{nhl} \), is given by

\[
V_{SG}^{nhl} = \sum_{j=1}^{n} \left( \frac{\dot{V}_j \lambda_j F_{SG}^{nhl}}{\lambda_j + (\dot{V}_j / \dot{Q}_j)} \right) \left( 1 - F_v \right) \left( 1 - F \right)
\]  
(2.12)

By analogy with equation 2.8, the net uptake of the second gas in the absence of the first gas in the nonhomogeneous lung, \( V_{SG}^{nhl} \), is given by

\[
V_{SG}^{nhl} = \sum_{j=1}^{n} \left( \frac{\dot{V}_j \lambda_j F_{SG}^{nhl}}{\lambda_j + (\dot{V}_j / \dot{Q}_j)} \right)
\]  
(2.13)

In the case of a nonhomogenous lung, the augmentation ratio for blood is therefore given by

\[
AR(\text{blood}) = \frac{\sum_{j=1}^{n} \left( \dot{V}_j \lambda_j F_{SG}^{nhl} / (\lambda_j + (\dot{V}_j / \dot{Q}_j)) \right) \left( 1 - F_v \right) \left( 1 - F \right)}{\sum_{j=1}^{n} \left( \dot{V}_j \lambda_j / (\lambda_j + (\dot{V}_j / \dot{Q}_j)) \right)}
\]  
(2.14)

Applying equation 2.6 to the \( j \)th compartment and simplifying, we obtain the following expression for the augmentation ratio in blood:

\[
AR(\text{blood}) = 1 + \left[ \lambda \left( F_v - F \right) \right] \left( \frac{I}{I_{SG}} - 1 \right)
\]  
(2.15)

Note here that with 70% nitrous oxide (i.e., \( F_v = 0.7 \)) for which \( \lambda = 0.47 \), the expression \( \left( \lambda_{SG} - \lambda(1 - F) \right) / \left( \lambda(1 - F_v) + (\dot{V}_j / \dot{Q}_j) \right) \) includes all the volatile anesthetic agents in current use. Assuming now that these series are both applied using a log-normal distribution of \( V/Q \) with log SD of ventilation-perfusion mismatch of \( \sigma_v - \sigma_S \), we replace each series with its equivalent Lebesgue-Stieltjes integral as described by Colburn et al.\(^{15}\) Thus, we have

\[
AR(\text{blood}) = 1 + \left( \frac{\lambda \left( F_v - F \right)}{\lambda_{SG} - \lambda(1 - F)} \right) \left( \frac{I}{I_{SG}} - 1 \right)
\]  
(2.16)

where

\[
I = \frac{1}{\sqrt{2\pi}} \int_{\infty}^{-\infty} \lambda(1 - F) e^{\left( x - \bar{x} \right) / \sigma} dx
\]

\[
= \sum_{j=1}^{n} \left( \frac{\dot{V}_j / \dot{Q}_j}{\lambda(1 - F_v) + (\dot{V}_j / \dot{Q}_j)} \right)
\]

\[
I_{SG} = \frac{1}{\sqrt{2\pi}} \int_{\infty}^{\infty} \lambda_{SG} e^{\left( x - \bar{x} \right) / \sigma} dx
\]

\[
= \sum_{j=1}^{n} \left( \frac{\dot{V}_j / \dot{Q}_j}{\lambda_{SG} + (\dot{V}_j / \dot{Q}_j)} \right)
\]  
(2.17)

Using the substitution \( F_v = F_1^{*}(F_v/F_1) \), we can now determine the augmentation ratio in blood, \( AR(\text{blood}) \), for a range of values of \( \lambda_{SG} \), \( \sigma \), and \( F_v/F_1 \) (representing different stages of nitrous oxide equilibration). However, Peyton et al. actually use the nitrous oxide uptake, \( V_{NO}^{SG} \) as an input variable.\(^{6–8}\) This enables us to eliminate the term \( (F_v - F) \), as described in equation 2.19, below. Using equation 2.7, the result derived by Colburn et al.\(^{15}\) for the uptake of nitrous oxide in a homogenous lung and summing the uptake in each compartment to obtain the total uptake, we obtain the following equation:

\[
V_{SG}^{nho} = \sum_{j=1}^{n} \left( \frac{\dot{V}_j \lambda_j F_{SG}^{nho}}{\lambda_j + (\dot{V}_j / \dot{Q}_j)} \right)
\]  
(2.18)

which, by analogy, produces the following expression for \( (F_v - F) \) if we assume a log-normal distribution of ventilation-perfusion ratios:

\[
(F_v - F) = \frac{V_{SG}^{nho}}{\lambda_{SG} I_{SG}} \tag{2.19}
\]

The final expression relating the second gas effect to the uptake of nitrous oxide and the degree of ventilation-perfusion mismatch in a nonhomogenous lung is therefore

\[
AR(\text{blood}) = 1 + \left( \frac{1}{\lambda_{SG} - \lambda(1 - F)} \right) \left( \frac{V_{SG}^{nho}}{V_0} - 1 \right)
\]  
(2.20)

We use WR, the previously defined washin ratio, as a variable on the x-axis. Note that given the assumption that only the first gas, nitrous oxide, contributes to changes in gas volume, \( V_I = V_I + V_{NO}^{SG} \).

Second Gas Effect in Gas Phase. Whereas the second gas is absorbed by the same volume of blood whether or not nitrous oxide is present, this is not the case in the gas phase.

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Here the second gas is contained in a smaller volume whose size depends on the rate of nitrous oxide uptake. The equations describing this phase are therefore more complicated. Only the final result is given here.

\[
\text{AR(gas)} = 1 + \left( \frac{1}{\lambda_{SG} - \lambda(1 - F_t) I} \right) \left( \frac{V_{\text{out}}}{V_0} \right) + \left( \frac{\lambda_{SG} I_{SG} - \lambda(1 - F_t) I}{1 - \lambda_{SG} I_{SG}} \right)
\]  

(2.21)

\[\text{AR(gas)} = 1 + k(1 - WR)\]

(2.22)

where \( k \) is a constant that differs for gas and blood and incorporates the effect of \( \theta \). When the augmentation ratio equals 1, there is no second gas effect, so when the second gas effect occurs, we can write second gas effect, SGE = \( k(1 - WR) \). This indicates how the second gas effect can be both a function of the degree of nitrous oxide uptake \( (1 - WR) \) and the degree of ventilation-perfusion mismatch (which appears in the term \( k \) along with the solubility of the first and second gases and the inspired concentration of the first gas).

Perhaps the most useful form of equation 2.21 involves the substitution of \( V_t - V_0 \) for \( V_{\text{out}} \). This gives rise to the following equation:

\[\text{AR} = 1 + k \left( \frac{V_t - V_0}{V_0} \right) \]

(2.23)

References