Effect of ventilation-perfusion inhomogeneity and N₂O on oxygenation: physiological modeling of gas exchange

PHILIP J. PEYTON,¹ GAVIN J. B. ROBINSON,² AND BRUCE THOMPSON³
Departments of ¹Anaesthesia and ²Respiratory Medicine, Austin and Repatriation Medical Centre, Heidelberg 3084; and ³Department of Anaesthesia and Pain Medicine, The Alfred, Prahan 3181, Melbourne, Victoria, Australia

Received 4 April 2000; accepted in final form 6 February 2001

Peyton, Philip J., Gavin J. B. Robinson, and Bruce Thompson. Effect of ventilation-perfusion inhomogeneity and N₂O on oxygenation: physiological modeling of gas exchange. J Appl Physiol 91: 17–25, 2001.—Ventilation-perfusion (VA/Q) inhomogeneity was modeled to measure its effect on arterial oxygenation during maintenance-phase anesthesia involving an inspired mixture of 30% O₂ and either N₂O or N₂. A multialveolar compartment computer model was constructed based on a log normal distribution of VA/Q inhomogeneity. Increasing the log SD of the distribution of blood flow from 0 to 1.75 produced a progressive fall in arterial Pao₂ (Pao₂). The fall was less steep in the presence of N₂O than when N₂ was present instead. This was due mainly to the concentrating effect of N₂O uptake on alveolar Pao₂ in moderately low VA/Q compartments. The improvement in Pao₂ when N₂O was present instead of N₂ was greatest when the degree of VA/Q 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 Pao₂. In the presence of VA/Q inhomogeneity, second-gas and concentrating effects may have clinically significant effects on arterial oxygenation even at “steady-state” levels of N₂O uptake.

alveolar-arterial difference; oxygen uptake

THE CONCENTRATING AND second-gas effects of rapid nitrous oxide (N₂O) uptake (VN₂O) early in an inhalational anesthetic and its effect on alveolar O₂ 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 VN₂O by the lungs do not produce a significant “concentrating effect” on other alveolar gases and, therefore, do not increase O₂ uptake (VO₂) 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 O₂ with N₂O for >0.5 h, compared with a group breathing O₂ with nitrogen (N₃). This result was surprising in view of the expected tendency of a soluble gas such as N₂O to hasten absorption atelectasis and worsen shunt (24).

Farhi and Olzowska (5) calculated the effects of differing inspired concentrations of N₂O on the relationship between the PO₂ and PCO₂ values and ventilation-to-perfusion ratio (VA/Q). They demonstrated that the shape of the curve on the O₂-CO₂ diagram was changed, with a significantly elevated PO₂ predicted in the presence of a moderately low VA/Q and high inspired N₂O. The implications for overall gas exchange in the lung were not explored further by these authors at the time.

More recently, Korman and Mapleson (11) 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 (VAE) and inspired alveolar ventilation (VA; VAi), 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 VAE 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 VA/Q 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 VAi, which serves to demonstrate that lung units with very low VA/Q may suffer collapse when gas uptake exceeds VAI and that this process is accelerated by the presence of N₂O (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).

http://www.jap.org 8750-7587/01 $5.00 Copyright © 2001 the American Physiological Society


The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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 \( P_{O2} \) (\( PaO_2 \)) 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 loge 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.

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.

**Analysis performed.** A scenario typical of the maintenance phase of an inhalational anesthetic was modeled involving administration of an inspired mixture of 30% \( O_2 \) and 70% \( N_2O \). This was contrasted with a parallel situation involving 70% \( N_2 \) instead. Regardless of what type of distribution of \( V_A \) was nominated (exped vs. inspired, with or without collapse of low \( V_{AE}/Q \) units), overall \( V_{AE} \) was kept at 4.1 l/min. Overall \( Q \) was maintained at 4.8 l/min, regardless of whether the effect of HPV was incorporated. Analyses were performed with constant gas uptakes (\( V_{O2} \): 250 ml/min; \( CO_2 \) uptake: 200 ml/min; \( V_{N2O} \): 100 ml/min). Output variables in the primary analysis were uptakes of individual gas species and alveolar and arterial partial pressures, on a global basis or by compartment. For the sake of simplicity in analysis of the data, there was no other soluble anesthetic agent in the inspired mixture.

The effects on \( PaO_2 \) of \( N_2O \) washout, such as occurs at the end of an inhalational anesthetic, were also investigated and contrasted with the situation in the presence of \( N_2 \) instead. The scenarios modeled utilized the algorithm described above applying a constant-outflow principle and with arterial \( PCO2 \) held constant (rather than \( V_{AE} \)). This was done on the assumption that, in the spontaneously breathing patient, maintenance of constant arterial \( PCO2 \) rather than \( V_{AE} \) is more physiologically realistic, given that \( V_{AE} \) will vary with net gas elimination. The inspired concentration of \( N_2O \) was set at zero. Two different rates of \( N_2O \) elimination (400 and 100 ml/min) were examined, with the \( V_{N2O} \) fixed at these values.

**RESULTS**

In the presence of \( V_{N2O} \) of 100 ml/min, \( PaO_2 \) 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 \( PaO_2 \) 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 \( PaO_2 \) 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 \( PaO_2 \) was predicted in the presence of \( N_2O \) compared with \( N_2 \) at all degrees of \( V_A/Q \) inhomogeneity (Fig. 2). The effect was relatively greatest at mild degrees of \( V_A/Q \) spread, where \( PaO_2 \) 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).

**DISCUSSION**

\( PaO_2 \) 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 \( PaO_2 \) 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
When V\textsubscript{N2O} is considered, the effect of a superimposed true shunt fraction will only be to reduce further the minor increase in Pa\textsubscript{O2} induced by the alveolar concentrating effects of V\dot{\textsubscript{N2O}}.

The level of V\dot{\textsubscript{N2O}} 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\dot{\textsubscript{N2O}} 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\dot{\textsubscript{AE}} and Q using the multiple inert-gas elimination technique (MIGET) in subjects under N\textsubscript{2}O anesthesia have demonstrated an increase in the spread of V\dot{\textsubscript{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\dot{\textsubscript{N2O}} from low V\dot{\textsubscript{AE}}/Q lung units may increase alveolar P\textsubscript{O2} and P\textsubscript{aO2} 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\textsubscript{2} produced by V\dot{\textsubscript{N2O}}, operating in lung compartments with moderately low V\dot{\textsubscript{A}}/Q. The effect of this is to increase P\textsubscript{aO2} and VO\textsubscript{2} within that compartment. Figure 3 shows that the increase in VO\textsubscript{2} in the presence of N\textsubscript{2}O compared with N\textsubscript{2} is greatest in those compartments with moderately low V\dot{\textsubscript{A}}/Q. These compartments obtain a high proportion of total Q and not surprisingly have a predominant
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 alveolar gas and blood is represented by columns A and B, respectively. Constant inflow before and after equilibration of alveolar gas and blood 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) 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.)

\[ \text{Nitrous oxide} \quad \text{Oxygen} \]

![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 \((A, \text{ before equilibration}; B, \text{ after equilibration})\), C and D: expired ventilation is kept constant and equal to 4.1 l/min \((C, \text{ before equilibration}; D, \text{ after equilibration})\). 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.)

In our modeling, the constant inflow \((V_{AI})\) model produced quantitatively different results for overall gas exchange, predicting a much smaller increase in \(P_{A02}\) with N2O than that predicted by the \(V_{AE}\)-based model, even when total gas uptakes and total \(V_{AI}\) and \(V_{AE}\) 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 \( P_{A02} \), 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 \( P_{A02} \) 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 \( P_{A02} \) 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, \( P_{A02} \) 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, \( P_{A02} \) was clinically and statistically significantly higher \( (107 \text{ vs. } 81 \text{ Torr, } P < 0.01) \) 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 \( P_{A02} \) in the presence of \( N_2O \) would be expected to be only \( \approx 5\% \), assuming no inhomogeneity of \( V_{AE}/Q \), (even less if the effect of a typical shunt of \( \approx 10–15\% \) 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 \( V_{A}/Q \) 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 \( O_2 \) 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 \( P_{A02} \). 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 \( PaO_2 \) predicted in our modeling to be lower in the presence of \( N_2O \), despite the larger proportion of total \( Q \) perfusing nonventilated 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 \( PaO_2 \), 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 \( PaO_2 \) 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 \( PaO_2 \) 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 \( PaO_2 \) 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 \( PaO_2 \) 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 \( V_{A} / Q \) inhomogeneity is mismatch of \( V_{A} / Q \) 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 \( PaO_2 \) 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 \( PaO_2 \) 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 multicompartment 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 \( V_{AI} / Q \) 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 \( PaO_2 \) produced by \( V_{N2O} \) is predicted to occur at levels of \( V_{AI} / Q \) 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 \( \dot{V}A \) in relation to gas uptake suggests that spontaneous ventilation is more consistent with a model characterized by a log normal distribution of \( \dot{V}AE \) (constant outflow principle). Controlled ventilation is consistent with a distribution predominantly of \( \dot{V}AI \) (constant inflow principle). Under this hypothesis, data from this modeling are consistent with previously published clinical measurements of \( Pao_2 \) 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 \( \dot{V}AE \) per unit volume of lung (\( \dot{V}AE/vol \)) or \( Q \) per unit volume (\( Q/vol \)) can be generated. The distribution is Gaussian in shape when the abscissa (\( \dot{V}AE/vol \)) 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 \( \dot{V}AE/vol \) 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 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 \( \dot{V}AE/vol \), \( \mu \) is log mode \( \dot{V}AE/vol \), and \( \sigma \) is log SD of \( \dot{V}AE/vol \).

A range of values of \( \dot{V}AE/vol \) or \( Q/vol \) spanning 3 log SDs on either side of the mode is taken (although, where the nominated log 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 \( \dot{V}AE/vol \)). From this range, the distribution is divided into a number of compartments evenly spaced along the abscissa. The components of the distribution can be even scaled so that the total \( \dot{V}AE \) of the compartments combined equals any given specified value. If \( Q/vol \) is given at a constant and equal value for each compartment and scaled similarly up to a given value, the resultant distribution of \( \dot{V}AE/Q \) for the compartments will also be log normal. The output of this subroutine is a series of paired values for \( \dot{V}AE \) and \( Q \) for each compartment, which, when summed, equal the selected total \( \dot{V}AE \) and \( Q \), give a desired overall \( \dot{V}AE/Q \), and have a predetermined variance.

Either \( \dot{V}AE \) or \( \dot{V}AI \) can be nominated for the distribution to be generated. By substituting ventilation rates over time for the various input parameters. Changes in gas exchange due, for example, to changes in fractional inspired or mixed venous gas content will not change \( \dot{V}AE \) for that compartment. This assumes that net uptake of alveolar gas causes further fresh gases to be passively drawn into the alveoli. Where \( \dot{V}AI \) is nominated, a constant inflow principle applies in which \( \dot{V}AI \) is constant, and net gas uptake causes shrinkage in alveolar volume and a lower \( \dot{V}AE \).

In addition, the effect of absorption atelectasis in compartments where \( \dot{V}AE/Q \) 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 \( \dot{V}AE \) 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 \( \dot{V}AE \) and \( \dot{V}AI \) 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 \( \dot{V}AI \) 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

\[
Q = Q_{\text{max}}(1 - 0.6218e^{-0.0146P_{\text{vol}}})
\]

where \( Q_{\text{max}} \) is the nominated \( Q \) of the compartment derived form 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**

\( VAE \)-based model. The system of equations used is based on those described by Olaszowska and Wagner (17).

Consider a lung compartment with a given ratio of \( \dot{V}AE \) 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

\[
\dot{V}AI \cdot F_{IG} - \dot{V}AE \cdot F_{AG} = k \cdot (C_{G}' - C_{G})
\]

was fulfilled, where \( F_{IG} \) and \( F_{AG} \) are the fractional concentrations of the gas in inspired and alveolar gas mixtures, respectively, \( C_{G}' \) is the fractional content in pulmonary end-capillary blood, \( C_{G} \) is the fractional mixed venous gas content within the compartment, and \( k \) 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 \( k \)

\[
\frac{\dot{V}AI \cdot P_{IG}}{P_B} - \frac{\dot{V}AE \cdot P_{AG}}{P_B} = 863 \frac{P_{IG}}{P_B} (C_{G}' - C_{G})
\]

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
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 $P_i$, then for an inert gas

$$V_{AI} \cdot P_i - V_{AE} \cdot PAO_2 = Q\lambda(P_{Ci} - PV_i)$$

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

If we assume that the lung compartment is an ideal compartment in which $PAO_2$ equals $P_{Ci}$, this can be transposed to solve for $PAO_2$

$$PAO_2 = \frac{V_{AI}}{Q} \cdot P_i + \lambda \cdot PV_i$$

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

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

$$\frac{V_{AI}}{Q} = \frac{863(C_{CO_2} - C_{CO_2}) + PAO_2 \cdot V_{AE}}{PO_2}$$

where $C_{CO_2}$ is the fractional content of $O_2$ in end-capillary blood, $C_{CO_2}$ is the mixed venous $O_2$ content, $PAO_2$ is the alveolar partial pressure of $O_2$, and $PO_2$ is the inspired partial pressure of $O_2$.

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

$$PB - (PAO_2 + P_{ACO_2} + PAO_2 + PAO_2 + PAO_2) = 0$$

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

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

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 $V_{AI}/Q$.

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 $V_{AI}/Q$ 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 Henderson-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

$$Base\ excess = [1 - Hb \cdot 0.023] \times [(HCO_3 - 24.41) + (2.3 \cdot Hb + 7.7)(pH - 7.4)]$$

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 $CO_2$-$HCO_3$-carboxy 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 Sigggaard-Andersen (20) relating base excess to $Hb$ saturation and also to $pH$ and $HCO_3$

$$Base\ excess = 0.19 \cdot Hb(1 - SO_2)$$

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 $PAO_2$, $PAO_2$, $PAO_2$, etc., and $PAO_2$ (and $C_{CO_2}$) for that lung compartment using an iterative approach that is based on a modified, continuous bisection technique. (However, where $V_{AI}$ 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, $V_{AE}/Q$, and net exchange of each gas species for all of the compartments.

$V_{AI}/Q$-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 $V_{AE}/Q$

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

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 $V_{Al}$ and then progressively coercing the distribution of $V_{Al}$ 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 $P_{ACO_2}$ and $Cc_{CO_2}$ consistent with the $V_{AE}/Q_{AE}$ obtained from Eq. A6 during every iteration in pursuit of the solution for each compartment.

REFERENCES
