O₂ Uptake and CO₂ Elimination during Mechanical Ventilation with High Frequency Oscillation

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This study was intended to elucidate gas exchange in a quasi-steady state during high frequency oscillatory ventilation (HFV) in terms of arterial blood gases, tidal volume (Vₜ) and frequency of oscillation (f). Firstly, experiments were performed on anesthetized, paralyzed and tracheostomized dogs using a piston-type oscillator with a fresh air bias flow. The f values employed in the animal experiments were 10 to 30 Hz, and Vₜ values were 1 to 3 ml/kg of body weight. Changes in Pao₂ observed during HFV could be expressed by the equation Pao₂ = 125.2 - 60.3/(Vₜ × f), which closely coincided with the alveolar ventilation equation for O₂, i.e., Pao₂ = 125 - 78/Vₐ, Where P(A-a) O₂ and O₂ consumption were assumed to be 25 Torr and 90 ml/min, respectively. Paco₂ during HFV deviated from the curve of the alveolar ventilation equation, Paco₂ = constant/Vₐ at a higher Vₜ × f, and was distributed along the hyperbolic curve of Paco₂ = 1/Vₐ + 14.7. This suggested that HFV shows a certain limitation in CO₂ elimination. Secondly, indicator gas transport through straight tube models for two directions, i.e., wash-in and wash-out, were observed. Wash-in of indicator gases (He, N₂ and SF₆) in terms of indicator appearance time at the other end of the tube changed as a function of Vₜ × f. The effect of increasing f at a fixed Vₜ on the wash-in was much less than that of increasing Vₜ at a fixed f. The heavier gas (SF₆) was washed in faster than the lighter gas (He) although wash-in of each indicator gas was closely related to the function Vₜ × f. Washout in terms of the appearance time of indicators in the opposite direction was, however, strongly dependent on Vₜ, and the effect of increasing f at a fixed Vₜ on wash-out reached a limit beyond a certain f. It was concluded from the present study, that both convective dispersion and augmented diffusion play important roles, although they are not clearly distinguished, as gas transport mechanisms during HFV. The difference between inspiratory and expiratory gas transport modes could be explained by differences in flow profiles, relative importance of convective dispersion, and/or time required for gas mixing in the airways.

(Key Words: HFV, convective dispersion, augmented diffusion, CO₂ elimination, airway gas transport)

INTRODUCTION

Among the three modes of high frequency ventilation (HFV), i.e., high frequency oscillation (HFO), high frequency jet ventilation (HFJV) and high frequency positive-pressure ventilation (HFPPV), HFO has the particular feature of utilizing positive and negative pressure oscillation at a very high frequency. The high oscillatory flow, coupled with positive and negative pressure swings, may accelerate both convective and diffusive gas mixing in the conductive airways. This makes the gas transport mechanism of HFO more complicated than those of other modes of high frequency.

Fredberg (5) and Slutsky et al (18) predicted based on their models that gas transport in the airways during HFV was determined by the product of oscillatory frequency and tidal volume of HFO, f × Vₜ. This hypothesis was confirmed experimentally for CO₂ experimentally from the lungs (4, 15, 16, 22, 24), but is yet to be explained for O₂ intake to the lungs.

Although more recent works have introduced...
much more sophisticated general equations of gas transport during high frequency ventilation, incorporating the tidal volume to dead space ratio (20) or the transit time through a dead space and its standard deviation (13), the product of tidal volume and frequency of oscillation is still a decisive component of these equation systems.

At first, we intended to clarify the difference between \( \text{O}_2 \) and \( \text{CO}_2 \) transports in the lungs by concurrent analysis in terms of \( \text{Pao}_2 \) and \( \text{Paco}_2 \) in anesthetized dogs at a quasi-steady state under HFO. We found in the animal experiments that changes in \( \text{Paco}_2 \) during HFO could be expressed as a function of the product of tidal volume (\( V_t \)) and oscillatory frequency (\( f \)), whereas \( \text{Paco}_2 \) at a wider range of \( V_t \times f \) deviated from the theoretical curve based on a modified alveolar ventilation equation. This finding led to some in-vitro experiments using straight tube models for elucidating the difference between wash-in and wash-out modes of indicator gases during HFO.

SUBJECTS AND METHODS

The study was composed of two experimental series. The first series consisted of in-vivo experiments on anesthetized dogs, and the second one of in-vitro experiments with acrylic tubes of 32 mm in diameter simulating gas transport in the airways.

The in-vivo experiments were carried out on 8 dogs weighing 10 kg on average. Figure 1 shows the experimental system. The animals were anesthetized with intravenous pentobarbital (Nembutal R) administration of 5 mg/kg of body weight. The dogs were placed in a supine position during the experiments. They were tracheostomized and intubated with a cuffed endotracheal tube of 8.5 mm ID, paralyzed with a bolus infusion of pancuronium at a dose of 0.2 mg/kg of body weight, and ventilated by a Harvard pump with a conventional mode to maintain eucapnic conditions. The right femoral artery was cannulated for blood gas analyses with a 16 G polyethylene tube filled with heparinized saline solution. The right femoral vein was also cannulated, and a lactated-Ringer solution (Lactec R) was infused continuously at a rate of 0.3 ml/min.

The high frequency oscillator consisted of a piston cylinder of 7.0 cm in diameter which was driven by an electric motor (SCD 200/100, Miki Pulley Co., Japan). The stroke volume of the oscillator could be precisely adjusted by changing the length of the piston arm to generate a volume of 1, 2 or 3 ml/kg of body weight. The actual volume output of the oscillator, which was directly measured, increased linearly with a frequency of oscillation of up to 30 Hz. The frequency of oscillation was varied by changing the voltage applied to the electric motor so that the desired frequency could be employed in the experiment. This was actually confirmed by recording the output of a modified hot-wire anemometer (Respiromonit R M-100, Mino Ikagaku Co., Japan).

In the present animal experiments, the actual frequencies of oscillation employed were 10 to 30 Hz, and the actual outputs of the oscillator, i.e., the product of stroke volume and oscillatory frequency were approximately from 0.9 to 5.4 l/min/kg. The bias air flow for the present HFO system was 1 l/min/kg of body weight.

**Fig. 1**

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**Oscillator \( \Phi 7.0\text{cm} \)\**

- **Stroke volume (\( V_t \))**
  - 0 - 75ml
- **Frequency**
  - 0 - 45Hz

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**Bias flow**

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**Low pass filter**

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**Dog**
Arterial blood of the animal was sampled during conventional mechanical ventilation and 15 minutes after induction of HFO for blood gas analyses using an IL 313 blood gas analyzer (Instrumentation Laboratory, MA, U.S.A).

On the other hand, the series of in vitro experiments were conducted using the system shown in Fig. 2. The experimental system consisted of a piston cylinder apparatus (A and B in the figure), a simulated conductive airway (F) and a rubber anesthetic bag as a lung reservoir (J). We employed two different simulated airways in the present study: one was a turbulent model made of an acrylic tube with an inner diameter of 32.4 mm and a length of 920 mm, with the first one third of the hollow space packed with 10 mm glass beads and the rest with 4 mm beads. The other was a steady flow model approximately identical in size, but with two thirds of the tube length packed with a bundle of glass capillary tubes with an inner diameter of 2.8 mm, instead of 4 mm glass beads as in the former model, to achieve a more steady flow in the peripheral airways.

In the in vitro experiments shown in Fig. 2, pressures were monitored by Validyne MP45-1-871 pressure transducers, gas flow at site I by a hot-wire anemometer (Respirometer RM-100, Minato Ikagaku Co., Japan) and indicator gas concentrations by a mass spectrometer (Centronic 200 MGA, 20th Century Electronics, England). In some experiments, a nitrogen analyzer (Anima Corporation, Japan), with a sampling volume of 0.2 ml/min, was used instead of the mass spectrometer. Procedures of wash-in and wash-out experiments

In the wash-in experiments, the indicator gas was stored in the piston cylinder and the remaining part of the experimental system was filled with 100% oxygen. Transport of the indicator gas by HFO into the rubber bag was monitored at sampling site G by a mass spectrometer. In the wash-out experiments, the indicator gas initially stored in the rubber bag (J) was monitored at sampling site D.

As indicator gases, helium (He), nitrogen (N2), carbon dioxide (CO2) and sulfur hexafluoride (SF6) were used.

The stroke volumes employed ranged from 5 to 20 ml and the frequencies of oscillation from 1.5 to 30 Hz.

RESULTS

Animal experiments: During the control periods of the animal experiments under conventional mechanical ventilation, PacO2 remained eucapnic, while the alveolar-arterial O2 tension difference, P(A-a) O2, which was derived from a simplified alveolar equation, was 24.5 ± 6.1 Torr.

Figure 3 shows changes in arterial oxygen tension (Pao2) under HFO. The abscissa represents a minute volume as a product of stroke volume of the oscillator and oscillator frequency (VT x f x 60 1/min/kg). The open, cross and filled circles in the figure represent the data obtained at stroke volumes of 3 ml, 2 ml and 1 ml/kg of body weight, respectively. All the data points, irrespective of the stroke volumes, could be smoothed out in the curve drawn in Fig. 3. The regression equation for these data points calculated by the method of least squares was:

\[ \text{Pao}_2 = 125.2 \times 60 / (\text{VT} \times f) \]

or

\[ \text{Pao}_2 = 125.2 - 60.3 / (\text{VT} \times f) \] (1)

The curve in Fig. 3 represents theoretical changes in PacO2 against changes in \( \dot{V}_A \), which was derived from a combination of the alveolar ventilation equation for O2, i.e., \( \dot{V}_A = .863 \times V_{O_2} \times R / PACO_2 \) and the simplified alveolar air equation, \( \text{Pao}_2 = \text{Pia}_2 - \text{Paco}_2 / R \). The combination of these two equations yields the following equation:

\[ (\text{Pia}_2 - \text{Paco}_2) \times \dot{V}_A = .863 \times \dot{V}_{O_2}, \] (2)

When we assume an inspired O2 tension of

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Fig. 2
149 Torr, an oxygen uptake ($\dot{V}O_2$) of 90 ml/min and P(A-a) $O_2$ of 25 Torr as observed during the control period, we may transform equations (2) as:

$$\text{Pao}_2 = 124 - 77 \, \dot{V}A$$ (3)

From a comparison of equations (1) and (3), it may be deduced that gas exchange for $O_2$ during HFO is determined by alveolar ventilation when $\dot{V}O_2$ and P(A-a) $O_2$ remain constant and that the product of stroke volume and oscillatory frequency provides a fairly good approximation of alveolar ventilation.

Figure 4 shows the effects of HFO on $\text{Paco}_2$ of the animals.

The regression equation for these data was obtained by method of least squares as follows:

$$\text{Paco}_2 = 14.7 + 37.8 \, (V_T \times f)$$ (4)

The curve drawn in Fig. 4 is derived from the alveolar ventilation equation, i.e., $\text{Paco}_2 = 0.863 \times \dot{V}CO_2 / \dot{V}A$. Since we employed a simplified alveolar air equation for PAO$_2$ during HFO assuming a gas exchange ratio of 1.0, VCO$_2$ can be assumed to be 90 ml, and the alveolar ventilation equation can be transformed into the following form.

$$\text{Paco}_2 = 77.7 \, \dot{V}A$$ (5)

In contrast to oxygen transport, the curve representing $CO_2$ elimination during HFO did not coincide with the curve predicted by the alveolar ventilation equation, especially in the higher range of $V_T \times f$. The hyperbolic curve of equation (4) has an asymptote parallel to the
abscissa, while the curve of equation (5) approaches the abscissa with an increase in \( V_T \times f \).

Model experiment: Figure 5 shows the results of \( N_2 \) wash-in during HFO through a turbulent model of the conducting airways. The abscissa represents time after onset of HFO and the numbers on each curve stand for the applied oscillatory frequencies. The three panels indicate results from respective experiments using different stroke volumes. It is evident that the greater the stroke volume or the oscillatory frequency the faster the rise in \( N_2 \) concentration. In other words, \( N_2 \) wash-in was a function of both the stroke volume and oscillatory frequency.

Fig. 6 indicates changes in “1% \( N_2 \) appearance time” against \( V_T \times f \) which is defined as the time required for the \( N_2 \) concentration to reach 1% after HFO was started in \( N_2 \) wash-in experiments. Open circles represent the appearance time at a stroke volume of 5 ml, the crosses that at 10 ml and the filled circles that at 20 ml. The data points were apparently distributed along a curve regardless of \( V_T \) and/or \( f \), which can be expressed as time \( = A/(V_T \times f)^B \) where \( A \) and \( B \) are constants. This means that, although it was affected by changes in either the stroke volume or the oscillatory frequency, the 1% \( N_2 \) appearance time would be identical if the products of both variables were identical. Thus, we may conclude that the
characteristics of N₂ wash-in in the present model experiments are primarily determined by VT × f.

The curves in Fig. 7 show the 1% appearance times for helium and SF₆ observed in the experiments using a steady flow model of the conducting airways. Although the modes of both helium and SF₆ wash-in were essentially similar to that of N₂, Fig. 7 indicates that a heavier gas, SF₆, washed in more rapidly than a lighter gas, He.

Fig. 8 shows the results of CO₂ washout under HFO, which was monitored by CO₂ transport from a rubber bag, H, to a sampling port, D, as indicated in Fig. 2.

We could not quantitatively compare the time-concentration relationships between wash-in and wash-out experiments because of some differences in experimental procedures. Nevertheless, the results of CO₂ wash-out were
clearly different from those of wash-in experiments, i.e., CO₂ wash-out was faster at a higher oscillatory frequency under a fixed stroke volume, but was not augmented further beyond a certain frequency (15.6 Hz in Fig. 7). These important findings were consistent with other wash-out experiments using different stroke volumes and different indicator gases.

In Fig. 9, the 2% CO₂ appearance time, which was defined as the time required for the CO₂ concentration at the sampling site D in Fig. 2 to reach 2%, was plotted against V̇T × f. In the CO₂ wash-out experiments, the 2% CO₂ appearance time was measured instead of the 1% value for technical reasons. In contrast to the wash-in experiments shown in Fig. 6 in which the data points were distributed fairly along particular curve, the appearance time against V̇T × f was consistently dependent on the stroke volume.

This means that, even when the product of V̇T × f was identical, CO₂ wash-out was more efficient when the stroke volume was larger. Thus, V̇T × f was not the primary determinant of CO₂ clearance in our in-vitro experiments. This finding was also obtained in the washout experiments using different indicator gases such as He, N₂, Ar and SF₆.

DISCUSSION

As the two exhaustive reviews in 1984 (2, 3) indicated on gas transport mechanisms during high frequency ventilation, it may be pertinent to assume that no single mechanism can explain various phenomena related to gas exchange under HFO. Among such mechanisms are direct alveolar ventilation (9), Pendelluft or out-of-phase HFO (7, 11), augmented diffusion (5, 18) and Taylor-type dispersion (23). Moreover, high frequency ventilation includes a few different modes such as high frequency jet ventilation (HFJV), high frequency positive pressure ventilation (HFPPV) and high frequency oscillation (HFO), which do not simply involve differences in ventilatory frequency. HFO differs from other modes in its very high ventilatory frequency with positive and negative pressure swings in the airways, which accordingly produce high oscillatory flows, and in the far smaller stroke (tidal) volume. The ventilatory mode in the present animal experiments, which used oscillatory frequencies up to 30 Hz and stroke volumes of 1 to 3 ml/kg body weight, belongs to the HFO category.

O₂ and CO₂ transport in animal lungs under HFO.

Fredberg (5), simulating HFO with a computer model, proposed the hypothesis that gas transport during HFO is primarily determined by a product of stroke volume and oscillatory frequency. This hypothesis seemed to be confirmed for CO₂ elimination by experimental studies on animals (4, 15, 16, 19, 24), but is less clear with respect to O₂ transport.

In the present study on anesthetized dogs, we found that Pao₂ under HFO was also a function of V̇T × f as shown in Fig. 3 and that the
curve obtained by the least squares method from data points fairly closely matched a theoretical curve derived from alveolar air and alveolar ventilation equations assuming a $V_2$ of 90 ml/min and $P(A-a)O_2$ of 25 Torr. Comparison of these two equations revealed that $V_T \times f$ acts like $V_A$ but has a smaller value than $V_A$ since $(V_T \times f)/V_A$ is approximately 60/77.

This finding led to the conclusion that $O_2$ transport during HFO was also determined by alveolar ventilation with fixed $V_O$ and $P(A-a)O_2$, leaving the question of now the physiological dead space changes under HFO. For conventional ventilation, the classical equation.

$$V_A = (V_T - V_d) \times f$$

holds for the relationship among alveolar ventilation ($V_A$), tidal volume ($V_T$) and dead space volume ($V_d$). In high frequency ventilation, the physiological dead space has to be smaller than the anatomic dead space since $V_T$ is smaller than $V_d$ and gas exchange takes place during HFO. This means that the above equation no longer holds for HFV, and Weinmann et al (22) showed that the physiological dead space fell sharply as $V_T$ was reduced to volumes associated with high frequency ventilation.

Now it is essential to consider the mechanism of this decrease in the physiological dead space. First, differences in the lengths of branching airways produce direct alveolar ventilation in part of the lungs. Asymmetry of the airways yields non-square flow profiles, which cause the front of the dead space gas to be skewed. We may also reasonably surmise that mechanisms of convective streaming (6), augmented dispersion (5, 18), Taylor-type dispersion and out-of-phase HFO (11) are related to the production of non-linear concentration gradients down to the alveoli, which may significantly decrease the physiological dead space. The conclusion reached by Slutsky et al (18) is that effective gas exchange can take place at tidal volumes as small as 20% of the dead space volume if the oscillatory frequency is sufficiently high to maintain tracheal flow amplitude above some critical level. In this situation, however, the classical concept of physiological dead space should be defined as a volume with a merely functional meaning which has no relation to the geometry of the conducting airways.

$CO_2$ elimination ($VCO_2$) by HFO in dogs is known to be largely a function of $V_T \times f$ (10, 14, 15, 19). In the present study, $VCO_2$ was not directly measured, but $PACO_2$ in a quasi steady state under HFO (14) changed as a function of $V_T \times f$. As seen in Fig. 4, however, $PACO_2$ deviated from the theoretical curve derived from an alveolar ventilation equation at higher $V_T \times f$ ranges and had an asymptote of $PACO_2$ of 14.7 Torr. This finding suggested that $CO_2$ elimination by HFO has a limitation at a higher $f$ or a larger $V_T \times f$. Slutsky et al (19) reported that $VCO_2$ increased linearly with an increase in $(V_T \times f)$, which was inconsistent in part with our results. However, they measured $VCO_2$ during a burst of HFO, whereas we measured $PACO_2$ under a quasi-steady state condition, i.e., 15 minutes after introduction of HFO. Moreover, judging from the figures in their paper, they dealt with a $V_T \times f$ range of up to 1.5 liter/s, and some of their animals showed non-linear (decreasing) changes in $VCO_2$ at higher ranges of $V_T \times f$, which was explained in their paper as a result of increasing $VCO_2$ beyond metabolic $CO_2$ production. We were concerned with a much higher $V_T \times f$ range and in $PACO_2$ under a quasi-steady state during HFO. Accordingly, we considered that there is a limitation on CO2 elimination by HFO, assuming constant $CO_2$ production.

Several different factors which might limit $CO_2$ elimination may be considered. First, mechanical factors in our oscillatory system, if any, should be considered. Our oscillator, however, was confirmed to provide the predicted $V_T$ until the oscillatory frequency exceeded 30 Hz, and we employed a maximum oscillatory frequency of 30 Hz in the present animal experiments. Since we employed a piston oscillatory system quite similar to that of Bohn et al (1), which used a bias flow of fresh gas through a long compliant tube, its output might not be delivered to the animal. In this regard, we conducted a series of model experiments where no bias flow was employed, and observed phenomena quite similar to those obtained in the animal experiments as discussed later.

Secondly, as suggested by Mead's theory (12), part of the tidal volume may be shunted into airway wall expansion at a higher frequency of ventilation. We can not rule out this possibili-
ty, but Watson et al (21) concluded from their results of impedance measurements in dogs that much less tidal volume was shunted into airway wall expansion in dogs than in rabbits. The roles of so-called shunt compliance (12) and dynamic head (8) may be less important since our model experiments, in which the tubes were non-compliant, showed similar results to the animal experiments.

Kamm et al (9) suggested the possibility such that, if the regional ventilation exceeds a certain limit, the regional blood flow becomes a limiting factor of CO₂ elimination. This would mean that renewal of alveolar gas is so rapid that the wasted part of ventilation in terms of CO₂ elimination increases, which results in a regional high Vₐ/Q ratio. This might occur as a transient phenomenon during a short burst of HFO, but is unlikely to affect PA₃O₂ at a quasi steady state unless the regional blood flow and the circulation time change drastically.

Finally, it may be more reasonable to consider that some phenomena related to underlying gas exchange mechanisms during HFO cause limitation of CO₂ elimination at higher Vₜ×f ranges. Possible mechanisms include blunting of velocity profiles with increases in frequency asymmetrical velocity profiles for inspiration and expiration, and the role of augmented dispersion which results in different PₐCO₂ for inspiration and expiration. Thus we attempted to elucidate the roles of these mechanisms through much simpler model experiments than the in vivo ones.

Wash-in experiments in the tube models

It is shown in Fig. 3 that O₂ wash-in the animals was a function of Vₜ×f as well as CO₂ elimination. We further analyzed the contributions of Vₜ×f to the transport of other indicator gases with different molecular weights through the tube models, while changing the stroke volume (Vₜ) and/or oscillatory frequency (f). As indicator gases, we employed He, N₂ and SF₆ which have different diffusivities and almost identical viscosities, except for He.

N₂ wash-in was found to be accelerated by increases in both Vₜ and f, and was a function of Vₜ×f (Fig. 6). The acceleration was not limited even at very high frequencies up to 30 Hz (Fig. 5). These observations were also consistent with the results of He and SF₆ wash-in shown in Fig. 7. However, the relationship between appearance time and Vₜ×f showed significant differences according to the type of gas, and a heavier gas was transported more rapidly than a lighter gas.

Since the most apparent difference among these experimental conditions was the molecular weight of indicator gases, the above finding strongly suggests significant contribution of Taylor-type dispersion, including both laminar and oscillatory dispersion, to gas transport during HFO, although physical and aerodynamic properties of the flow in the present model experiments could not be precisely determined. The molecular weight of an indicator gas is a direct determinant of the virtual dispersion coefficient in cases of laminar dispersion, and affects the dispersion indirectly through both Womersley and Reynolds numbers in cases of oscillatory dispersion.

Washout experiments in the tube models

In contrast to N₂ wash-in, CO₂ wash-out to the opposite direction of the tube was not accelerated further beyond a certain frequency, i.e., 15.6 Hz in the experiment shown in Fig. 8. It was also significantly dependent on the magnitude of Vₜ. These findings were consistent with other wash-out experiments using different VₜS and different indicator gases. Thus, it was concluded that the transport of indicator gases in the opposite direction (wash-out) is primarily determined by Vₜ and the effect of increasing oscillatory frequency on the transport was limited to a certain frequency and was not seen at higher frequencies.

The above difference between wash-in and wash-out in the model experiments could be explained on the basis of a physical difference between the inspiratory and expiratory flows as described by Schrotter and Sudlow (17). They reported that inspiratory and expiratory flows had different velocity profiles at the bifurcation of a tube, and that the expiratory flow profile was flatter than that of the inspiratory flow. Haselton and Scherer (6) indicated in their bronchial tree models that the effective dispersion constant for inspiratory flow was 1.08/0.37 times higher than that for expiratory flow. The applicability of these analysis to our tube model experiments is not clear since we used straight tubes without bifurcations, although packed
with glass beads. However, we assumed an analogy between the respiratory system and our tube models with respect to the flow regime in the central and small airways and the alveolar space as shown in Fig. 2. Therefore, it is not warranted to surmise that the difference between wash-in and wash-out was derived from physically different phenomena as reported in the above papers.

The phenomena observed in the present model experiments may be expressed in differently so that a larger Vt is necessary for expiration than for inspiration to maintain an equal gas transport. Slutsky et al. (19) called this the tidal volume (Vtr) effect. They explained the Vt effect theoretically by the fact that the greater Vt causes more effective convective purging in airway opening and enhances gas transport at the alveolar-dead-space interface. This relative importance of Vt may be related to the results in the present model experiments where an increase in f was ineffective for wash-out at higher f x Vt.

Weinmann et al. (22) found in their HFV experiments using dogs that the frequency required to maintain constant alveolar ventilation rose sharply as Vt was decreased to less than 7 ml/kg and that the data deviated substantially from the conventional alveolar ventilation equation, but could be approximated as a product of f x Vt. They further developed a model (15) where the mean deviation of the transit times was directly related to gas exchange. According to their predictions, gas exchange was proportional to (standard deviation of transit time/mean transit time across dead space) in addition to f and Vt. Although it was not directly mentioned in the paper, as long as they assumed well-mixed compartments and predicted transit times, their model may be indirectly related to the hypothesis that the time required for gas transport or for gas mixing might be a limiting factor of CO2 transport in the lungs during HFO. This time factor may also explain the critical frequency phenomenon observed in our wash-out experiments using the tube models.

The role of out-of-phase HFO or high frequency pendelluft in producing a difference between wash-in and wash-out modes remains to be analyzed.

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