Ventilation-perfusion inhomogeneity increases gas uptake: theoretical modeling of gas exchange

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Received 7 November 2000; accepted in final form 6 February 2001

Peyton, Philip J., Gavin J. B. Robinson, and Bruce Thompson. Ventilation-perfusion inhomogeneity increases gas uptake: theoretical modeling of gas exchange. J Appl Physiol 91: 3–9, 2001.—Ventilation-perfusion (V˙A/Q˙) inhomogeneity was modeled to measure its effect on gas exchange in the presence of inspired mixtures of two soluble gases using a two-compartment computer model. Theoretical studies involving a mixture of hypothetical gases with equal solubility in blood showed that the effect of increasing inhomogeneity of distributions of either ventilation or blood flow is to paradoxically increase uptake of the gas with the lowest overall uptake in relation to its inspired concentration. This phenomenon is explained by the concentrating effects that uptake of soluble gases exert on each other in low V˙A/Q˙ compartments. Repeating this analysis for inspired mixtures of 30% O2 and 70% nitrous oxide (N2O) confirmed that, during “steady-state” N2O anesthesia, uptake of N2O is predicted to paradoxically increase in the presence of worsening V˙A/Q˙ inhomogeneity.

Methods

IT IS GENERALLY ASSUMED THAT reduced alveolar gas exchange is an inevitable consequence of increased inhomogeneity of the distribution of alveolar ventilation (V˙A) and blood flow (Q˙) in the lungs (6). This assumption is often justified by reference to the extreme situation of complete dispersion of ventilation-to-perfusion ratios (V˙A/Q˙), where all of the ventilation is distributed to one lung and all of the Q˙ to the other. The obvious inhibition of gas exchange of this scenario is extrapolated to situations of lesser degrees of V˙A/Q˙ inhomogeneity.

However, a great deal of modern anesthesia continues to be conducted with mixtures of O2 and nitrous oxide (N2O). N2O is a soluble inert gas, whose uptake (V˙N2O) has been shown to significantly alter the concentration of other gases in the alveolar gas mixture at high inspired concentrations, with rapid uptake early in the course of anesthesia (2, 10). Thus it is possible that uptake of gases in a multiple-gas mixture may alter existing assumptions about the relationship between V˙A/Q˙ and gas exchange. The behavior of such mixtures of soluble gases in the presence of V˙A/Q˙ inhomogeneity has not been investigated by previous workers.

We used a two-compartment computer model to investigate the predicted effects of differing degrees of V˙A/Q˙ inhomogeneity on gas exchange when two soluble gases are present. Modeling was performed using two hypothetical gases of equal solubility in blood and was extended to include physiological mixtures of O2, CO2, and N2O.

METHODS

A computer model was designed to calculate the exchange of multiple gases across the alveolar-capillary membrane within two alveolar compartments, according to principles of steady-state mass balance for each gas. The model assumes that, within a compartment, end-capillary and alveolar partial pressures for each gas species are identical. The independent variables for the calculation of gas exchange for each gas are its inspired fractional concentration, the mixed venous content (or partial pressure and Ostwald solubility coefficient), and expired V˙A (V˙AE) and Q˙ for that compartment.

For each gas species G1, G2 . . . Gn in the alveolar gas mixture, the equations

\[
\frac{\dot{V}_A \cdot P_{I_G} - \dot{V}_{AE} \cdot P_{A_G}}{P_B - P_{I_G}} = \kappa \dot{Q} (C_{G1} - C_{VG})
\]

and

\[
P_{A_G1} + P_{A_G2} + \ldots + P_{A_Gn} = P_B - P_{I_G}
\]

were fulfilled, where \(\dot{V}_A\) is inspired \(\dot{V}_A\); \(P_{I_G}\) and \(P_{A_G}\) are the partial pressures of the gas in inspired and alveolar gas mixtures, respectively; \(C_{G1}\) is the fractional content in pulmonary end-capillary blood; \(C_{VG}\) is the fractional mixed ve-
nous gas content within the compartment; $P_b$ is barometric pressure; $P_{H_2O}$ is the partial pressure of water vapor at body temperature; and $k$ is the constant that embodies the appropriate corrections for the effect of temperature on measured gas volumes. 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 (3, 4) for $CO_2$ and $O_2$, which characterize the dissociation curves of these gases.

The output variables for the whole lung were the content and 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 were 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 recalculated to arrive at final values for arterial partial pressures of $CO_2$ and $O_2$. A further iterative process allows nomination of the exchange (uptake or elimination) of any or all of the gases as an independent variable. This was performed by varying the mixed venous point for each gas by continuous bisection until the set of mixed venous values that corresponds to the nominated exchange is obtained. The structure and data flow of this model are outlined in more detail in the companion paper (8).

In the two-compartment analysis, the perfectly homogeneous lung has one-half of its ventilation and perfusion distributed to each compartment. Inhomogeneity of the distribution of ventilation is represented by varying the proportion of total ventilation assigned to the first compartment between 0 (shunt) and 1.0, with the balance being assigned to the second compartment, while holding $Q$ evenly distributed between the compartments. Similarly, inhomogeneity of $Q$ is produced by varying the proportion of total perfusion assigned to the first compartment between 0 (dead space) and 1.0, while holding ventilation evenly distributed.

Analysis Performed

The effect on gas exchange of increasing inhomogeneity of the distribution of ventilation was calculated for a simplified hypothetical gas mixture and a physiologically realistic one. Overall $V_{AE}$ from both lung compartments was arbitrarily held at 4.1 l/min, and $Q$ was 4.8 l/min in all scenarios.

Hypothetical Gases Study

A mixture of two hypothetical gases, $G_1$ and $G_2$, was examined, both with a blood-gas partition coefficient of 1.0.

In the first set of scenarios, inspired concentrations and mixed venous partial pressures for the two gases ($P_{V,G_1}$ and $P_{V,G_2}$) were specified and manipulated. The following sequence was performed: equal inspired concentrations and equal mixed venous partial pressures (scenario 1a); narrowly diverging mixed venous partial pressures (scenario 1b); widely diverging mixed venous partial pressures (scenario 1c); diverging inspired concentrations (scenario 1d); and further diverging mixed venous partial pressures (scenario 1e).

The inspired concentrations were made equal again, and $P_{V,G_1}$ was held at its original value. The uptake of $G_2$ ($V_{G_2}$) was made an independent variable (instead of $P_{V,G_2}$) and altered, and the effect on $V_{G_1}$ was calculated as follows: $V_{G_2}$ was raised to 200 ml/min (scenario 2a), and $V_{G_2}$ was lowered to 50 ml/min (scenario 2b).

Physiological Gases Study

Modeling of physiological scenarios typical of the maintenance phase of an inhalational anesthetic was performed involving administration of an inspired mixture of 30% $O_2$ and 70% $N_2O$ (Ostwald solubility coefficient $= 0.47$). Mixed venous partial pressure of $N_2O$ was set at 468 Torr, thus producing an $V_{N_2O}$ of 100 ml/min for the homogeneous lung. This level of uptake is consistent with maintenance-phase anesthesia, according to the formula of Severinghaus (9)

$$V_{N_2O} = \frac{1,000}{5}$$

where $V_{N_2O}$ (ml/min) is at time $t$ minutes after introduction of an inspired $N_2O$ concentration of 70%. It should be noted that steady-state gas exchange does not take into account the change in input variables that occurs in the physiological anesthetic situation where mixed venous $N_2O$ content is continually rising and $V_{N_2O}$ falling with time. However, differentiating Severinghaus’s equation with respect to time shows that the rate of change of $V_{N_2O}$ is only 0.5 ml·min$^{-1}$·min$^{-1}$ where $V_{N_2O}$ is 100 ml/min ($t = 100$ min). Such a low rate of change with time means that a steady-state approach gives an excellent approximation of the conditions of maintenance-phase inhalational anesthesia.

Two scenarios were examined in which the effect of increasing inhomogeneity on $V_{N_2O}$ was calculated: mixed venous partial pressure of $O_2$ ($P_{V,O_2}$) and $CO_2$ ($P_{V,CO_2}$) were held constant (scenario 3), and $O_2$ and $CO_2$ uptake were held constant at 250 and 200 ml/min, respectively, instead (scenario 4). Because distributions of $V_{AE}$ and $V_{AI}$ may produce different effects, the results of models based on each were compared (scenario 4a). In addition, the effect of inhomogeneity of $Q$ was examined for comparison (scenario 4b).

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**Fig. 1.** $A$: point of neutrality of effect of inhomogeneity of ventilation on gas exchange. Gas exchange is plotted for 2 hypothetical gases, $G_1$ and $G_2$, with increasing inhomogeneity of expired alveolar ventilation ($V_{AE}$) (moving from left to right along the x-axis). Inspired gas fraction ($P_{I,G_1}$) is 0.5, and mixed venous partial pressure of gas ($P_{V,G_1}$) is held constant at 340 Torr for each gas. The behavior of the 2 gas species is identical in this scenario, and their combined uptake is plotted by the thick line. $V_{AE},$ ventilation-to-perfusion ratio; $V_{G},$ gas uptake. $B$: paradoxical augmentation of $V_{G_1},$ $P_{V,G_1}$ is shifted (from 340 Torr) upwards for $G_1$ and downward for $G_2$ by 20 Torr, and their $V_G$ alters accordingly. The effect of increasing inhomogeneity of $V_{AE}$ is to reduce $V_{G_2}$ and increase $V_{G_1},$ and net combined gas exchange remains unaltered from $A.$ $C:$ $P_{V,G_1}$ is shifted (from 340 Torr) upwards for $G_1$ and downward for $G_2$ by 170 Torr, and $V_{G_2}$ and $V_{G_1}$ alter accordingly. The effect of increasing inhomogeneity of $V_{AE}$ is to reduce exchange (in absolute terms) of both gases, and net combined gas exchange is unaltered from the scenario in $A.$ $D:$ altered point of neutrality of effect of inhomogeneity on gas exchange with different inspired concentrations of gases. The $P_{I,G_1}$ is now 0.75, and $P_{I,G_2}$ is 0.25, and the $V_G$ and $P_{V,G_1}$ of the $2$ gases at the neutral point have shifted proportionately. At this new point of neutrality, $P_{V,G_1}$ is 510 Torr, and $P_{V,G_2}$ is 170 Torr. The combined $V_G$ of the 2 gases remains unchanged. $E:$ the scenario of Fig. $5$ repeated with the $P_{V,G_1}$ of the $2$ gases shifted slightly; $P_{V,G_1}$ is raised slightly (20 Torr) from the neutral point (and $P_{V,G_1}$ is lowered by an equal amount). Paradoxical augmentation of $V_{G_1}$ commences, whereas $V_{G_2}$ declines with increased inhomogeneity. The effect of the higher inspired concentration for $G_1$ has been to raise the threshold value for $V_{G_1}$ (150 ml/min) at which paradoxical augmentation supervenes for that gas.
RESULTS

Hypothetical Gases Study

Scenario 1a. As a starting point, the mixed venous partial pressure for both gases was set at 340 Torr, and inspired concentration was set at 50%. Their solubilities are identical, and, from considerations of symmetry, the uptake from each compartment for each gas will also be identical. These input values gave total uptakes from both compartments (V_{G1} and V_{G2}) of 100
ml/min for each gas. In this situation, inhomogeneity of ventilation will have a neutral effect on total uptake of either gas in this situation, as displayed in Fig. 1A. The lefthand end of the x-axis represents the homogeneous lung, where one-half of the ventilation is distributed to compartment 1. Inhomogeneity of ventilation increases from left to right as more ventilation is distributed to compartment 1 and less (the balance) to compartment 2. As gas uptake in compartment 1 rises linearly with increasing ventilation, uptake in the other compartment falls to compensate, and total uptake of the gas species is unchanged. The combined uptake of the two gases remains at 200 ml/min, regardless of the degree of inhomogeneity.

Scenario 1b. The mixed venous point was altered for both gases but symmetrically in opposite directions around the first value. \( P_{V_G1} \) was raised by 20 Torr so that \( V_G1 \) was reduced below 100 ml/min, whereas \( P_{V_G2} \) was lowered by the same amount so that \( V_G2 \) was increased. From Fig. 1B, whereas the combined uptake of the two gases is still unchanged throughout, the effect of increasing inhomogeneity of ventilation is to increase \( V_G1 \). This effect of increasing \( V_A/Q \) inhomogeneity on uptake of a gas species we term "paradoxical augmentation."

Scenario 1c. Mixed venous partial pressures were altered further. \( P_{V_G1} \) was halved from its original value to 170 Torr, and \( P_{V_G2} \) increased by the same amount to 510 Torr. Figure 1C shows that, for the homogeneous lung, \( V_G2 \) is increased and \( V_G1 \) decreased by the same amount so that elimination of \( G_1 \) by the lung is now occurring. However, now with larger baseline levels of gas exchange, increasing inhomogeneity decreases gas exchange for both gases, in line with traditional understanding of the effect of \( V_A/Q \) inhomogeneity. A similar pattern to that shown in Fig. 1B is seen. If elimination of \( G_1 \) is viewed as "negative uptake," then \( V_G1 \) is still being increased in this scenario by worsening inhomogeneity. Note that, in this scenario, the combined uptake of the two gases still remains unaffected by the degree of inhomogeneity.

Scenario 1d. The effect of different inspired concentrations for the two gases is shown in Fig. 1D. The inspired concentration for each gas was changed in equal proportion to the change in mixed venous partial pressures made in scenario 1c. A new point was reached for both gases at which their combined uptake is unchanged and the effect of inhomogeneity of ventilation is still neutral. At this new neutral point, \( P_{V_G1} \) is 510 Torr with an inspired \( G_1 \) fraction of 75%, and \( P_{V_G2} \) is 170 Torr with an inspired \( G_2 \) fraction of 25%. Combined uptakes are still unchanged with increasing inhomogeneity, as the sum of the mixed venous partial pressures of the two gases is unchanged.

Scenario 1e. \( P_{V_G1} \) was raised further by 20 Torr from this point, and \( P_{V_G2} \) was lowered by an equal amount. As shown in Fig. 1E, paradoxical augmentation of \( V_G1 \) commenced, whereas \( V_G2 \) declined with increased inhomogeneity. However, the effect of the higher inspired concentration for \( G_1 \) has been to raise the threshold at which paradoxical augmentation supervenes for that gas. Paradoxical augmentation is now seen if \( V_G1 \) is <150 ml/min. Once again, combined uptake of the two gases is constant.

Scenario 2a. The starting point was returned to where \( P_{V_G1} \) was set at 340 Torr and inspired concentration at 50%. The effect was examined of fixing \( V_G2 \) instead of \( P_{V_G2} \) in the presence of increasing inhomogeneity. \( P_{V_G1} \) was allowed to change with increasing inhomogeneity so that \( V_G2 \) was held at 200 ml/min, whereas \( P_{V_G1} \) was held at 340 Torr. The results are shown in Fig. 2A. Whereas it has already been shown in Fig. 1A that, at this \( P_{V_G1} \), the effect of inhomogeneity of ventilation on \( V_G1 \) is neutral, at this higher \( V_G2 \) paradoxical augmentation of \( V_G1 \) is now seen with
increasing inhomogeneity. Note that now the combined uptake of the two gases has been increased as well.

Scenario 2b. \( \dot{V}_{G2} \) was lowered to 50 ml/min, and \( \dot{P}_{V G1} \) was held at 340 Torr. As shown in Fig. 2B, the paradoxical effect is no longer present, and increasing inhomogeneity lowers \( \dot{V}_{G1} \).

**Physiological Scenario**

Scenario 3. Figure 3 shows the \( \dot{V}_{N2O} \) with increasing inhomogeneity of ventilation, with an inspired mixture of 30% \( O_2 \) and 70% \( N_2O \). Paradoxical augmentation of \( \dot{V}_{N2O} \) was seen with increasing inhomogeneity where \( \dot{P}_{V O2} \) and \( \dot{P}_{V CO2} \) are held constant. This scenario is analogous to the hypothetical scenario 1b or 1e.

Scenario 4a. Figure 4A shows that paradoxical augmentation of \( \dot{V}_{N2O} \) is also predicted where \( O_2 \) and \( CO_2 \) uptake are held steady as inhomogeneity worsens. This scenario is analogous to the hypothetical scenario 2a. The effect was seen where increasing inhomogeneity was modeled from distributions of either \( \dot{V}_{AE} \) or \( \dot{V}_{AI} \).

Scenario 4b. These results contrast with the effects of inhomogeneity of \( Q \) with uniform ventilation. Figure 4B shows that this produces quantitatively different but qualitatively similar predictions on the effect of inhomogeneity on \( \dot{V}_{N2O} \) in the above scenario. However, at extremes of \( \dot{V}/Q \), where significant dead space ventilation is occurring, paradoxical augmentation is curtailed.

**DISCUSSION**

Using two-compartment modeling, we have shown that, between certain extremes, the predicted effect of increased inhomogeneity of distribution of either ventilation or \( Q \) is to paradoxically increase the uptake of one soluble inert gas in a two-gas mixture. Although somewhat counterintuitive and at odds with traditional assumptions (5, 6, 11, 12), we have shown, furthermore, that this phenomenon is predicted for physiological mixtures of inspired gas routinely used in inhalational anesthesia.

The simplified hypothetical gas model provides a useful tool for distinguishing the cause of this apparently paradoxical relationship between gas exchange
and V_A/Q inhomogeneity. Figure 1A shows that a point exists at which the effect of V_A/Q inhomogeneity on gas exchange in a mixture of two gases is neutral. It may seem self-evident that this occurs when the inspired concentrations and mixed venous gas content of one gas equal those of the other gas of equal solubility. However, at different inspired concentrations, a neutral point still exists, but the position is altered, as shown in Fig. 1D. That is, the corresponding mixed venous content and uptake of each gas are different.

Figure 1B shows that raising P_VG1, relative to P_VG2 (and thus reducing V_G1) induces paradoxical augmentation of V_G1 in response to increasing inhomogeneity. P_VG1 at the neutral point represents a threshold above which paradoxical augmentation is predicted. In this scenario, paradoxical augmentation is seen if V_G1 is <100 ml/min. A different threshold exists at different inspired concentrations, as shown by Fig. 1E. The same principle applies in both scenarios. Below a certain level of gas uptake (above certain mixed venous content), paradoxical augmentation will supervene for one gas while disappearing for the other gas.

Figures 2A shows that, for the simplified two-gas analysis at equal inspired concentration, the gas with higher overall uptake will produce paradoxical augmentation of the other gas with worsening inhomogeneity. Paradoxical augmentation of the uptake of a gas species is a phenomenon of a relatively low baseline level of uptake of that gas and is more pronounced when there is a low inspired-to-mixed venous partial pressure gradient. Thus it is seen in the physiological scenarios (scenarios 3 and 4), where relatively low, steady-state V_N2O is being modeled and where uptake is driven by a relatively small difference between alveolar and mixed venous partial pressures for N2O. Small increases in alveolar N2O partial pressure produce significant changes in V_N2O.

The mechanism for the effect is illustrated in Fig. 5, which shows the partial pressures for both gases in each compartment in scenario 1b. The greater V_G2 under the influence of the lower mixed venous partial pressure lowers its alveolar partial pressure and raises that of G1. This is the “concentrating effect” (10). In the homogeneous lung, G1 is being concentrated in the alveolus by the greater V_G2. The higher alveolar concentration of G1 will drive up the V_G1, of course, and the scenario plotted represents the balance point for uptake of the two gases given three factors: the relative solubilities of the gases in blood and their inspired and mixed venous partial pressures. Uptake of both gases produces competing concentrating effects, but obviously in a two-gas mixture the sum of these effects can only be unidirectional. Both gases cannot concentrate each other simultaneously. The direction in which this occurs is dependent on the factors mentioned.

Figure 5 shows that, although this occurs in all compartments, it is most pronounced where V_A/Q is lowest, i.e., in compartment 2 on the right. The effect is assymmetric between the V_A/Q values of the compartments, with the more powerful concentrating effects on G1 in the low V_A/Q compartment predominating in their influence on the composition of blood leaving the lung and, therefore, on uptake. Given that the perfusion of the two compartments is equal, the partial pressure of G1 in blood leaving the lung will be higher on the right of Fig. 5 (greater inhomogeneity of ventilation), when the blood from compartments 1 and 2 is mixed, and thus V_G1 will be higher. The overall concentrating effect on G1 is, in fact, magnified by increasing inhomogeneity. This produces paradoxical augmentation of V_G1.

For comparison, the partial pressures corresponding to scenario 1a, where P_VG1 and P_VG2 are equal, are also plotted in Fig. 5. These are uniform in all compartments. For each gas, partial pressures across all of the compartments and at all degrees of inhomogeneity are identical at this point, and it can, therefore, be shown that no gradient will exist between mixed alveolar and arterial blood for either gas at the neutral point.

It should be noted that, in scenarios 1a–1e, V_A as well as V_VG were constant, as total gas uptake of the two gases combined was 200 ml/min in all cases with increasing inhomogeneity. Therefore, the effects observed can be put down entirely to the concentrating effects of V_G2 on G1. There is no contribution to the final balance of the alveolar gas mixture from the in-drawing of further fresh gas because of changes in V_G2 with increasing inhomogeneity. This latter factor will modify or contribute to the paradoxical response of gas uptake to inhomogeneity in the other scenarios but is not necessary to generate the phenomenon of paradoxical augmentation.
Paradoxical augmentation is more pronounced with inhomogeneity of ventilation as opposed to Q, as illustrated by Fig. 4, A and B. This is because more powerful concentrating effects are produced in low V˙A/Q˙ compartments where gas uptake occurs in the presence of small minute volumes of inspired alveolar gas.

Paradoxical augmentation is predicted by a number of different models and approaches, as illustrated in the subsequent diagrams. Modeling of distributions of either V˙AI or V˙AE produces qualitatively similar results. Similarly, the phenomenon is predicted, regardless of whether the P#VO2 and P#CO2 are fixed or the rate of respiratory gas exchange is fixed instead.

At extremes of inhomogeneity, the paradoxical augmentation effect is curtailed. Figure 4B shows that, in the presence of very low levels of Q in one compartment (on the right of Fig. 4B), total VN2O declines where total O2 uptake is fixed. Obviously, in these compartments, perfusion-driven uptake of either gas becomes negligible, and the concentrating effects dissipate.

Whereas results based on distributions of V˙AE and V˙AI appear to give very similar results, these distributions are not identical in their effects. At very low V˙A/Q, negative values of V˙AE are calculated from distributions of V˙AI. Previous authors (1) have used this relationship as the basis for modeling of absorptionatelectasis, where gas uptake from a compartment exceeds its V˙AI. Extrapolating this premise to steady-state gas exchange modeling, we may assume that these compartments are shunt, and the effect will be sudden curtailment of paradoxical augmentation of VN2O. However, the shortcomings of a two-compartment analysis become apparent as examination of this limiting case using two compartments immediately imposes a 50% shunt, which is obviously well outside the range of physiological normality, even for patients under anesthesia.

It is of interest, therefore, to find out how likely these limiting cases of V˙A/Q inhomogeneity are to exist in the lung in the physiological situation. Dantzker et al. (1) showed that absorptionatelectasis was likely to occur in the presence of N2O-O2 mixtures where V˙AI/Q was <0.1. Thus it is likely that, in most of the lung, the conditions present will lead to a paradoxical relationship between VN2O and V˙A/Q inhomogeneity. However, in this study, inhomogeneity of the distribution of either ventilation or perfusion was modeled. In fact, in the real lung, both ventilation and Q are maldistributed simultaneously, possibly making these extremes more prevalent.

Furthermore, the likelihood of a threshold phenomenon for paradoxical augmentation in the physiological setting is less clear given that the relationships defined above are expected to be more complex for gases with dissimilar solubilities and/or alinear dissociation curves in the face of widely varying V˙A/Q values. Modeling of physiological distributions may help define the probability and clinical relevance of the paradoxical augmentation effect and are explored in the companion paper (7).

Conclusion

Modeling of V˙A/Q inhomogeneity using a two-compartment model of alveolar gas exchange predicts that the effect of increased inhomogeneity of distribution of either ventilation or Q is to paradoxically increase the uptake of one soluble inert gas in a two-gas mixture. The phenomenon is produced by the concentrating effects of uptake of one gas on the other, which take place mainly in the low V˙A/Q compartments and which become more significant as the range of V˙A/Q values widens. Paradoxical augmentation of VN2O is predicted to occur in the presence of inspired mixtures of O2 and N2O routinely used in inhalational anesthesia.

REFERENCES