Effect of ventilation-perfusion inhomogeneity and $N_2O$ on oxygenation: physiological modeling of gas exchange

PHILIP J. PEYTON, GAVIN J. B. ROBINSON, AND BRUCE THOMPSON

Departments of Anaesthesia and Respiratory Medicine, Austin and Repatriation Medical Centre, Heidelberg 3084; and Department of Anaesthesia and Pain Medicine, The Alfred, Prahan 3181, Melbourne, Victoria, Australia

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Peyton, Philip J., Gavin J. B. Robinson, and Bruce Thompson. Effect of ventilation-perfusion inhomogeneity and $N_2O$ on oxygenation: physiological modeling of gas exchange. J Appl Physiol 91: 17–25, 2001.—Ventilation-perfusion ($V_A/Q_I$) inhomogeneity was modeled to measure its effect on arterial oxygenation during maintenance-phase anesthesia involving an inspired mixture of 30% $O_2$ and either $N_2O$ or $N_2$. A multialveolar compartment computer model was constructed based on a log normal distribution of $V_A/Q_I$ inhomogeneity. Increasing the log SD of the distribution of blood flow from 0 to 1.75 produced a progressive fall in arterial $P_{O_2}$ ($P_{A_{O_2}}$). The fall was less steep in the presence of $N_2O$ than when $N_2$ was present instead. This was due mainly to the concentrating effect of $N_2O$ uptake on alveolar $P_{O_2}$ in moderately low $V_A/Q_I$ compartments. The improvement in $P_{A_{O_2}}$ when $N_2O$ was present instead of $N_2$ was greatest when the degree of $V_A/Q_I$ inhomogeneity was in the range typically seen in anesthetized patients. Models based on distributions of expired and inspired alveolar ventilation give quantitatively different results for $P_{A_{O_2}}$. In the presence of $V_A/Q_I$ inhomogeneity, second-gas and concentrating effects may have clinically significant effects on arterial oxygenation even at “steady-state” levels of $N_2O$ uptake.

alveolar-arterial difference; oxygen uptake

THE CONCENTRATING AND second-gas effects of rapid nitrous oxide ($N_2O$) uptake ($V_{N_2O}$) early in an inhalational anesthetic and its effect on alveolar $O_2$ concentration were described by Stoelting and Eger (4, 21). It is generally assumed that, after the immediate postinduction phase of anesthesia, maintenance-phase levels of $V_{N_2O}$ by the lungs do not produce a significant “concentrating effect” on other alveolar gases and, therefore, do not increase $O_2$ uptake ($V_{O_2}$) or improve arterial oxygenation.

However, in a series of studies by Nunn and co-workers (15, 16, 24), it was demonstrated that arterial oxygenation was unimpaired or improved in patients who were undergoing inhalational anesthesia, breathing $O_2$ with $N_2O$ for >0.5 h, compared with a group breathing $O_2$ with nitrogen ($N_2$). This result was surprising in view of the expected tendency of a soluble gas such as $N_2O$ to hasten absorption atelectasis and worsen shunt (24).

Farhi and Olzowska (5) calculated the effects of differing inspired concentrations of $N_2O$ on the relationship between the $P_{O_2}$ and $P_{CO_2}$ values and ventilation-to-perfusion ratio ($V_A/Q_I$). They demonstrated that the shape of the curve on the $O_2$-$CO_2$ diagram was changed, with a significantly elevated $P_{O_2}$ predicted in the presence of a moderately low $V_A/Q_I$ and high inspired $N_2O$. The implications for overall gas exchange in the lung were not explored further by these authors at the time.

More recently, Korman and Mapleson (10) have offered an expanded description of the mechanism of the concentrating and second-gas effects. Their treatment distinguishes “constant outflow” and “constant inflow” models based on predetermined values for expired ($V_{AE}$) and inspired alveolar ventilation ($V_{A_I}$), respectively, within a single lung compartment. These different models may be expected to give different results when applied to the calculation of overall gas exchange in the lung.

The application of a multicompartment analysis of log normal distributions of $V_{AE}$ and blood flow (Q) in the lung has been used by previous workers investigating the causes of reduced efficiency of gas exchange under worsening inhomogeneity of $V_A/Q_I$ throughout the lung. This was demonstrated by West (25, 26) and Kelman (10) to result in a widening of the predicted alveolar-arterial difference for all gases. However, these early models did not take into account the interdependent nature of exchange of multiple soluble alveolar gases. More sophisticated models have since been applied to scenarios representing multiple gas exchange during inhalational anesthesia. These include a variant based on a log normal distribution of $V_{AI}$, which serves to demonstrate that lung units with very low $V_A/Q_I$ may suffer collapse when gas uptake exceeds $V_{AI}$ and that this process is accelerated by the presence of $N_2O$ (2).

The present authors have sought to investigate further the relationship between concentrating and sec-

Address for reprint requests and other correspondence: P. J. Peyton, Dept of Anaesthesia, Austin & Repatriation Medical Centre, Heidelberg 3084, Melbourne, Australia (E-mail: phil@austin.unimelb.edu.au).

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ond-gas effects and distributions of $V_A/Q$ and their effect on overall $O_2$ exchange. We have constructed a multialveolar compartment computer model of alveolar-capillary exchange of multiple gases ($O_2$ and $CO_2$ and any combination of inert gases such as $N_2O$ or $N_2$). This was used to predict the effects of differing degrees of $V_A/Q$ inhomogeneity on $V_{O2}$ and arterial $P_{O2}$ ($P_{A\text{O}_2}$) in scenarios related to inhalational anesthesia. Results were sought from two models based on log normal distributions of $V_{AE}$ and $V_{AI}$. These were considered to represent constant outflow and constant inflow principles of ventilation, respectively, applied to multiple compartments.

**METHODS**

A computer model was designed to represent the exchange of multiple gases across the alveolar-capillary membrane. Log normal distributions of $Q$ and ventilation were generated with log$_{se}$ SDs varying between 0 (homogeneous lung) and 1.75. West (25, 26) showed that, for any given mode and log SD, identical results are obtained with a primary distribution of either $Q$ or ventilation. The structure and data flow of this model are outlined in more detail in the APPENDIX.

Either $V_{AE}$ or $V_{AI}$ can be nominated for the distribution to be generated. Where $V_{AI}$ was nominated, the effect of absorption atelectasis in compartments where $V_{AE}/Q$ was less than zero was modeled. This is based on similar assumptions as those made by Dantzker et al. (2), who assumed that compartments with negative calculated $V_{AE}$ would suffer collapse. Given that steady-state gas exchange was being modeled, it was assumed that perfusion of such compartments was shunt, with an end-capillary gas content identical to that of mixed venous blood. Both $V_{AE}$ and $V_{AI}$ for these compartments was made zero, and the inspired ventilation from them was redistributed to the remaining compartments by multiplying each by a scaling factor to restore total $V_{AI}$ to its nominated value.

Modifications incorporated by Dantzker et al. (2) to simulate the effect of hypoxic pulmonary vasoconstriction (HPV) on the distribution of $Q$ were included. Once again, perfusion of all compartments was scaled so that total $Q$ remained at the nominated value. An iterative approach is required for these processes, where the scaling of ventilation and perfusion progressively reduces, so that final distributions obtained for each are consistent with nominated target values for exchange of each gas.

West (25) demonstrated that 10 compartments are adequate to obtain maximal precision of results for output variables from such a model. It was found, however, that when collapse of compartments with critically low $V_{AE}/Q$ was incorporated, 50 compartments were required to avoid noticeable quantization error because of inclusion or exclusion of compartments with $V_{AE}/Q$ values near the critical value.

**RESULTS**

In the presence of $V_{N2O}$ of 100 ml/min, $P_{AO2}$ decreased progressively as the log SD of the distribution of $Q$ increased, reflecting worsening $V_A/Q$ inhomogeneity. However, where a log normal distribution of $V_{AE}$ or constant outflow model was employed, the fall was significantly less steep in the presence of $N_2O$ than when $N_2$ was present instead.

The difference in predicted $P_{AO2}$ in the presence of $N_2O$ compared with $N_2$ was smallest at lower SDs of $Q$ (more homogeneous lungs) and greatest (an increase of ~50%) at more severe levels of $V_A/Q$ inhomogeneity (Fig. 1).

The constant inflow ($V_{AI}$ based) model produced quantitatively different results, predicting a much smaller increase in $P_{AO2}$ when $N_2O$ replaces $N_2$ than that predicted by the $V_{AE}$-based model, even where total gas uptakes were constrained to the same values.

In the $N_2O$ washout scenarios, a lower $P_{AO2}$ was predicted in the presence of $N_2O$ compared with $N_2$ at all degrees of $V_{AE}/Q$ inhomogeneity (Fig. 2). The effect was relatively greatest at mild degrees of $V_{AE}/Q$ spread, where $P_{AO2}$ is reduced significantly in the presence of rapid $N_2O$ elimination (400 ml/min), although much more modestly at low rates of $N_2O$ excretion (100 ml/min).

**DISCUSSION**

$P_{AO2}$ steadily declined as the log SD of the distribution of $Q$ increased. This is consistent with previously held assumptions regarding the effect of $V_A/Q$ inhomogeneity on gas uptake (10, 25, 26). However, the results of this modeling suggest that substituting $N_2$ with $N_2O$ can produce significant increases in arterial oxygenation, even at a low rate of $V_{N2O}$ by the lung, and that this effect is a direct result of the presence of $V_A/Q$ inhomogeneity. Improvement in oxygenation of this degree is not expected in a homogeneous lung (indicated by a log SD of zero in Fig. 1), where a minor rise in $P_{AO2}$ of only ~4 Torr is predicted.

Importantly, improved oxygenation is not predicted by a traditional three-compartment model of $V_A/Q$ scatter, where only shunt, dead space, and a uniform compartment are considered. If the homogeneous lung just
mentioned is considered, the effect of a superimposed true shunt fraction will only be to reduce further the minor increase in $P_{\text{AO}_2}$ induced by the alveolar concentrating effects of $V_{\text{N}_2\text{O}}$.

The level of $V_{\text{N}_2\text{O}}$ applied to these calculations, using the formula of Severinghaus (19), is consistent with the situation well into the maintenance phase of anesthesia, where essentially steady-state kinetics of gas exchange can be considered to be present. At this stage, the concentrating and second-gas effects of the phase of rapid $V_{\text{N}_2\text{O}}$ early in the course of the anesthetic are customarily considered to have passed.

A number of authors (1, 3, 6, 12, 13) studying distributions of $V_{\text{AE}}$ and $Q$ using the multiple inert-gas elimination technique (MIGET) in subjects under $\text{N}_2\text{O}$ anesthesia have demonstrated an increase in the spread of $V_{\text{AE}}/Q$ throughout the lung (as indexed by the log SD of the distributions) after induction of anesthesia. Dueck et al. (3) suggested that $V_{\text{N}_2\text{O}}$ from low $V_{\text{AE}}/Q$ lung units may increase alveolar $P_{\text{O}_2}$ and $P_{\text{AO}_2}$ and that this might continue for some time after induction of anesthesia, although the mechanism for this was not explored in detail.

The explanation for this phenomenon lies in the increased concentration of alveolar $O_2$ produced by $V_{\text{N}_2\text{O}}$, operating in lung compartments with moderately low $V_{\text{A}}/Q$. The effect of this is to increase $P_{\text{AO}_2}$ and $V_{\text{O}_2}$ within that compartment. Figure 3 shows that the increase in $V_{\text{O}_2}$ in the presence of $\text{N}_2\text{O}$ compared with $\text{N}_2$ is greatest in those compartments with moderately low $V_{\text{A}}/Q$. These compartments obtain a high proportion of total $Q$ and not surprisingly have a predominant

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Comparison of predicted arterial $P_{\text{O}_2}$ ($P_{\text{AO}_2}$) with increasing ventilation-to-perfusion ratio ($V_{\text{A}}/Q$) inhomogeneity [as indexed by log SD of blood flow ($Q$)] in the presence of 70% $\text{N}_2\text{O}$ or $\text{N}_2$ in the inspired mixture. Data from 2 different models [constant outflow based on a log normal distribution of expired alveolar ventilation ($V_{\text{AE}}$), constant inflow based on a log normal distribution of inspired alveolar ventilation ($V_{\text{AI}}$)] are presented. $O_2$ uptake ($V_{\text{O}_2}$; 250 ml/min), $CO_2$ uptake (200 ml/min), $\text{N}_2\text{O}$ uptake (100 ml/min), and overall $V_{\text{AE}}$ (4.1 l/min) were identical in all scenarios.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Comparison of predicted $P_{\text{AO}_2}$ with increasing $V_{\text{A}}/Q$ inhomogeneity (as indexed by log SD of $Q$) during $\text{N}_2\text{O}$ washout at a high and a low rate of elimination, compared with the situation where $\text{N}_2$ is present instead. Inspired fraction of $\text{N}_2\text{O}$ was 0, inspired fraction of $O_2$ concentration was 0.3 with the balance $\text{N}_2$, and all solutions constrained to an arterial $P_{\text{CO}_2}$ of 45 Torr.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Distributions of $Q$ and $V_{\text{O}_2}$ for a given mixed venous $O_2$ content across compartments where the log SD of $Q$ was 1.5. In the presence of inspired $\text{N}_2\text{O}$, $V_{\text{O}_2}$ is considerably higher in low $V_{\text{AE}}/Q$ compartments than when $\text{N}_2$ is present instead, producing a much higher mixed pulmonary end-capillary $O_2$ content.}
\end{figure}
effect on the composition of mixed blood leaving the lung. It should be noted that, according to Farhi and Olzowska (5), significant increases in alveolar PO2 in moderately low VA/Q lung units are not expected if the inspired N2O concentration fraction is less than ~50%. Thus the effect of N2O on arterial oxygenation would not be expected to be as significant at a low inspired fraction of N2O concentration.

Two phenomena of interest emerge from these results. These are, first, the significant second-gas and concentrating effects occurring in moderately low VA/Q compartments where N2O is present in sufficient concentration and, second, the quantitatively different predictions of models based on generated distributions of inspired and expired ventilation.

The historical development of our understanding of the mechanism of the effect of uptake of one gas on that of other inspired gases is somewhat confused. The term “second-gas effect” was originally applied to the observed increase in the rate of rise of the alveolar concentration of volatile agent when N2O was administered. The mechanism was postulated to be that further fresh gas was indrawn to replace the volume of inspired alveolar concentration fraction is less than one-half of the N2O in the inspired gas mixture during rapid VN2O).

Korman and Mapleson (11) recently provided a more complete description of these processes that distinguishes constant outflow and constant inflow models based on predetermined values for VAE and VAI, respectively. Unlike the earlier classic description (21), their treatment predicts final alveolar concentrations that agree with those calculated by equations based on principles of mass balance applied to the relationship of VA to gas uptake. The constant outflow principle assumes a predetermined expired alveolar volume for a lung compartment. Net uptake of alveolar gas causes further fresh gas to be passively drawn into the alveolus, evoking the second-gas effect. When a constant inflow principle applies, inspired alveolar volume is predetermined for the compartment, and net gas uptake causes shrinkage in alveolar volume, producing a concentrating effect and a lower expired volume. When the terms second-gas effect and concentrating effect are used in the present study, it is to refer to the effects of these two distinct but often concurrent mechanisms relating VA to gas exchange.

The difference between these two principles for a single compartment is illustrated diagramatically by Korman and Mapleson (11), and Fig. 4 is adapted from their diagram. Constant inflow before and after equilibration of alveolar gas and blood is represented by columns A and B, respectively. Constant outflow before and after equilibration is represented by columns C and D. Figure 4 is based on a simplified analysis in which no net exchange of vehicle gas (here denoted as O2) to function as the insoluble vehicle gas. The VA/Q of the compartment has been adjusted so that one-half of the N2O in the inspired gas mixture is taken up. (This figure was adapted from Ref. 9 with kind permission from the publishers and authors.)

![Fig. 4. Constant inflow and outflow cases before and after uptake. A and B: inspired ventilation is kept constant and equal to 4.1 l/min (A, before equilibration; B, after equilibration). C and D: expired ventilation is kept constant and equal to 4.1 l/min (C, before equilibration; D, after equilibration). This figure is based on a simplified analysis in which no net exchange of vehicle gas takes place. Assume a respiratory exchange ratio of 1.0. The VA/Q of the compartment has been adjusted so that one-half of the N2O in the inspired gas mixture is taken up. (This figure was adapted from Ref. 9 with kind permission from the publishers and authors.)](image)

Fig. 4. Constant inflow and outflow cases before and after uptake. A and B: inspired ventilation is kept constant and equal to 4.1 l/min (A, before equilibration; B, after equilibration). C and D: expired ventilation is kept constant and equal to 4.1 l/min (C, before equilibration; D, after equilibration). This figure is based on a simplified analysis in which no net exchange of vehicle gas takes place. Assume a respiratory exchange ratio of 1.0. The VA/Q of the compartment has been adjusted so that one-half of the N2O in the inspired gas mixture is taken up. The diagram illustrates that, regardless of whether a constant outflow or constant inflow principle is applied, the final gas concentrations at equilibrium will be the same, dictated by the VA/Q and inspired concentration. However, the volumes of gas inspired, taken up, and expired are very different.

These principles can be applied to multiple compartments and, substituting ventilation rates over time for static volumes, have been applied to the computer modeling performed here. When VAE is nominated for each lung compartment according to a specified distribution, the model can be considered analogous to a constant outflow model. Changes in gas exchange due, for example, to changes in fractional inspired or mixed venous gas content will alter the calculated VAI for that compartment, but VAE is predetermined. When a distribution of VAI is nominated instead, the model performs as a constant inflow model, and VAE is the dependent variable.

In our modeling, the constant inflow (VAI based) model produced quantitatively different results for overall gas exchange, predicting a much smaller increase in PaO2 with N2O than that predicted by the VAE-based model, even when total gas uptakes and total VAI and VAE were constrained to the same values. The reason for this lies in the different shapes of the
distributions produced for ventilation (Fig. 5). In the constant inflow model, the relatively high proportion of inspired ventilation taken up produces very low or even negative values for \( V_{AE} \) in low \( V_{AI}/Q \) compartments. In these compartments, when net gas uptake occurs, \( V_{AI} \) is necessarily higher in the constant outflow model than in the constant inflow model, with greater \( V_{O2} \) and \( V_{N2O} \) for a given combination of alveolar and mixed venous partial pressures. The different performance of the two distributions is accentuated in a situation of relatively low overall inert-gas uptake, in which perfusion-driven \( V_{O2} \) forces down alveolar \( P_{O2} \) and mixed venous \( P_{O2} \), whereas further concentrating retained inert gas in the poorly ventilated alveolus. The steepness of the HBO2 dissociation curve at lower \( P_{O2} \) values depresses the overall \( P_{A_{O2}} \), when end-capillary blood from these low \( V_{AI}/Q \) lung units mixes with the smaller volume of blood from better ventilated regions.

**Clinical implications.** It is notable that the predicted increment in \( P_{A_{O2}} \) produced by the substitution of inspired \( N_2 \) with \( N_2O \) (especially as calculated using a constant outflow model) is maximal in the range of \( V_{A/Q} \) inhomogeneity commonly seen in healthy, anesthetized patients. This corresponds with SDs of the distribution of \( Q \) used in these lung models of 1.0–1.5 (1, 3, 6, 12, 13). This has possible clinical implications, and, whereas the mechanism of the effect has been outlined above, the theoretical factors modulating this effect as well as existing clinical data were also examined.

Nunn and co-workers (15, 16, 24) measured \( P_{A_{O2}} \) in a series of 50 patients who had undergone an average of 36–45 min of general anesthesia with either spontaneous or controlled ventilation breathing \( O_2 \) in either 70% \( N_2 \) or \( N_2O \). They were unable to find any evidence of poorer arterial oxygenation in the \( N_2O \) group. In fact, after their findings were adjusted for the slightly different inspired fraction of \( O_2 \) of the groups, \( P_{A_{O2}} \) was the same in the presence of \( N_2 \) and \( N_2O \) in the controlled ventilation groups. This surprised the authors, who were unable to explain the findings. Moreover, analysis of their figures (using Fisher’s test and \( z \)-test) shows that, for the spontaneous ventilation groups, \( P_{A_{O2}} \) was clinically and statistically significantly higher (107 vs. 81 Torr, \( P < 0.01 \)) in the presence of \( N_2O \) than in the presence of \( N_2 \).

They did not explore the possibility of a concentrating effect as an explanation of higher alveolar \( P_{O2} \) values, presumably because of the assumption that, at expected rates of \( V_{N2O} \), this would be trivial. With the use of their data, the expected improvement in \( P_{A_{O2}} \) in the presence of \( N_2O \) would be expected to be only ~5%, assuming no inhomogeneity of \( V_{AE}/Q \), (even less if the effect of a typical shunt of ~10–15% is incorporated). However, with the assumption of a typical degree of \( V_{A/Q} \) inhomogeneity of an essentially log normal pattern among their anesthetized subjects, improvements in arterial oxygenation in the presence of \( N_2O \) are entirely explained by our model.

**Alveolar collapse and absorption atelectasis.** The clinical phenomenon and theoretical basis of absorption atelectasis have been well described, and the kinetics of reduction of gas volume in a homogeneous segment of lung due to \( V_{O2} \), where conducting airways are obstructed, has been quantified by previous authors (2, 7, 24). Compared with the situation prevailing when pure \( O_2 \) is inhaled, it can be shown that the speed and magnitude of the effect is greater when \( N_2O \) is present and markedly reduced when \( N_2 \) is present instead. Dantzker et al. (2) applied a computer model involving a log normal distribution of \( V_{AI} \) to demonstrate that lung units with very low \( V_{AI}/Q \) may suffer collapse when gas uptake exceeds \( V_{AI} \). This threshold level of \( V_{AI}/Q \) was higher in the presence of soluble gases, such as \( N_2O \), and at higher inspired \( O2 \) concentrations.

These authors pointed out that the fate of these segments is not clear. They may remain open and receive collateral ventilation from adjacent areas or even further fresh gas from the anatomic dead space or may suffer a loss of alveolar volume, leading to collapse. In the latter case, any continuing perfusion of these collapsed units would be effectively shunted, and the effect of this can be predicted to be a reduction of \( P_{A_{O2}} \). Because steady-state gas exchange consistent with maintenance-phase anesthesia was examined, the effect of alveolar collapse in the presence of critically low \( V_{AI}/Q \) was incorporated in all cases examined in the present study, with the associated \( Q \) considered to be shunt. Dantzker et al. (2) showed that the threshold value of \( V_{AI}/Q \) for alveolar collapse when \( N_2O \) is
present is considerably higher. This predictably produced a much greater number of low \( V_{AI}/Q \) compartments suffering collapse and a higher proportion of total \( Q \) becoming shunt in all scenarios modeled by us with \( N_2O \). However, at no point was \( P_{A\text{O}_2} \) predicted in our modeling to be lower in the presence of \( N_2O \), despite the larger proportion of total \( Q \) perfusing non-ventilated lung compartments. Therefore, the concentrating effects of \( V_{N2O} \) on alveolar \( P_{O2} \) in moderately low \( V_{AI}/Q \) compartments consistently outweighed the effect of the increased proportion of \( Q \) involved in shunting.

**Relationship of ventilation to gas exchange.** This type of computer modeling of gas exchange requires that a distribution of ventilation be nominated. This distribution must be assumed to be a reasonable generalization of the type of distribution seen in the population being modeled. Previous workers (1, 3, 6, 12, 13, 18, 22) have demonstrated, using the MIGET, that subjects both awake (spontaneously breathing) and undergoing general anesthesia with controlled ventilation exhibit patterns of \( V_{A}/Q \) matching throughout the lung, essentially consistent with a log normal distribution, although variations on this pattern are seen in a variety of physiological and pathological situations. Common variations are seen in patients with normal lungs, such as a “shelf” of low \( V_{A}/Q \) subunits, which can transform into true shunt, typically seen after administration of 100% \( O_2 \). The SD of the distribution is seen to increase with age and also with anesthesia.

The different predictions of \( V_{AE} \) (constant outflow) models and \( V_{AI} \) (constant inflow) models, particularly in relation to calculated \( P_{A\text{O}_2} \), pose the question for computer modeling of gas exchange: what ventilatory distribution, when applied to such a model, gives the most physiologically realistic results? Is it inspired ventilation, expired ventilation, or some other ventilatory parameter? The different predicted behavior of the lung in oxygenation of the blood in the presence of a soluble and an insoluble gas, such as \( N_2O \) and \( N_2 \), may provide some guidance when correlated with the available clinical data.

Clinical studies carried out in the past using MIGET are based on calculations of the proportion of expired ventilation that is not part of anatomic dead space (19) and thus relate to a \( V_{AE} \)-based or constant outflow principle and computer model. However, the function of many artificial ventilators used in clinical anesthesia practice may be better described by a constant inflow principle (11, 14), where the inspired tidal volume delivered to the patient is set. It has also been suggested that a constant outflow model relates more closely to the situation of spontaneous ventilation. Here the subjects regulate the degree of expansion of the thorax with each breath in response to their respiratory drive. All gas inflow is the result of the negative intrathoracic pressure generated whether actively by chest expansion or passively by uptake of gas across the alveolar-capillary membrane.

The findings of the studies of Nunn and co-workers (15, 16, 24) are consistent with these assumptions. A significant difference in \( P_{A\text{O}_2} \) was seen between their \( N_2O \) and \( N_2 \) groups when spontaneous ventilation took place, as was predicted by the constant outflow model based on a log normal distribution of \( V_{AE} \). However, there was no difference (adjusting their findings for the slightly different inspired fraction of \( O_2 \) concentration of the groups) in the presence of controlled ventilation, as was predicted by the constant inflow model based on a log normal distribution of \( V_{AI} \) with collapse of critically low \( V_{AI}/Q \) segments. Dueck et al. (3), studying subjects under controlled ventilation with \( O_2 \) and either \( N_2 \) or \( N_2O \), also found no difference in arterial oxygenation.

When compared with the predictions of the computer models outlined, these studies provide evidence, on the basis of arterial oxygenation, that each mode of ventilation is characterized by its own predominant \( V_{A} \) principle (constant inflow or constant outflow).

**Diffusion hypoxia and \( V_{A}/Q \) inhomogeneity.** Not surprisingly, a lower \( P_{A\text{O}_2} \) was predicted in the presence of \( N_2O \) compared with \( N_2 \) at all degrees of \( V_{A}/Q \) inhomogeneity. This is the basis of so-called “diffusion hypoxia.” The effect is relatively most severe at mild degrees of \( V_{AE}/Q \) spread, where \( P_{A\text{O}_2} \) is reduced significantly in the presence of rapid \( N_2O \) elimination (400 ml/min), although much more modestly at low rates of \( N_2O \) excretion (100 ml/min). Whereas this depression of \( P_{A\text{O}_2} \) is greater the higher the rate of \( N_2O \) elimination occurring, it can be seen that the major contributor to hypoxemia at severe degrees of \( V_{AE}/Q \) inhomogeneity is mismatch of \( V_{AE}/Q \) itself rather than \( N_2O \) elimination.

For any gas for which the inspired concentration is zero, the predicted effect of increasing \( V_{A}/Q \) inhomogeneity is to reduce fractional elimination (26). The practical outcome of this in terms of \( N_2O \) kinetics will be a prolongation of the phase of washout of inert gas from the body. The reduction in \( P_{A\text{O}_2} \) during \( N_2O \) washout (as compared with an \( O_2-N_2 \) mixture) is less in absolute terms at higher levels of inhomogeneity. Furthermore, the \( N_2O \) elimination rate will be lower with more severe inhomogeneity; therefore, the reduction in \( P_{A\text{O}_2} \) expected at a given time postanesthesia with \( N_2O \) compared with \( N_2 \) can be expected to be still less. However, the clinical consequences of any reduction may be considered more severe: when the baseline is low, the duration of the effect is more prolonged.

**Conclusion.** A multicompart ment model of a log normal distribution of \( V_{A}/Q \) values predicts that concurrent administration of \( O_2-N_2O \) mixtures results in clinically significant second-gas and concentrating effects in low \( V_{A}/Q \) lung units. The effect of the enrichment of alveolar \( O_2 \) in these compartments is improved arterial oxygenation compared with an \( O_2-N_2 \) mixture, even in the presence of the very modest rates of \( V_{N2O} \) seen well into a prolonged inhalational anesthetic.

The most significant increase in \( P_{A\text{O}_2} \) produced by \( V_{N2O} \) is predicted to occur at levels of \( V_{A}/Q \) inhomogeneity typically seen in anesthetized subjects. The increase is small when a log normal distribution of \( V_{AI} \) is modeled but is substantial when a log normal distribution of \( V_{AE} \) is nominated.
Consideration of the mechanics of $V_A$ in relation to gas uptake suggests that spontaneous ventilation is more consistent with a model characterized by a log normal distribution of $V_{AE}$ (constant outflow principle). Controlled ventilation is consistent with a distribution predominantly of $V_{AI}$ (constant inflow principle). Under this hypothesis, data from this modeling are consistent with previously published clinical measurements of $P_{aO_2}$ under anesthesia.

In the presence of significant $V_A/Q$ inhomogeneity, second-gas and concentrating effects on oxygenation may be clinically significant even at steady-state levels of $V_{N_2O}$.

**APPENDIX**

**Computer Program: Generation of Log Normal Distributions**

Using a routine described by West (25), a frequency distribution of $V_{AE}$ per unit volume of lung ($V_{AE}/\text{vol}$) or $Q$ per unit volume ($Q/\text{vol}$) can be generated. The distribution is Gaussian in shape when the abscissa ($V_{AE}/\text{vol}$) is plotted logarithmically. As pointed out by Kelman (10), description of a log normal distribution in terms of a “mean” is unhelpful, and the distribution can best be described in terms of two parameters: the mode (or $V_{AE}/\text{vol}$ of peak frequency) and the log SD. The position of the first SD with a log normal distribution can be located as that point at which the frequency is 60.65% of the mode frequency on the left of it. This is also the point of maximal negative slope. Second and third and negative SDs will be placed equidistantly along the abscissa. The magnitude of the log SD of the distribution can be varied around a mode, and both can be specified.

The equation used is

$$y = \frac{1}{\sigma \sqrt{2\pi}} \exp \left\{ -\frac{1}{2} \left( \frac{x - \mu}{\sigma} \right)^2 \right\}$$

where $y$ is frequency or relative volume of lung, $x$ is log$_e$ $V_{AE}/\text{vol}$, $\mu$ is log$_e$ mode $V_{AE}/\text{vol}$, and $\sigma$ is log SD of $V_{AE}/\text{vol}$.

A range of values of $V_{AE}/\text{vol}$ or $Q/\text{vol}$ spanning 3 log SDs on either side of the mode is taken (although, where the nominated log$_e$ of the SD was set at > 1.0, a fourth SD is added to the lower end of the range, as suggested by West (25), in view of the presence of appreciable amounts of $Q$ in the small volume of lung represented by negligible values of $V_{AE}/\text{vol}$).

From this range, the distribution is divided into a number of compartments evenly spaced along the abscissa. The components of the distribution can be evenly scaled so that the total $V_{AE}$ of the compartments combined equals any given specified value. If $Q/\text{vol}$ is given at a constant and equal value for each compartment and scaled similarly up to a given value, the resultant distribution of $V_{AE}/Q$ for the compartments will also be log normal. The output of this subroutine is a series of paired values for $V_{AE}$ and $Q$ for each compartment, which, when summed, equal the selected total $V_{AE}$ and $Q$, giving a desired overall $V_{AE}/Q$, and have a predetermined variance.

Either $V_{AE}$ or $V_{AI}$ can be nominated for the distribution to be generated. By substituting ventilation rates over time for static volumes, where $V_{AE}$ is nominated for a lung compartment, the model can be considered analogous to a constant outflow model as defined by Korman and Mapleson (11), i.e., $V_{AE}$ remains constant, despite gas exchange within the alveolus, and gas uptake and $V_{AI}$ are calculated from the various input parameters. Changes in gas exchange due, for example, to changes in fractional inspired or mixed venous gas content will not change $V_{AE}$ for that compartment. This assumes that net uptake of alveolar gas causes further fresh gas to be passively drawn into the alveoli. Where $V_{AI}$ is nominated, a constant inflow principle applies in which $V_{AI}$ is constant, and net gas uptake causes shrinkage in alveolar volume and a lower $V_{AE}$.

In addition, the effect of absorption atelectasis in compartments where $V_{AE}/Q$ was less than zero was modeled, on the basis of similar assumptions as those made by Dantzker et al. (2) that compartments with negative calculated $V_{AE}$ would suffer collapse. Given that steady-state gas exchange was being modeled, it was assumed that perfusion of such compartments was shunt, with an end-capillary gas content identical to that of mixed venous blood. Both $V_{AE}$ and $V_{AI}$ for these compartments were made zero, and the inspired ventilation from them was redistributed to the remaining compartments by multiplying each by a scaling factor to restore total $V_{AI}$ to its nominated value. Modifications incorporated by Dantzker et al. to simulate the effect of HPV on the distribution of $Q$ were included. For each compartment, $Q$ is given by

$$Q = Q_{max}(1 - 0.6218e^{-0.0146P_{O_2}})$$

where $Q_{max}$ is the nominated $Q$ of the compartment derived from the log normal distribution. Once again, perfusion of all compartments was scaled so that total $Q$ for the lung remained at the nominated value. An iterative approach is required for these processes where the scaling of ventilation and perfusion progressively reduces so that final distributions obtained of each are consistent with nominated target values for exchange of each gas.

**Derivation of a Formula for a Computer Program to Calculate Alveolar Gas Concentrations in the Presence of Multiple Gas Uptake**

**$V_{AE}$-based model.** The system of equations used is based on those described by Olazowska and Wagner (17).

Consider a lung compartment with a given ratio of $V_{AE}$ and $Q$, which is ventilated with an inspired mixture of $O_2$ and inert gases $G$, $G'$, $G''$, etc. The lung compartment takes up these gases in a physiologically realistic manner that is dependent on the gradient between alveolar and mixed venous content of these gases and also eliminates $CO_2$.

For each gas $G$ in the alveolar gas mixture, the equation

$$V_{AI} \cdot F_{IG} - V_{AE} \cdot F_{AG} = \kappa \cdot Q(C'_{CG} - C_{VG})$$

was fulfilled, where $F_{IG}$ and $F_{AG}$ are the fractional concentrations of the gas in inspired and alveolar gas mixtures, respectively, $C'_{CG}$ is the fractional content in pulmonary end-capillary blood, $C_{VG}$ is the fractional mixed venous gas content within the compartment, and $\kappa$ is a constant that embodies the appropriate corrections for the effect of temperature on measured gas volumes. Converting to partial pressures and substituting the appropriate temperature conversion factor for $\kappa$

$$V_{AI} \frac{P_{IG}}{P_B} - V_{AE} \frac{P_{AG}}{P_B} = \frac{863}{P_B} Q(C'_{CG} - C_{VG})$$

was fulfilled, where $P_{IG}$ and $P_{AG}$ are partial pressures of gas in inspired and alveolar gas mixtures, respectively, and $P_B$ is dry gas barometric pressure (barometric pressure – partial pressure of water vapor) assumed to be 713 mmHg, body temperature is 37°C, and gas volumes are measured at STPD. For inert gases with linear dissociation curves, content is defined by

\[ \frac{V_{AE}}{V_{AI}} = \frac{P_{AG}}{P_{IG}} \]

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the Ostwald partition coefficient ($\lambda$), which embodies the appropriate temperature correction (26). Converting content in blood and gas phases to partial pressures and multiplying both sides by $P_G$, then for an inert gas

$$V_{AI} \cdot P_{IG} - V_{AE} \cdot P_{AG} = \bar{Q} (P_{C_G} - P_{V_G})$$

where $P_{C_G}$ is partial pressure in pulmonary end-capillary blood and $P_{V_G}$ is mixed venous gas partial pressure.

If we assume that the lung compartment is an ideal compartment in which $P_{AG}$ equals $P_{C_G}$, this can be transposed to solve for $P_{AG}$

$$P_{AG} = \frac{\bar{Q} \cdot V_{AI}}{\bar{Q} \cdot V_{AE} + \lambda} \cdot P_{IG} + \lambda \cdot P_{V_G}$$

Equation A2 can be applied to all other inert gases, $G'$, $G''$, etc., in the alveolar mixture.

$V_{AI}/\bar{Q}$ can be defined by transposing Eq. A1 for $O_2$

$$\frac{V_{AI}}{\bar{Q}} = \frac{863(C_{CO_2} - C_{VCO_2}) + P_{AO_2} \cdot \frac{V_{AE}}{\bar{Q}}}{P_{AO_2}}$$

where $C_{CO_2}$ is the fractional content of $O_2$ in end-capillary blood, $C_{VCO_2}$ is the mixed venous $O_2$ content, $P_{AO_2}$ is the alveolar partial pressure of $O_2$, and $P_{AO_2}$ is the inspired partial pressure of $O_2$.

Finally, this set of simultaneous equations can be solved using an appropriate iterative technique knowing that

$$P_B - (P_{AO_2} + P_{ACO_2} + P_{AGO_2} + P_{AG}) = 0$$

where $P_{ACO_2}$ is alveolar partial pressure of CO$_2$. When a nominated distribution of $V_{AE}$ is employed, the calculation is somewhat simplified, as pointed out by Farhi and Olszowska (5) by the fact that the value of $P_{ACO_2}$ and the fractional content of $CO_2$ in end-capillary blood ([C$_{CO_2}$]) is predetermined (allowing for acid-base buffering considerations) as, in the model, it depends only on $V_{AE}$, $Q$, and mixed venous $CO_2$ content ($C_{CO_2}$), not on $V_{AI}$. Thus

$$P_{ACO_2} = \frac{863(C_{CO_2} - C_{VCO_2})}{V_{AE}}$$

The relationship between partial pressure and gas content for $O_2$ and $CO_2$ in both end-capillary and mixed venous blood was expressed using the routines of Kelman (8, 9) for $CO_2$ and $O_2$ that characterize the dissociation curves of these gases. Modeling is incorporated from the Bohr and Haldane effects on $O_2$ and $CO_2$ carriage within each compartment in the presence of widely varying $V_{AI}/\bar{Q}$.

As well as estimating the different acid-base status of mixed venous and pulmonary arterial blood, it is necessary to take into account the acute disturbances in acid-base balance that occur within compartments, particularly in the face of relatively extreme degrees of $V_{AI}/\bar{Q}$ mismatch that are seen in some of these. Widely varying HbO$_2$ saturations and P$_{CO_2}$ values are seen across the compartments, and the Bohr and Haldane effects produced vary widely, affecting $O_2$ and $CO_2$ carriage. For this purpose, the Hendersen-Hasselbalch equation was used to relate P$_{CO_2}$ and pH in conjunction with the following equation relating base excess of the blood to plasma pH and bicarbonate (HCO$_3^-$) and Hb content

$$\text{Base excess} = \left[ \frac{[\text{Hb} \cdot 0.023]}{[\text{Hb} \cdot 0.023]} \times [(\text{HCO}_3^- - 24.41) + (2.3 \cdot \text{Hb} + 7.7)(\text{pH} - 7.4)] \right]$$

where all variables except pH are expressed in mmol/l.

It was assumed that, within the time course of pulmonary blood transit, no acute buffering of acid-base changes produced by acute changes in P$_{CO_2}$ occurred other than that of the CO$_2$–HCO$_3^-$–carbonic anhydrase system. The base excess was assumed to remain unchanged with the exception of the shift in the blood buffer line produced by acute changes in HbO$_2$ saturation (SO$_2$), which was characterized by the equations given by Siggaard-Andersen (20) relating base excess to Hb saturation and also to pH and HCO$_3^-$

$$\text{Base excess} = 0.19 \cdot \text{Hb}(1 - \text{SO}_2)$$

The interdependent nature of CO$_2$ carriage, pH, and HbO$_2$ carriage requires an iterative approach for its solution. Kelman demonstrated that a single repeat iteration only is needed to achieve sufficient precision (9).

Thus it can be seen that, for a lung compartment characterized by a given combination of input values for $V_{AE}$, $Q$, mixed venous partial pressure (or mixed venous content), and inspired partial pressure of a gas, we can solve for alveolar partial pressure of the gas (and fractional end-capillary blood content for that compartment) if we know the alveolar partial pressure of the other gases in the alveolar mixture. Assuming that there is one unique set of alveolar gas concentrations that meets the conditions set by any combination of input values, it is possible to calculate $P_{AG}$, $P_{AOG}$, $P_{AGO_2}$, etc., and $P_{AGO_2}$ (and C$_{CO_2}$) for that lung compartment using an iterative approach that is based on a modified, continuous bisection technique. (However, where $V_{AE}$ is stipulated, it is necessary to solve for $V_{AE}$ to determine $P_{ACO_2}$ for that compartment, and thus an iterative mechanism is required for its solution.) These alveolar fractional concentrations will be those that reflect the effects of uptake or output of all of the gases in the alveolar gas mixture.

The output variables for the whole lung were partial pressure of each gas species (including CO$_2$) in mixed alveolar gas and mixed end-capillary blood, mixed end-capillary blood content, and uptake of each gas. These were calculated by taking a flow-weighted average of the outputs of all of the compartments for both alveolar gas and end-capillary blood and total uptakes obtained by summing the uptakes of all of the compartments. After each of these steps, the acid-base status of the mixed end-capillary or arterial blood was further calculated by using an iterative approach, as described above, to arrive at final values for $P_{ACO_2}$ and $P_{AO_2}$.

A further iterative process allows nomination of the uptake of any or all of the gases as an input variable. This was performed by varying the mixed venous point for each gas by continuous bisection until the set of mixed venous values is obtained that meets the conditions specified by the inspired fractional concentration, $V_{AE}/\bar{Q}$, and net exchange of each gas species for all of the compartments.

$V_{AI}$-based model. Consider a similar lung compartment with a given ratio of $V_{AI}$ and $Q$.

Equation A3 above can be transposed to solve for $V_{AE}/\bar{Q}$

$$\frac{V_{AE}}{\bar{Q}} = \frac{P_{AO_2} \cdot V_{AI}}{863(C_{CO_2} - C_{VCO_2})}$$

The solution of the simultaneous set of alveolar gas concentrations is achieved in a similar way to that described above. However, the solution for $P_{ACO_2}$ needs to be included in the iterative process.
An alternative method involves using Eqs. A1–A5 and solving for VAI and then progressively coercing the distribution of VAI to be log normal using an iterative method. The resulting solution is identical to that achieved using Eq. A6. This method was often found to be faster, as it obviates the need for calculation of paired values for PA2CO2 and CcCO2 consistent with the VAE/Q obtained from Eq. A6 during every iteration in pursuit of the solution for each compartment.

REFERENCES


