Ventilation-perfusion inhomogeneity increases gas uptake in anesthesia: computer modeling of gas exchange

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Peyton, Philip J., Gavin J. B. Robinson, and Bruce Thompson. Ventilation-perfusion inhomogeneity increases gas uptake in anesthesia: computer modeling of gas exchange. J Appl Physiol 91: 10–16, 2001.—Ventilation-perfusion (VA/Q) inhomogeneity was modeled to measure its effect on overall gas exchange during maintenance-phase N2O anesthesia with an inspired O2 concentration of 30%. A multialveolar compartment computer model was used based on physiological log normal distributions of VA/Q inhomogeneity. Increasing the log standard deviation of the distribution of perfusion from 0 to 1.75 paradoxically increased O2 uptake (VO2) where a low mixed venous partial pressure of N2O [high N2O uptake (VN2O)] was specified. With rising mixed venous partial pressure of N2O, a threshold was observed where VO2 began to fall, whereas VN2O began to rise with increasing VA/Q inhomogeneity. This phenomenon is a magnification of the concentrating effects that VO2 and VN2O have on each other in low VA/Q compartments. During “steady-state” N2O anesthesia, VN2O is predicted to paradoxically increase in the presence of worsening VA/Q inhomogeneity.

alveolar-arterial difference; oxygen uptake

THE EFFECT ON GAS EXCHANGE of inhomogeneity of ventilation-to-perfusion ratios (VA/Q) in the lung has been explored by previous authors (1). Analysis of log normal distributions of expired alveolar ventilation (VA; VAE) and blood flow (Q) by West (17, 18) and Kelman (8) predicted reduced gas exchange for any gas species. For the sake of simplicity, this early modeling assumed the presence of no soluble accompanying gases in the inspired mixture.

However, two-compartment modeling of the effect of increasing inhomogeneity of ventilation and Q predicted a paradoxical increase in the uptake of one gas when mixtures of two soluble gases are administered, such as is the case during inhalational anesthesia with oxygen and nitrous oxide (N2O). These findings are presented in the accompanying paper (12).

To determine the clinical relevance of these findings, we have extended this study using a computer model of physiological distributions of ventilation and Q to investigate the predicted effects of differing degrees of VA/Q inhomogeneity on gas exchange in the presence of a typical inspired mixture of O2 and N2O. The model first employed theoretical log normal distributions. Because distributions of VAE and inspired VA (VAI) may produce different effects, results based on each were compared. In addition, measured distributions of VAE and Q published previously by other authors using the multiple inert-gas elimination technique (6) were modeled to see whether the patterns of widening of distributions measured in patients are expected to produce the same effects on gas exchange as widening of the smooth theoretical distributions.

METHODS

A computer model was used to calculate the exchange of multiple gases across the alveolar-capillary membrane according to principles of mass balance for each gas. The model assumes that, within a compartment, arterial and alveolar partial pressures for each gas species are identical. The independent variables for the calculation of alveolar partial pressures and gas exchange for each gas are its inspired fractional concentration [or partial pressure and Ostwald solubility coefficient (λ)], and VAE or VAI and Q for that compartment. The structure and data flow of this model are outlined in more detail in the accompanying papers (12, 13). The distributions of ventilation and Q given to the model were obtained as follows.

Theoretical Log Normal Distributions

Log normal distributions of Q and ventilation were generated. The log SD of the distribution is the index of its spread, varying between 0 (homogeneous lung) and 1.75. West (17) showed that, for any given mode and log SD, identical results are obtained with a primary distribution of either Q or ventilation. Log normal distributions of either VAE or VAI can be nominated.

When a log normal distribution of VAI was nominated, the effect of absorption atelectasis was modeled as follows. No inspired ventilation was distributed to compartments where VAI/Q was below a critical value at which VAE was calculated to be less than zero. This is based on similar assumptions to those made by Dantzker et al. (5) that such compartments would suffer collapse. Given that steady-state gas exchange was being modeled, it was assumed that perfusion of such
components 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 hypoxic pulmonary vasoconstriction 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 modifications so that final distributions obtained were consistent with all of the input variables.

West (17) 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 \( V_{AI}/Q_{AI} \) was incorporated, 50 compartments were required to avoid noticeable quantization error because of inclusion or exclusion of compartments with \( V_{AI}/Q_{AI} \) values near the critical value.

**Measured Distributions**

Three pairs of distributions of ventilation and \( Q \) were taken from the previously published paper by Dueck et al. (6). These were distributions of their subjects 6, 7, and 8. Each pair consisted of a narrower and a wider distribution (taken before and after induction of anesthesia in Dueck’s subjects) whose log SD (as given by Dueck) is listed in Table 1.

**Analysis Performed**

**Theoretical log normal distributions.** 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% \( N_2O \). For purposes of comparison, regardless of whether a distribution of \( V_{AE} \) or \( V_{AI} \) was nominated, overall \( V_{AE} \) was held at 4.1 l/min and \( Q \) was 4.8 l/min. Parameters examined in the primary analysis were uptakes of \( O_2 (V_{O2}) \), \( CO_2 (V_{CO2}) \), and \( N_2O (V_{N2O}) \) on a global basis and by compartment. Analyses were performed with either specified mixed venous partial pressures or specified gas uptakes (or combinations of these for different gases). Where specified, \( V_{O2} \) and \( V_{CO2} \) were set at 250 and 200 ml/min, respectively.

**Measured distributions.** The analysis was repeated using the three pairs of measured distributions. Gas exchange was calculated and compared for each pair of distributions using the input variables listed above. For purposes of standardization, the distributions were scaled so that overall \( V_{AE} \) and \( Q \) (including shunt and dead space), inspired concentrations, and \( V_{O2} \) and \( V_{CO2} \) were set at the values given above. The mixed venous \( N_2O \) partial pressure (\( P_{VN2O} \)) was set at a value giving an \( V_{N2O} \) of 100 ml/min for the narrower distribution of each pair.

**RESULTS**

**Theoretical Log Normal Distributions**

Paradoxical augmentation of steady-state \( V_{N2O} \). A \( P_{VN2O} \) of 468 Torr was nominated, giving a \( V_{N2O} \) for a homogeneous lung (0 log SD) of 100 ml/min. Increasing the log SD of the distribution of \( Q \) (increasing inhomogeneity of \( V_{A/Q} \) matching) produced an increased arterial partial pressure of \( N_2O (P_{AN2O}) \) and \( V_{N2O} \). This occurred in the presence of either fixed \( O_2 \) and \( CO_2 \) exchange or fixed mixed venous partial pressures of these gases. The predicted \( V_{N2O} \) at a log SD of 1.75 was more than twice the value predicted at 0 log SD.

Figure 1 demonstrates that the trend is predicted by models based on log normal distributions of either \( V_{AE} \) or \( V_{AI} \), although the results are quantitatively different for each. The increase in \( V_{N2O} \) at a given \( P_{VN2O} \) was lower when modeling incorporated the effect of shunt because of collapse of compartments with critically low \( V_{AI}/Q_{AI} \). Paradoxical augmentation in fact peaked at a log SD of ~1.25 and then declined using this model. However, incorporation of the effect of hypoxic pulmonary vasoconstriction increased uptake somewhat by reducing shunt fraction, particularly at more severe levels of \( V_{A/Q} \) inhomogeneity.

**Rising \( P_{VN2O} \).** The effect of the \( P_{VN2O} \) on this phenomenon was investigated by repeating the study (Fig. 2) at different values of \( P_{VN2O} \) between 0 and 600 Torr (where it exceeds \( P_{AN2O} \) and net \( N_2O \) elimination is expected to occur in the homogeneous lung). Mixed venous partial pressures of \( O_2 \) and \( CO_2 \) were held constant. At low \( P_{VN2O} \) where high \( V_{N2O} \) was simulated, \( P_{AN2O} \) and \( V_{N2O} \) fell progressively with increasing \( V_{A/Q} \) inhomogeneity. This fall became less steep as \( P_{VN2O} \) rose to a threshold (\( P_{VN2O} \) of ~300 Torr in this scenario), where the slope reversed and \( V_{N2O} \) increased with worsening inhomogeneity. At a \( P_{VN2O} \) of ~300 Torr, paradoxical augmentation of \( V_{N2O} \) occurs.

**Table 1. Results of modeling changes in \( V_{N2O} \) when moving from narrower to wider distributions measured using the multiple inert-gas elimination technique**

<table>
<thead>
<tr>
<th>Distribution No.</th>
<th>Subject</th>
<th>6b narrower</th>
<th>6b wider</th>
<th>7b narrower</th>
<th>7b wider</th>
<th>8b narrower</th>
<th>8b wider</th>
</tr>
</thead>
<tbody>
<tr>
<td>log SD blood flow</td>
<td>0.86</td>
<td>1.67</td>
<td>1.42</td>
<td>2.37</td>
<td>1.17</td>
<td>1.95</td>
<td></td>
</tr>
<tr>
<td>True inert-gas shunt, %</td>
<td>1.8</td>
<td>26.7</td>
<td>0.0</td>
<td>3.0</td>
<td>0.0</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>( V_{N2O}/VT ), %</td>
<td>51.0</td>
<td>53.9</td>
<td>38.5</td>
<td>38.4</td>
<td>24.6</td>
<td>49.5</td>
<td></td>
</tr>
<tr>
<td>( V_{N2O}, l/min )</td>
<td>0.100</td>
<td>0.095</td>
<td>0.100</td>
<td>0.207</td>
<td>0.100</td>
<td>0.122</td>
<td></td>
</tr>
<tr>
<td>( P_{VN2O}, Torr )</td>
<td>485.5</td>
<td></td>
<td></td>
<td>498.2</td>
<td></td>
<td>498.7</td>
<td></td>
</tr>
<tr>
<td>( \Delta V_{N2O}, % )</td>
<td>-5.0</td>
<td></td>
<td>107.0</td>
<td></td>
<td>+22.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The multiple inert-gas elimination technique is by Dueck et al. (6). \( V_{N2O}/VT \), ratio of dead space to tidal volume; \( V_{N2O} \), \( N_2O \) uptake; \( P_{VN2O} \), mixed venous partial pressure of \( N_2O \); \( \Delta \), change.
The slope became steeper as $P_{N_2O}$ rose, but the intercept with the ordinate (at log SD of 0) fell progressively, eventually becoming negative. At this point, net $V_{\dot{N}_2O}$ is calculated to be negative for the homogeneous lung and still positive for the lung with significant $V_{\dot{A}}/Q_{\dot{A}}$ inhomogeneity, despite identical inspired and mixed venous gas content.

$O_2$ exchange. $V_{\dot{O}_2}$ was calculated simultaneously with $V_{\dot{N}_2O}$ at increasing $P_{N_2O}$ (Fig. 3). It was found that paradoxical augmentation of $V_{\dot{O}_2}$ [and thus arterial $O_2$ partial pressure ($P_{O_2}$)] occurred as the log SD of the distribution of perfusion was increased from 0 to 1.75. The augmentation effect was similar in nature but reciprocal to that found for $N_2O$, in that it diminished as $P_{N_2O}$ rose and ceased around the same threshold $P_{N_2O}$, where augmentation of the inert-gas uptake commenced. At higher values of $P_{N_2O}$ (lower $V_{\dot{N}_2O}$), $V_{\dot{O}_2}$ and $P_{O_2}$ fell with worsening $V_{\dot{A}}/Q_{\dot{A}}$ inhomogeneity, as is normally expected, and was demonstrated in the accompanying paper (13) modeling a low "maintenance-phase" level of $V_{N_2O}$.

**Measured Distributions**

The results of modeling using the three pairs of measured distributions are summarized in Table 1. The log SD of the distributions as given by Dueck et al. (6) are listed in the first row, and the associated values for true shunt fraction and dead space fraction are shown. The calculated percent change in $V_{\dot{N}_2O}$, moving from the narrower to the wider distribution of each pair, incorporating the effects of changes in shunt and dead space, are given in the bottom row. It can be seen that predicted $V_{N_2O}$ doubled in subject 7 as the log SD

Fig. 1. Predicted $N_2O$ uptake ($V_{\dot{N}_2O}$) with increasing ventilation-to-perfusion ratio ($V_{\dot{A}}/Q_{\dot{A}}$) inhomogeneity as indexed by the log SD of the distribution of blood flow ($Q$) for a constant mixed venous partial pressure of $N_2O$ ($P_{N_2O}$) (468 Torr). $O_2$ uptake ($V_{\dot{O}_2}$) (and respiratory quotient) was held constant. Predictions from a model based on a log normal distribution of expired alveolar ventilation (VAE), a model based on a log normal distribution of inspired alveolar ventilation (VAI), are shown. The constant inflow model was also modified to incorporate the effects of alveolar collapse of compartments with critically low $V_{\dot{A}}/Q_{\dot{A}}$ and also with the effect of hypoxic pulmonary vasoconstriction (HPV).

Fig. 2. Effect of rising $P_{N_2O}$ on the relationship of $V_{\dot{N}_2O}$ to the severity of $V_{\dot{A}}/Q_{\dot{A}}$ inhomogeneity. In the scenario modeled, with an inspired fraction of $N_2O$ of 0.7 and constant mixed venous partial pressures of $O_2$ and $CO_2$, the threshold for paradoxical augmentation of $V_{N_2O}$ was a $P_{N_2O}$ of 300 Torr.

Fig. 3. Effect of rising $P_{N_2O}$ on the relationship of $V_{\dot{O}_2}$ to the severity of $V_{\dot{A}}/Q_{\dot{A}}$ inhomogeneity. In an identical scenario to that modeled in Fig. 2, the threshold $P_{N_2O}$ for paradoxical augmentation of $V_{\dot{O}_2}$ is the same (300 Torr), but the direction of the effect of rising $P_{N_2O}$ is opposite.
of \( Q \) increased from 1.42 to 2.37. \( \dot{V}_{N_2O} \) in subject 8 increased by 22% as the log SD increased from 1.17 to 1.95, despite a doubling of dead space ventilation from 25 to 50% and an increase in true shunt. Predicted \( \dot{V}_{N_2O} \) in subject 6 was 5% lower as the log SD increased from 0.86 to 1.67. This change was seen in the presence of an increase in true shunt from 2 to 27%.

**DISCUSSION**

**Paradoxical Increase in Inert-gas Uptake**

This study applies distributions of ventilation and \( Q \), which are more physiologically realistic than those used in the simple two-compartment modeling of the accompanying paper (12). It confirms that, between certain extremes, increase of uptake of one gas is predicted with worsening \( V_{A/Q} \) inhomogeneity with inspired mixtures of two soluble gases. The clinical relevance of this phenomenon needs to be explored, as previous authors have demonstrated an increase in the spread of \( V_{A/Q} \) throughout the lung after induction of anesthesia (3, 6, 7, 10, 11, 14).

At first glance, this increase in gas uptake seems somewhat counterintuitive, given that it has been well demonstrated by computer modeling by previous authors (8, 17, 18) that the expected result of increasing inhomogeneity in \( V_{A/Q} \) matching is a reduction in gas exchange for all gas species. Modeling of gas elimination showed that this reduction is maximal for gases with an Ostwald blood-gas partition coefficient \( \lambda \) equal to the overall \( V_{A/Q} \) of the lung (4). In the presence of an overall \( V_{A/Q} \) of 0.86, exchange of a gas such as \( N_2O \) with a \( \lambda \) of 0.47 would be expected to be significantly reduced by \( V_{A/Q} \) inhomogeneity. Where gas uptake was modeled (18), this value of \( \lambda \) was higher, but inert-gas exchange was still predicted to be decreased at any level of inhomogeneity compared with that in a perfectly homogeneous lung.

The important limitation of some of these early studies was that they assumed an insoluble vehicle gas as the balance of the inspired mixture. More physiologically realistic models have since been applied that allow for the interdependent exchange of multiple alveolar gases, including \( N_2O \). Dantzker et al. (5) applied a modified form of such a computer model, involving a log normal distribution of \( V_{A/Q} \), to demonstrate that lung units with very low \( V_{A/Q} \) may suffer collapse where gas uptake exceeds \( V_{AV} \). These later models of multiple gas exchange (5, 6), which looked at \( O_2-N_2O \) mixtures, did not explore the relationship of global gas exchange to \( V_{A/Q} \) inhomogeneity.

Examination of the exchange of individual gas species on a compartment-by-compartment basis provides some insight into the mechanism for paradoxical augmentation. Figure 4 plots the distribution of exchange of individual gas species in a heterogeneous lung. For simplicity, the exchange of \( O_2 \) and \( CO_2 \) is shown as a single plot representing net respiratory gas exchange (\( \dot{V}_{O_2}-\dot{V}_{CO_2} \)), where \( \dot{V}_{O_2} \) predominates in the lower \( V_{A/Q} \) compartments and \( \dot{V}_{CO_2} \) in the better ventilated areas. It shows that \( \dot{V}_{O_2} \) and \( \dot{V}_{N_2O} \) occur predominantly within low \( V_{A/Q} \) compartments and largely follow the distribution of \( Q \). This is consistent with the perfusion-limited nature of uptake of these gases.

Uptake of one gas within the lung will raise the concentration of other gases in the alveolar gas mixture. The net exchange of \( O_2 \) and \( CO_2 \) governs the magnitude of the concentrating effects on alveolar \( N_2O \) within each compartment. \( N_2O \) exchange will also exert similar effects on \( O_2 \) and \( CO_2 \). The asymmetric nature of respiratory gas exchange across the distribution of \( V_{A/Q} \) shown in Fig. 4 results in an asymmetric concentrating effect on alveolar \( N_2O \). This is demonstrated by Fig. 5, which shows the different distributions of \( N_2O \) partial pressures in two lungs of differing degrees of inhomogeneity. In the moderately low \( V_{A/Q} \) compartments, substantial \( \dot{V}_{O_2} \) concentrates \( N_2O \) in the alveolus and drives \( \dot{V}_{N_2O} \) there. These compartments have the greatest \( Q \), and here the concentrating effect on alveolar \( N_2O \) is most powerful. Lung units with moderately low \( V_{A/Q} \) receive a substantial proportion of total pulmonary \( Q \) and thus would be expected to have a dominating influence on the content of these perfusion-limited gases in arterial blood and thus on total exchange of these gases.

Figure 6 demonstrates quantitatively the process of paradoxical augmentation by comparing two lungs of differing \( V_{A/Q} \) homogeneity. For both the more uniform and the more inhomogeneous lung, the area under the \( N_2O \) curve is the overall \( \dot{V}_{N_2O} \). As the SD of the distribution increases, there is redistribution of a greater proportion of total \( Q \) to lower \( V_{A/Q} \) areas. \( \dot{V}_{N_2O} \) increases markedly in these compartments as this occurs, and this increase outweighs the reduced uptake in higher \( V_{A/Q} \) lung units that occurs as their \( Q \) is
reduced. Figure 6 shows that, for the overall lung, the concentrating effects of $V\dot{O}_2$ on alveolar $N_2O$ are magnified by greater inhomogeneity.

$V\dot{O}_2$ and $V\dot{N}_2O$ produce competing concentrating effects, predominantly in these low $V_{A/Q}$ compartments, the balance of which is determined by their solubilities, inspired concentration, and mixed venous content. The mutual enhancement of uptake that $O_2$ and $N_2O$ possess is limited only by the approach of their alveolar partial pressures to the mixed venous for each gas within these compartments and to a lesser extent by dilution of alveolar gas by $CO_2$.

An interesting manifestation of paradoxical augmentation is that when $Pa_{N_2O}$ is very close to $Pv_{N_2O}$, such that net inert-gas exchange is calculated to be negative for the homogeneous lung, it is still positive for the lung with significant $V_{A/Q}$ inhomogeneity, despite identical inspired and mixed venous gas content. Examination of gas exchange in such an inhomogeneous lung on a compartment-by-compartment basis shows that $N_2O$ is being taken up by low $V_{A/Q}$ units and eliminated by high $V_{A/Q}$ units, with the balance determining the direction of global gas exchange. This “flow through” of gas within the lungs has been predicted to occur for $N_2$ in the presence of $V_{A/Q}$ inhomogeneity, and raised urinary $N_2$ has been used as a test for the severity of chronic pulmonary obstructive disease (1, 9). It can be seen for other inert gases at particular ranges of inspired and mixed venous partial pressures. At high degrees of inhomogeneity, $V\dot{N}_2O$ in low $V_{A/Q}$ units is magnified to a considerably greater extent than $N_2O$ exchange in other compartments (Fig. 7).

Dueck et al. (6) measured $V\dot{N}_2O$ in their subjects during maintenance-phase anesthesia. However, there is no data available in the literature measuring $V\dot{N}_2O$ and changes in $V_{A/Q}$ distributions simultaneously. Most studies employing the multiple inert-gas elimina-

![Fig. 5. Distributions of end-capillary $N_2O$ partial pressure ($Pc_{N_2O}$) across 10 compartments with 2 distributions of $Q$ with low and high degrees of inhomogeneity (log SD of 0.5 and 2.0, respectively).](image)

![Fig. 6. Distributions of $V\dot{N}_2O$ and $Q$ across the 10 compartments with 2 distributions of $Q$ with low and high degrees of inhomogeneity (log SD of 0.25 and 1.75, respectively). The higher $V\dot{N}_2O$ and high perfusion in the moderately low $V_{A/Q}$ compartments are obvious in the more severely inhomogeneous distribution.](image)

![Fig. 7. Distributions of $V\dot{N}_2O$ across the lung compartments at a high $Pn_{N_2O}$ plotted at 3 different levels of inhomogeneity of $V_{A/Q}$. In the less inhomogeneous lung, $N_2O$ is eliminated by all lung units, whereas, at higher degrees of inhomogeneity, concentrating effects in low $V_{A/Q}$ compartments predominate, making net $N_2O$ exchange positive.](image)
tion technique in anesthetized patients have measured distributions before and after induction of anesthesia to generate widening of these distributions. There are obvious difficulties in directly measuring changes in 
N2O exchange that occur in patients who are not receiving anesthesia when the first distribution is taken. For this reason, we have used computer modeling to simulate gas exchange with given V_A/Q distributions. Where this was applied to Dueck's published distributions, the predictions of modeling of both two-compartment (12) and theoretical log normal distributions were confirmed; widening inhomogeneity of V_A/Q increases V_N2O where maintenance-phase levels of inert-gas exchange are modeled. This also casts some light on the physiological factors that will limit paradoxical augmentation. These measured distributions were collected from patients with significant chronic lung disease and also incorporate varying degrees of true shunt and dead space ventilation. The calculated increase in V_N2O was greatest for the distributions of subject 7, where there was no significant change in true shunt or dead space moving from the narrower to the wider distribution. Using the distributions of subject 8, an increase in V_N2O was still predicted, despite a large increase in dead space ventilation i.e., a doubling of the amount of ventilation that was effectively wasted. The greater uptake by perfused lung units still overcame the effects of reduced V_A to them. Similarly, the distributions of subject 6 predicted only a small reduction in V_N2O, despite the superimposition of a large proportion of true shunt accompanying the wider distribution. Thus augmentation of V_N2O in ventilated lung units largely compensated for the reduction in effective pulmonary capillary Q imposed by the increased shunt.

It is of interest that, in the study by Dueck et al. (6), the measured V_N2O was highest (325 ml/min uptake after 85 min of N2O anesthesia) in subject 7, who demonstrated the most severe degree of inhomogeneity of pulmonary Q. Examination of the distributions measured for this subject show that there was a significant proportion of lung units with low V_AE/Q at the time of the measurement. We have shown that it is in these compartments that the most powerful concentrating effects occur, which drive the paradoxical increase in inert-gas exchange.

At higher levels of V_N2O, augmentation of V_O2 with increasing V_A/Q inhomogeneity is predicted (Fig. 3). This may produce clinically significant increases in Pao2 compared with the homogeneous lung. The corresponding clinical scenario is the immediate postinduction phase. The concentrating and second gas effects of rapid V_N2O early in an inhalational anesthetic were described by Stoelting and Eger (16). They demonstrated that high V_N2O raises the alveolar concentration of accompanying gases, including O2, by contraction of alveolar volume with or without inlaying of further inspired gas to replace the lost volume. However, Fig. 3 shows that a more pronounced postinduction increase in Pao2 is expected at more severe levels of V_A/Q inhomogeneity.

The accompanying paper (12) shows that competing concentrating effects of uptake of one gas on the other are inevitably present in any lung compartment where two gases are being taken up. Logically, the net concentrating effect can only be in one direction at any given time. The position of balance of these processes and the direction of the net concentrating effect are determined by the relative inspired concentrations and uptakes of the two gases. In the more complex physiological model presented here, the point of balance is complicated by a number of factors not encompassed in the simplified treatment given by the accompanying paper (12). These are the presence of alveolar CO2 exchange, the differing solubilities of the gases involved, and the ainline nature of the dissociation curve for O2, which cause these gases to be taken up unequally in lung compartments of different V_A/Q.

As shown by Figs. 2 and 3, the direction of the overall concentrating effect changes at a certain P_N2O and V_N2O. Inhomogeneity simply magnifies these existing concentrating effects, and thus paradoxical augmentation can only be seen for one gas or the other at any time.

Clinical Considerations: Inert-gas Exchange

Paradoxical augmentation of gas uptake with worsening V_A/Q inhomogeneity is predicted, regardless of the nature of the distributions used to generate the data. It is predicted by simple two-compartment models and more physiologically realistic log normal distributions. Given the increase in V_A/Q inhomogeneity seen normally in anesthetized patients, paradoxical augmentation of V_N2O is likely to be prevalent in any patient during maintenance-phase N2O anesthesia.

![Fig. 8](http://jap.physiology.org/) Effect of N2 elimination of 10 ml/min from the lungs on paradoxical augmentation of V_N2O with increasing V_A/Q inhomogeneity, compared with a lung with no N2 elimination. Mixed venous partial pressures of O2 and CO2 were held constant.
It can be seen from Fig. 2 that the phenomenon of paradoxical augmentation of gas uptake only commences when the mixed venous partial pressure has risen above a certain threshold (in this scenario 300 Torr). Thus it is a product of a relatively low inspired-to-mixed venous partial pressure gradient and commences when uptake of the gas has declined below a certain value. Consideration of changing gas exchange over time shows that this threshold \( P_{V_n,O} \) is reached after only a short time after induction of anesthesia. Figure 2 shows that, in our scenario, the threshold for paradoxical augmentation of \( V_{N_2,O} \) is at \( \sim 550 \text{ ml/min} \). Severinghaus (15) states that the \( V_{N_2,O} \) (ml/min) at time \( t \) (min) after introduction of an inspired \( N_2O \) concentration of 70% is given by

\[
V_{N_2,O} = \frac{1,000}{\sqrt{t}}
\]

Thus we can expect to reach this point after several minutes in a typical patient, and for the remainder of time under anesthesia \( V_{N_2,O} \) is predicted to increase with worsening \( V_{A/Q} \) inhomogeneity.

One of the physiological factors that might be expected to minimize paradoxical augmentation of \( V_{O_2} \) and \( V_{N_2,O} \) is incomplete denitrogenation of the body. This is due to accumulation of the poorly soluble \( N_2 \) in low \( V_{A/Q} \) lung compartments as shown by Dantzker et al. (5), where its presence dilutes the most potent concentrating effects of \( V_{O_2} \) and \( V_{N_2,O} \). The effect of this was examined by repeating the analysis of Fig. 1, superimposing an excretion of \( N_2 \) of 10 ml/min from the lungs. This level of \( N_2 \) elimination is consistent with the findings of Beatty et al. (2) for patients during maintenance-phase anesthesia. Figure 8 shows that \( V_{N_2,O} \) is reduced in the presence of \( N_2 \) elimination to a greater extent at higher levels of \( V_{A/Q} \) inhomogeneity, but that paradoxical augmentation still clearly occurs for \( V_{N_2,O} \) despite this.

The lack of effect of \( N_2 \) retention on paradoxical augmentation of \( V_{N_2,O} \) may not hold true for \( V_{O_2} \), however. Paradoxical augmentation of \( V_{O_2} \), if it is a clinical reality, occurs during the early postinduction phase of rapid \( V_{N_2,O} \), when incomplete denitrogenation of the alveolar volume is likely. The presence of significant levels of retained alveolar \( N_2 \) throughout the lung is likely to ablate much of the early concentrating effect on alveolar \( O_2 \).

Conclusion

A model of physiological distributions of \( V_{A/Q} \) values confirms that concurrent administration of \( O_2-N_2O \) mixtures results in competing second gas and concentrating effects modulating uptake of both gases. During steady-state conditions typical of the maintenance-phase of a \( N_2O \) anesthetic, this results in a paradoxical increase in \( V_{N_2,O} \) with increasing \( V_{A/Q} \) inhomogeneity. This paradoxical augmentation is due to increasing concentration of alveolar \( N_2O \) by \( V_{O_2} \) in a greater proportion of lung compartments with low \( V_{A/Q} \) ratios. At higher levels of \( V_{N_2,O} \), such as are seen in the early phases after anesthetic induction (and in the absence of retained alveolar \( N_2 \)), paradoxical augmentation of \( V_{O_2} \) with worsening \( V_{A/Q} \) inhomogeneity is seen instead. The effect on \( O_2 \) is not seen concurrently with that for \( N_2O \). This is because the effect of inhomogeneity is to magnify the existing concentrating effects of uptake one gas on the other. These can only operate in one direction or the other at a time, depending on the relative uptakes and inspired concentrations of the gases.

REFERENCES