0031-3998/90/2701-0064$02.00/0
PEDIATRIC RESEARCH

Vol. 27, No. 1, 1990
Printed in U.S.A.

Frequency, Tidal Volume, and Mean Airway Pressure Combinations that Provide Adequate Gas Exchange and Low Alveolar Pressure during High Frequency Oscillatory Ventilation in Rabbits

MICHAEL D. KAMITSUKA, BRUCE R. BOYNTON, DINA VILLANUEVA,
PATRICIA N. VREELAND, AND IVAN D. FRANTZ III

Tufts University School of Medicine, Department of Pediatrics, Floating Hospital for Infants and Children, New England Medical Center, Boston, Massachusetts 02111

ABSTRACT. We studied healthy and saline lavaged rabbits during high frequency oscillatory ventilation to determine what combination of frequency (f), tidal volume (V_t), and mean airway pressure ($\bar{P}_{aw}$) produced the lowest peak-to-peak alveolar pressure amplitude (P_{alv}) and physiologic blood gas tensions. Sinusoidal volume changes were delivered through a tracheostomy by a piston pump driven by a linear motor. Tracheal pressure amplitude (P_{tr}) was measured through a tracheal catheter and alveolar pressure amplitude was measured in a capsule glued to the right lower lobe. PaO_2, $PaCO_2$, P_{tr}, and P_{alv} were measured at the following settings: $FiO_2 = 0.5$, frequency 2–28 Hz, V_t 1–3 mL/kg (50 150% dead space) and $\bar{P}_{aw}$ 5–15 cm H_2O. Many combinations of frequency and V_t resulted in the same PaO_2 and $PaCO_2$. $\bar{P}_{aw}$ had a large effect on P_{alv} and minimal effect on blood gas tensions. In lavaged rabbits, the composite variable f × V_t^2 described the trends in P_{alv} and blood gas tensions. As the product of f × V_t^2 increased, PaO_2 initially increased and then decreased, whereas $PaCO_2$ decreased and P_{alv} increased. No single combination of frequency, V_t and $\bar{P}_{aw}$ simultaneously provided the lowest P_{alv} and physiologic blood gas tensions. Adequate blood gas tensions and low P_{alv} were obtained at frequencies less than 12 Hz, a V_t of 2 mL/kg and a $\bar{P}_{aw}$ of 10 cm H_2O. In healthy and lavaged rabbits PaO_2 increased and $PaCO_2$ decreased as frequency increased at lower $V_t \cdot PaO_2$ decreased as frequency increased at higher V_t in lavaged rabbits only. P_{alv} tended to be greater in lavaged rabbits. (*Pediatr Res* 27: 64–69, 1990)

Abbreviations

f, frequency
V_t, tidal volume
$\bar{P}_{aw}$, mean airway pressure
P_{tr}, peak-to-peak tracheal pressure amplitude
P_{alv}, peak-to-peak alveolar pressure amplitude
HFOV, high frequency oscillatory ventilation
$\dot{V}_{osc}$, oscillatory ventilation
$\dot{V}_A/\dot{Q}$, ventilation-perfusion ratio
$\dot{V}CO_2$, expired CO_2

Selected effects of f, V_t, and $\bar{P}_{aw}$ on gas exchange and pressure amplitude have been studied previously in healthy and lung damaged animal models during HFOV. Oxygenation and ventilation have been shown to depend on frequency and V_t (1, 2). Previous work indicating there is a relationship between CO_2 elimination and the product of oscillatory frequency and V_t [$\dot{V}CO_2 = a(f)^b(V_t)^c$ where a, b, c are constants] (3, 4) led us to evaluate the relationship of arterial blood gas tensions to the product f × V_t^2 (5). We observed that many combinations of frequency and V_t produced equivalent blood gas tensions and that the composite variable f × V_t^2 was a good descriptor of our mean arterial blood gas tensions during HFOV in healthy rabbits. Others have found that different combinations of frequency, V_t and $\bar{P}_{aw}$ can produce equivalent blood gas tensions (3, 4) but the resultant pressure swings in the trachea and alveolus may not be equivalent. Near the resonant frequency of the respiratory system, pressure swings in the alveolus may exceed those at the airway opening during HFOV (8, 9). Allen *et al.* (10) reported that the ratio, P_{alv}/P_{ao}, increased as $\bar{P}_{aw}$ increased near the resonant frequency in excised rabbit lungs. Although increasing $\bar{P}_{aw}$ has not been shown to improve gas exchange in healthy animals (11) it does improve oxygenation in lung damaged animal models (12–14).

We wished to determine whether there is a combination of frequency, V_t and $\bar{P}_{aw}$ that provides adequate blood gas tensions (*i.e.* the highest PaO_2 and a $PaCO_2$ between 35 and 55 torr) and minimizes airway pressure amplitude. We examined systematically the combined effects of frequency, V_t and $\bar{P}_{aw}$ on gas exchange and airway pressure swings during HFOV. Because of the previous conflicting results of $\bar{P}_{aw}$ effect on PaO_2 in healthy and lung damaged animals, we also compared healthy and saline lavaged rabbits to determine how frequency, V_t and $\bar{P}_{aw}$ affected gas exchange and airway pressure swings in each model.

MATERIALS AND METHODS

Animal preparation. Ten juvenile male New Zealand White rabbits ranging in wt from 2.05 to 3.03 kg were studied. They were anesthetized with ketamine (40 mg/kg), acepromazine (0.4 mg/kg), and xylazine (6 mg/kg) by intramuscular injection. A tracheostomy was performed and a 3.0 mm inner diameter endotracheal tube was inserted. The animals were paralyzed with pancuronium (0.8 mg) and ventilated. Sinusoidal volume changes were delivered through the endotracheal tube by a piston pump ventilator, driven by a linear motor (Hummingbird High Frequency Oscillator, Senko Medical Products, Tokyo, Japan).

Received February 28, 1989; accepted September 7, 1989.
Correspondence Michael D. Kamitsuka, M.D., Box 44, Department of Pediatrics, Floating Hospital for Infants and Children, New England Medical Center, 750 Washington Street, Boston, MA 02111.
Supported by NIH Grant HL34616.

A high impedance bias flow (6 L/m) supplied fresh humidified gas.

To produce a model of lung injury, we used a modification of Lachmann's pulmonary lavage technique (15). The rabbit was disconnected from the ventilator. Thirty mL/kg of warmed saline were instilled through the endotracheal tube at a pressure of 50 cm H_2O and left for 10 s before drainage. The rabbit was reconnected to the ventilator. No sustained inflation was given before the next lavage. The lavage was repeated every 5 min until the Pa_{O_2} was less than 70 torr at $F_{IO_2} = 1.0$. A median of two lavages (range 1–5) with 91% (range 84–97%) saline returned was required to reach the desired impairment of gas exchange. Body temperature was continuously monitored with a rectal temperature probe, and heating pads were used to maintain normothermia.

Measurement of V_t. V_t was measured by integrating the flow signal from a no. 0 Fleisch pneumotachograph connected to a high fidelity differential pressure transducer (Celesco Transducer Products, Inc., Canoga Park, CA). The pneumotachograph was calibrated by adjusting the volume signal to equal a known V_t measured using a 30L pressure plethysmograph. The frequency response of the pneumotachograph-transducer system was studied by comparing its output with that of a pressure plethysmograph with a known dynamic response. The pneumotachograph had a flat amplitude response ± 16% from 3 to 30 Hz. Correction factors were obtained from the frequency response curve. The ventilator stroke volume was adjusted appropriately to ensure that equal V_t were delivered at all frequencies. Brusasco *et al.* (7) have shown that during HFOV, delivered gas volume to the lungs may differ from the stroke volume delivered by the piston pump. To validate that the V_t delivered to the lung was equal to the V_t measured by the pneumotachograph, we placed a tracheostomized rabbit in the plethysmograph and attached the endotracheal tube to the pneumotachograph and compared V_t as measured by the plethysmograph and pneumotachograph at different frequencies. The plethysmograph and pneumotachograph measured V_t were equal at frequencies of 4 and 28 Hz in the unlavaged rabbit. The pneumotachograph V_t was no more than 5% more than the plethysmograph V_t at a frequency of 28 Hz and equal at a frequency of 4 Hz in the lavaged rabbit.

Measurement of airway pressure. To measure peak-to-peak tracheal pressure amplitude about the mean P_{tr}, an air filled side hole catheter was placed next to the endotracheal tube so that its tip extended 0.5 cm beyond the endotracheal tube. Both the endotracheal tube and the pressure catheter were secured in place with an umbilical tie and sealed with cyanoacrylate glue to prevent air leaks.

To measure peak-to-peak alveolar pressure about the mean P_{alv}, a plastic capsule was attached to the visceral pleura of the right lower lobe in a modification of the method of Fredberg *et al.* (8). After the chest was opened at the 6th right intercostal space, the lungs were distended to 10 cm H_2O. A thin sheet of soft plastic wrap, cut approximately 1 cm more than the capsule, was attached to the flat surface of the capsule with cyanoacrylate glue, and the plastic surface glued to the right lower lobe. Four punctures were made into the visceral pleura through the opening of the plastic capsule with a 20-gauge needle to a depth of 3 mm. The pressure transducer was then connected to the capsule. The chest remained open throughout the experiment. All pressures were measured using piezoresistive pressure transducers (Endevco Corp., San Juan Capistrano, CA).

From previous studies we have found that both transducer and catheter or transducer and alveolar capsule combinations had a flat amplitude response within ± 0.5% and a flat phase response ± 5° from 0.5 to 30 Hz (16). All signals were amplified using Tektronix AM502 amplifiers (Tektronix Inc., Beaverton, OR) and displayed on an oscilloscope.

Measurement of arterial blood gas tensions. To obtain arterial blood samples, a 22-gauge angiocath was placed in the central ear artery. Blood gases tensions were measured with a BMS 3 Mark 2 Blood Micro System (Radiometer, Copenhagen, Denmark), and corrected to 37°C. The electrodes were calibrated before each experiment with certified gas standards, and were accurate within 0.02%. Duplicate measurements of blood samples never varied more than ± 0.5 torr.

Experimental protocol. Five healthy and five lavaged rabbits were studied while receiving F_{IO_2} of 0.5. Similar combinations of frequency, V_t and $\overline{P}_{aw}$ were studied but the order was randomized for each rabbit. Frequencies of 4, 8, 16, 24 Hz and V_t of 1 and 3 mL/kg were studied in healthy rabbits. Frequencies of 2, 12, 20, 24, 28 Hz and V_t of 1, 2, and 3 mL/kg were studied in lavaged rabbits [a V_t of 2.0 mL/kg was estimated to equal physiologic dead space (1)]. At the largest V_t (3 mL/kg), the maximum frequency attainable was 24 Hz. $\overline{P}_{aw}$ of 5.0, 10.0, and 15.0 cm H_2O were studied in each rabbit at every combination of frequency and V_t. To ensure that each combination of frequency, V_t and $\overline{P}_{aw}$ was presented after the same volume history the lungs were inflated by increasing the $\overline{P}_{aw}$ to 20 cm H_2O for 10 s before each combination was studied. Arterial blood samples were drawn after an equilibration period (10–20 min) determined by the f × V_t^2 at each setting. From our previous studies in healthy rabbits, we found that those settings with a f × V_t^2 less than 12.0 $mL^2\ kg^{-2}\ s^{-1}$ required a 20-min period for blood gas tensions to fully equilibrate. Blood gas tensions at settings with a higher f × V_t^2 equilibrated faster and samples could be drawn after 10 min. P_{tr} and P_{alv} were measured just before changing to the next designated combination.

Analysis of data. To analyze the data statistically, we performed an N-way analysis of variance evaluating the effects of frequency, V_t and $\overline{P}_{aw}$ on the dependent variables Pa_{O_2}, Pa_{CO_2}, and P_{alv}. We also performed a one way analysis of variance using Bonferroni comparison of dependent variable values at different frequencies, V_t or $\overline{P}_{aw}$. All calculations were made using the computer program STATA version 1.5 (Computing Resource Center, Los Angeles, CA). Data are summarized as the mean of five rabbits ± SE with statistical significance taken as $p < 0.05$.

RESULTS

We will first present results describing how frequency, V_t and $\overline{P}_{aw}$ affected blood gas tensions and alveolar pressure amplitude in saline lavaged rabbits and then indicate how the lavaged animals differ from normals. As frequency increased (Fig. 1), there was a trend for Pa_{O_2} to increase at a V_t of 1 mL/kg, remain constant at 2 mL/kg and decrease at a V_t of 3 mL/kg ($\overline{P}_{aw} = 10$ cm H_2O), but these trends were not statistically significant. Pa_{CO_2} significantly ($p < 0.01$) decreased with increasing frequency at all V_t. P_{alv} increased significantly ($p < 0.05$) with frequency at $V_t = 2$ mL/kg but not at $V_t = 1$ or 3 mL/kg ($\overline{P}_{aw} = 10$ cm H_2O).

As V_t increased ($\overline{P}_{aw} = 10$ cm H_2O) (Fig. 1), Pa_{O_2} was relatively unaffected, increasing significantly ($p < 0.05$) only at a frequency of 2 Hz. Pa_{CO_2} significantly decreased with V_t at all frequencies ($p < 0.001$) and P_{alv} significantly increased at all frequencies ($p < 0.05$).

As $\overline{P}_{aw}$ increased at a V_t of 2 mL/kg (Fig. 2), there was a trend for Pa_{O_2} to increase, but this was significant ($p < 0.01$) only at 2 Hz, Pa_{CO_2} was not affected, and P_{alv} amplitude significantly ($p < 0.05$) increased with $\overline{P}_{aw}$ at all frequencies ($p < 0.001$).

P_{alv} amplitude was low (<approximately 6 cm H_2O) at every setting tested. The lowest P_{alv} was observed when V_t was 1 mL/kg (Fig. 1) and $\overline{P}_{aw}$ was 5 cm H_2O (Fig. 2) but values of P_{alv} at a V_t of 2 mL/kg and a $\overline{P}_{aw}$ of 10 cm H_2O were not statistically different (Figs. 1 and 2).

Pa_{O_2} and Pa_{CO_2} from Figures 1 and 2 were replotted as functions of f × V_t^2 at all $\overline{P}_{aw}$ (Fig. 3). As the product f × V_t^2 increased, Pa_{O_2} initially increased ($p < 0.001$) then decreased ($p < 0.05$) when the product was greater than 80 $mL^2\ kg^{-2}\ s^{-1}$. As the product f × V_t^2 increased Pa_{CO_2} decreased ($p < 0.001$) and P_{alv} tended to increase for $\overline{P}_{aw} \leq 10$ cm H_2O but was not statistically significant (Fig. 4).

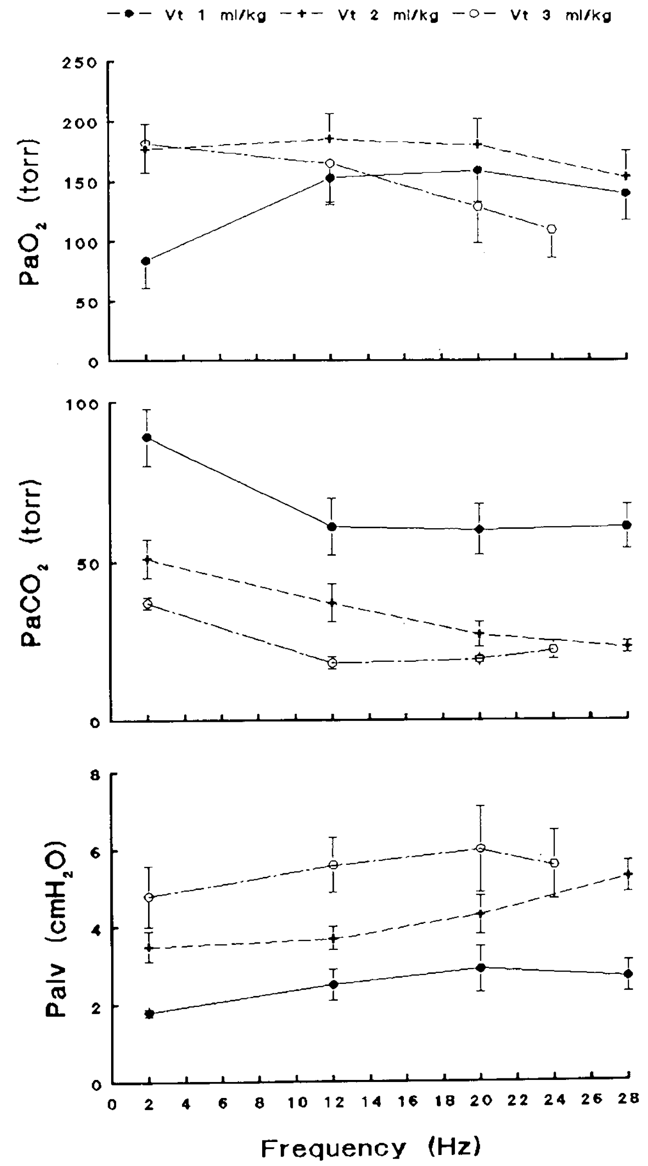

Fig. 1. Pa_{O_2}, Pa_{CO_2}, and P_{alv} as functions of frequency and $V_t \cdot \bar{P}_{aw}$ = 10 cm H_2O. $F_iO_2 = 0.5$. Each point is the mean of five lavaged rabbits ± SE.

Blood gas tensions were similar in healthy and lavaged rabbits (Fig. 5) but greater P_{alv} amplitudes were required to obtain these blood gases in lavaged rabbits (Fig. 5). $\bar{P}_{aw}$ had little effect on Pa_{O_2} in healthy (Fig. 6*A*) or lavaged rabbits (Fig. 6*B*). Comparison of Figures 3 and 7 indicates differing relationships between Pa_{O_2} and $f \times V_t^2$ in healthy and lavaged rabbits. Pa_{O_2} increased with $f \times V_t^2$ in healthy rabbits (Fig. 7) but decreased after an increase in lavaged rabbits (Fig. 3). Pa_{CO_2} decreased as $f \times V_t^2$ increased in both healthy and lavaged rabbits (Figs. 3 and 7). As $f \times V_t^2$ increased, P_{alv} tended to increase for $\bar{P}_{aw} < 10$ cm H_2O in lavaged rabbits but showed no change in healthy rabbits (Fig. 8).

DISCUSSION

We observed many combinations of frequency and V_t that resulted in the same Pa_{O_2} and Pa_{CO_2}. $\bar{P}_{aw}$ had a large effect on P_{alv} amplitude but little effect on blood gas tensions. We found that in lavaged rabbits, the composite variable frequency multiplied by the square of the tidal volume ($f \times V_t^2$) well described the trends in P_{alv} and blood gas tensions such that as the product of $f \times V_t^2$ increased, Pa_{O_2} initially increased, then decreased, Pa_{CO_2} decreased and P_{alv} amplitude increased in lavaged rabbits. Therefore, we did not find one combination that simultaneously provided the lowest alveolar pressure amplitude and physiologic blood gas tensions. Compromises were necessary to reach either maximum blood gas tensions or minimal airway pressures. Combinations that simultaneously provide both a low P_{alv} amplitude and adequate blood gas tensions are frequencies less than 12 Hz, a V_t of 2 mL/kg (approximately equal to dead space) and $\bar{P}_{aw}$ of 10 cm H_2O.

Possible sources of errors that may have affected our results will be reviewed. All experiments were lengthy because of the time required for equilibration of Pa_{O_2} and Pa_{CO_2} values. The length of the experiment may have resulted in deterioration of the animal preparation resulting in deterioration of blood gas tensions toward the end of each experiment. Although Pa_{O_2} and Pa_{CO_2} appeared to be well maintained during the experiment, the animals did tend to develop a metabolic acidosis toward the end of the experiment. The random order of measurements should have served to minimize these effects. Although blood

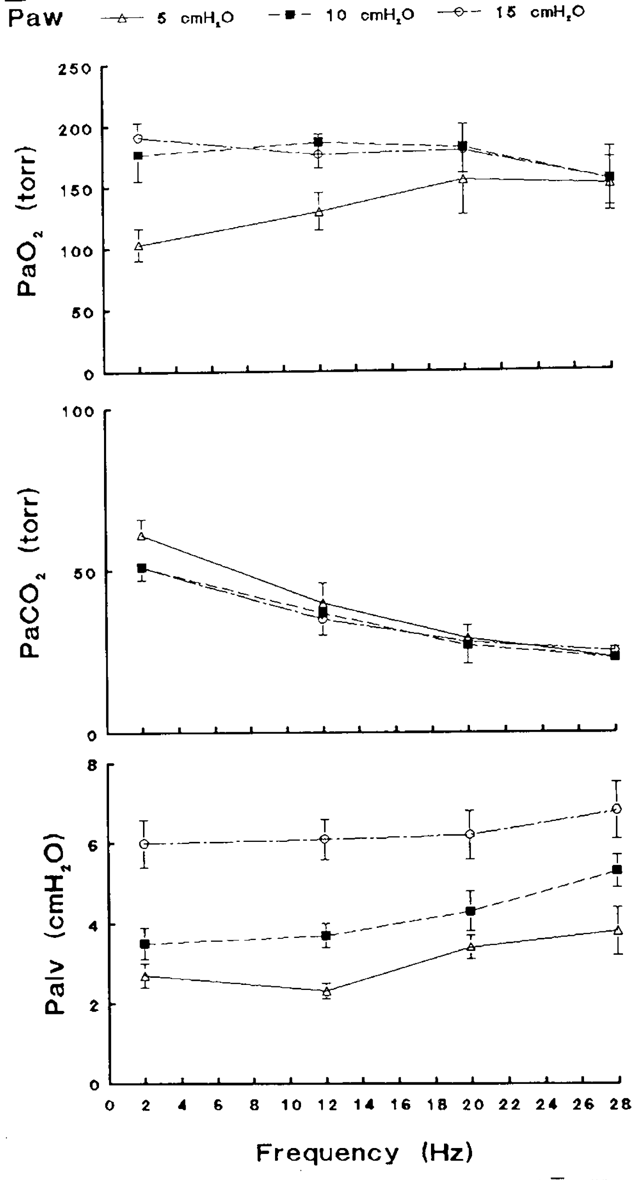

Fig. 2. Pa_{O_2}, Pa_{CO_2}, P_{alv} as functions of frequency and $\bar{P}_{aw} \cdot V_t = 2$ mL/kg. $FiO_2 = 0.5$. Each point is the mean of five lavaged rabbits ± SE.

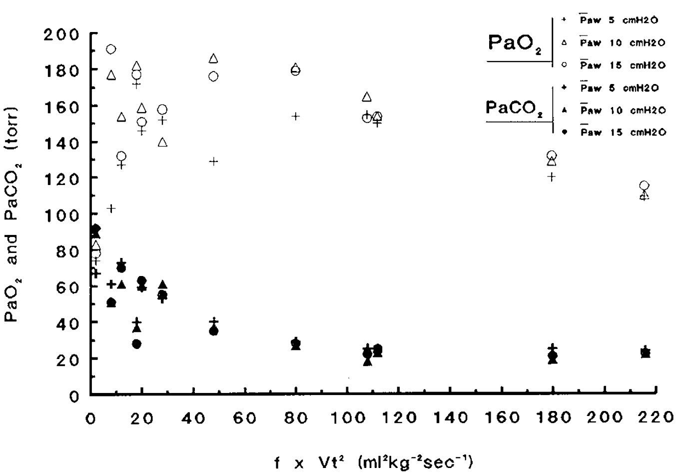

Fig. 3. Pa_{O_2} and Pa_{CO_2} functions of f × V_t^2 for $\overline{P}_{aw}$ 5, 10, 15 cm H_2O. $FiO_2 = 0.5$. Each point is the mean of three to five lavaged rabbits.

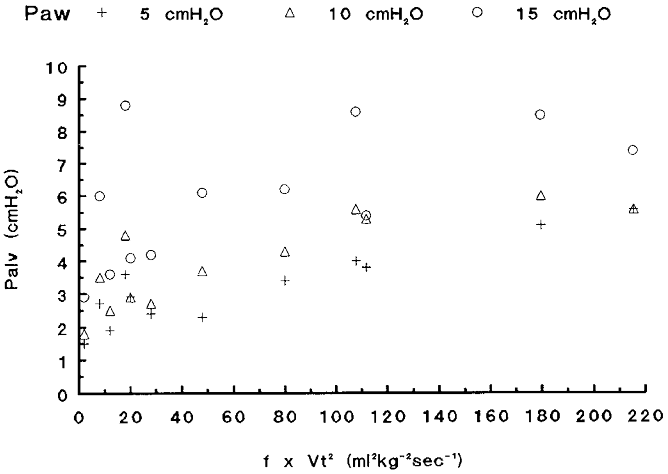

Fig. 4. P_{alv} as a function of f × V_t^2 for $\overline{P}_{aw}$ 5, 10, 15 cm H_2O. $FiO_2 = 0.5$. Each point is the mean of three to five lavaged rabbits.

gas tensions were similar in healthy and lavaged rabbits (Fig. 5), we believe that the lavaged rabbits were lung damaged because greater P_{alv} amplitudes were required to obtain these blood gases in lavaged rabbits.

Our P_{alv} measurements may not have been representative of "global" P_{alv} because the alveolar capsule samples only those units close to the pleural surface in the region of the capsule. Allen *et al.* (17) have demonstrated marked differences in P_{alv} between the apex and base and slight differences between the right and left lung at higher frequencies. Fredberg *et al.* (18) determined that the lung responds in a nonhomogeneous manner to inhaled histamine and they assumed that because frequency dependence of impedance alone cannot explain the regional P_{alv} difference, intrinsic regional differences must always exist. Inasmuch as we only measured P_{alv} in one location we are unable to comment on P_{alv} in other regions of the lung and how they affected oxygenation.

Next we will discuss our blood gas tension results. Our results suggest that the combined effect of a V_t of 2 mL/kg and a $\overline{P}_{aw}$ greater than or equal to 10 cm H_2O are necessary to produce adequate oxygenation. We assume that $\overline{P}_{aw}$ improved oxygenation by increasing lung volume and decreasing venous admixture (14). The suboptimal oxygenation that occurs at lower frequencies for a V_t of 1 mL/kg and $\overline{P}_{aw}$ of 5 cm H_2O (Figs. 1 and 2) is most likely due to a combination of alveolar hypoventilation and increased $\dot{V}_A/\dot{Q}$ inequality (5). At the same V_t and $\overline{P}_{aw}$ oxygenation is adequate at higher frequencies. Fletcher and Epstein (1) suspect the increase in minute ventilation at higher frequencies increases mean and end expiratory alveolar pressure, thus improving Pa_{O_2} by enhancing ventilation of poorly ventilated alveoli and preventing the closure of small airways (1). We are unable to say if gas trapping occurred at the higher frequencies because we did not measure final lung volume at the higher frequencies.

Others have tried to define "optimal settings" based on Pa_{CO_2}. Bohn (19) reported the optimal oscillatory frequency to be 15 Hz because at a fixed stroke volume (1.9 mL/kg) this frequency produced the lowest values of Pa_{CO_2} over a range of frequencies. However, V_t may have fluctuated due to variable losses through the bias flow and due to the frequency dependence of impedance of the animals' respiratory systems. If V_t rather than stroke volume was fixed as in our experiment, a different result may have been obtained. Wright *et al.* (13) obtained the lowest Pa_{CO_2} in rabbits with oleic acid lung damage at a frequency of 20 Hz, independent of stroke volume between 2.6 to 8.9 mL. However, they believed that the Vt decreased at higher frequencies due to

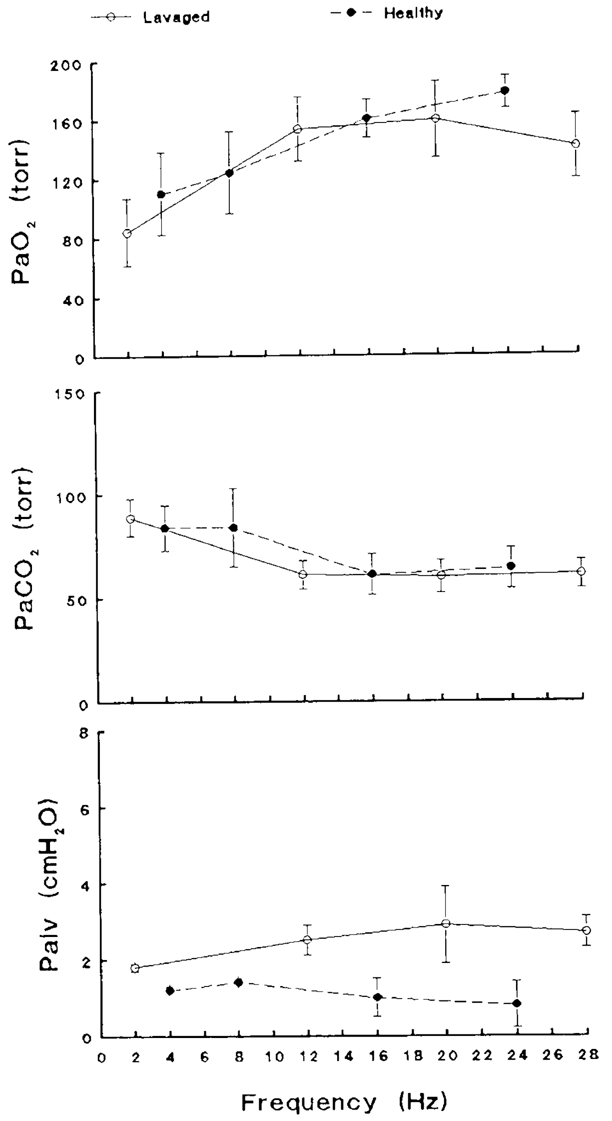

Fig. 5. Pa_{O_2}, Pa_{CO_2}, P_{alv} as functions of frequency at a $V_t = 1$ mL/kg and $\overline{P}_{aw} = 10$ cm H_2O in lavaged and healthy rabbits. $FiO_2 = 0.5$. Each point is the mean of three to five lavaged rabbits ± SE.

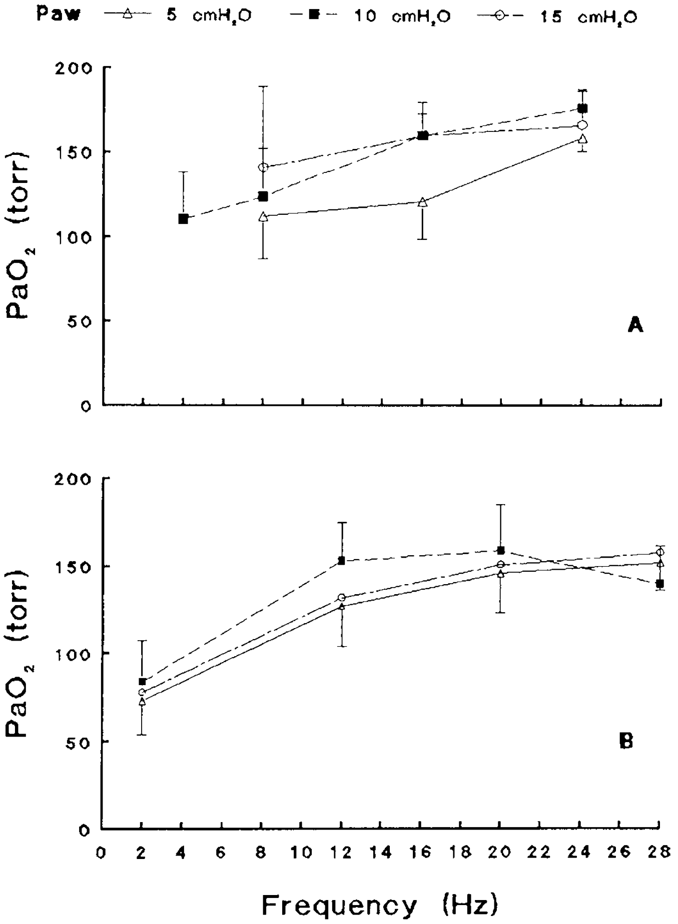

Fig. 6. PaO_2 in lavaged (*A*) and healthy rabbits (*B*) as a function of frequency and $\bar{P}_{aw}$ at a $V_t = 1$ ml/kg. $FiO_2 = 0.5$. Each point is the mean of three to five rabbits ± SE.

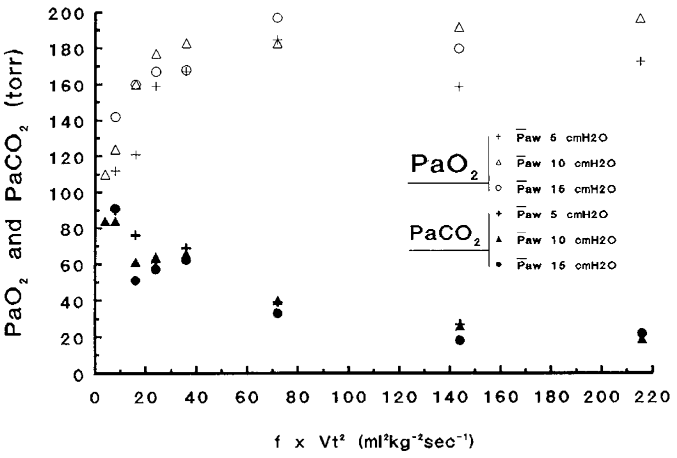

Fig. 7. PaO_2 and $PaCO_2$ as functions of f × V_t^2 for $\bar{P}_{aw}$ 5, 10, 15 cm H_2O. $FiO_2 = 0.5$. Each point is the mean of three to five healthy rabbits.

gas compression in the apparatus. When V_t was corrected for gas compression, they found that $PaCO_2$ decreased with increasing frequency at a constant V_t that no longer suggested a frequency optimum. Consistent with Wright's data, we found the lowest $PaCO_2$ (23 torr) at a frequency of 28 Hz and a V_t of 2 mL/kg. Lower values may have been reached if greater frequencies and V_t were tested.

Perhaps it is not appropriate to think of an optimal frequency or an optimal V_t in isolation. Slutsky *et al.* (3, 4) found CO_2 elimination to be dependent on $\dot{V}_{osc}$ as determined by the product of oscillatory frequency and V_t. Slutsky concluded that although $\dot{V}_{osc}$ is an important factor in determining CO_2 elimination, frequency and V_t have independent effects with V_t having a greater effect on CO_2 elimination than frequency at any given $\dot{V}_{osc}$. In a previous study, we further evaluated this hypothesis by plotting $PaCO_2$ and PaO_2 as functions of f × V_t^2 in healthy rabbits (5). We found that PaO_2 and $PaCO_2$ data for many combinations of frequency and V_t collapsed onto a single curve suggesting that PaO_2 and $PaCO_2$ in healthy rabbits are dependent on factors associated with oscillatory flow.

In this study, we plotted PaO_2 and $PaCO_2$ as a function of f × V_t^2 for lavaged rabbits. We found that the PaO_2 in lavaged rabbits unlike healthy rabbits initially increased, then decreased as f × V_t^2 increased. The relationship of $PaCO_2$ to f × V_t^2 was similar in both healthy and lavaged rabbits, decreasing as f × V_t^2 increased. Our data suggest the highest PaO_2 and eucapnic $PaCO_2$ can be obtained at frequencies less than 12 Hz and V_t equal to 2 mL/kg.

We plotted peak-to-peak excursions in P_{alv} *versus* f × V_t^2 to understand the pressure excursions necessary to achieve a given PaO_2 and $PaCO_2$ at any frequency and V_t combination. Although this is clinically relevant, *i.e.* it tells us what degree of barotrauma may occur at a given combination, a mechanically more appropriate relationship is that of P_{alv} *versus* the product of elastance and tidal volume. Elastance, or its reciprocal, compliance, is dependent on mean distending pressure and has a slight negative frequency dependence. One might thus expect the data in Figures 4 and 8 to collapse onto a single curve if plotted in this fashion, and in fact one can glean such an impression from examination of the figures. We do not have sufficient data to calculate elastance and plot the relationship of interest.

We found that neither PaO_2 nor $PaCO_2$ was affected by $\bar{P}_{aw}$. Yamada *et al.* (11) found that as $\bar{P}_{aw}$ increased, $PaCO_2$ increased and PaO_2 decreased. He associated these findings with decreased alveolar ventilation caused by an increase in the volume of the conducting airways. The difference between our results and those of Yamada may be explained by differences in the animal model studied or because any increase in the volume of the conducting airways of rabbits may have been small compared to the dead space of our ventilator circuit (7 mL). However, Slutsky *et al.* (3) predicted that an increase in lung volume could produce two competing phenomena. Increased cross-sectional area of airways may either increase CO_2 elimination as a result of increased minute ventilation or decrease CO_2 elimination as a result of decreased velocity of flow in the airways resulting in decreased

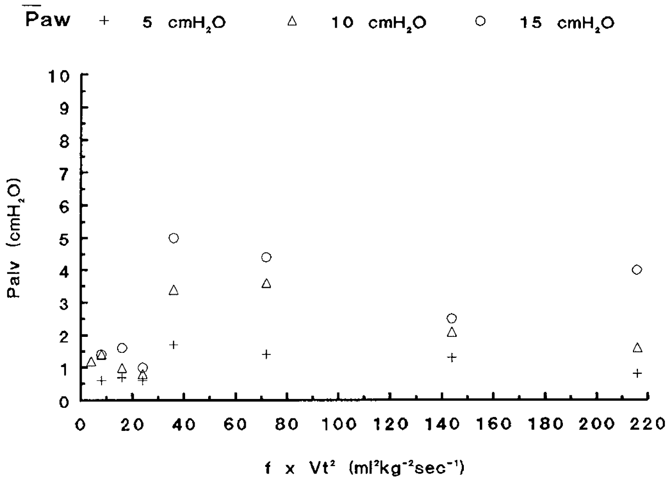

Fig. 8. P_{alv} as a function of f × V_t^2 for $\bar{P}_{aw}$ 5, 10, 15 cm H_2O. FiO_2 = 0.5. Each point is the mean of three to five healthy rabbits.

gas mixing. Korvenranta *et al.* (20) found that CO_2 elimination increased as V_t increased up to 3 mL/kg. For $V_t > 3$ mL/kg CO_2 elimination began to decrease as a result of inadvertent positive end-expiratory pressure resulting from increased gas trapping. When inadvertent positive end-expiratory pressure was held constant at 5 or 10 cm H_2O, CO_2 elimination increased as V_t increased, a finding more consistent with our results.

We were surprised to find that healthy and lavaged rabbits were similar in their blood gas response to changes in frequency, V_t and $\overline{P}_{aw}$. We expected our results to show that increasing $\overline{P}_{aw}$ in lavaged rabbits would improve oxygenation compared to healthy rabbits. Kolton *et al.* (12) and Lachmann *et al.* (15) demonstrated that FRC decreases after lavage. We have previously shown that increasing lung volume in lavaged rabbits decreases venous admixture and improves oxygenation (14). Healthy and lavaged rabbits may not have differed with respect to effects of $\overline{P}_{aw}$ because 5 cm H_2O, the lowest value studied, may have exceeded closing pressure for the lavaged animals, or because the inflation maneuver between changes of settings may have transiently eliminated differences in lung volume. If the animals were maintained at a $\overline{P}_{aw} = 5$ cm H_2O for longer periods of time before blood gas specimens were obtained, they may develop atelectasis and decreased Pa_{O_2}.

Our findings have several important clinical implications. First, both oxygenation and carbon dioxide tension depend on $f \times V_t^2$ such that several combinations of frequency and V_t may result in similar gas exchange. Second, P_{alv} amplitude depends on both $f \times V_t^2$ and $\overline{P}_{aw}$. Thus, to optimize gas exchange while minimizing pulmonary barotrauma, one may wish to choose the lowest possible $\overline{P}_{aw}$ and $f \times V_t^2$ product resulting in adequate gas exchange.

In conclusion, we did not find one combination of frequency, V_t, and $\overline{P}_{aw}$ that simultaneously provided the lowest alveolar pressure amplitude and physiologic blood gas tensions. Our results indicate that trade offs for either more desirable blood gas tensions or lower airway pressure swings are necessary. In the animals studied, the combination of frequency, V_t and $\overline{P}_{aw}$ that provided the greatest Pa_{O_2}, Pa_{CO_2} between 35–55 torr, and a low P_{alv} were frequencies less than 12 Hz, a V_t of 2 mL/kg and a $\overline{P}_{aw}$ of 10 cm H_2O. Higher frequencies may be useful in lowering Pa_{CO_2} in subjects with more severe lung disease but as the product $f \times V_t^2$ increases, Pa_{O_2} may decrease and alveolar pressure amplitude may increase. Healthy and lavaged rabbits were similar in that as frequency increased at lower V_t, Pa_{O_2} increased and Pa_{CO_2} decreased. They differed in that as frequency increased at higher V_t, Pa_{O_2} decreased in lavaged but not healthy rabbits. P_{alv} was slightly greater in lavaged rabbits to maintain similar blood gas tensions, but this was not statistically significant.

REFERENCES

1. Fletcher PR, Epstein RA 1982 Constancy of physiological dead space during high-frequency ventilation. Respir Physiol 47:39–49
2. Rieke H, Hook CL, Meyer M 1983 Pulmonary gas exchange during high-frequency ventilation in dogs. Respir Physiol 54:1–17
3. Slutsky AS, Kamm RD, Rossing TH, Loring SH, Lehr J, Shapiro AH, Ingram Jr RH, Drazen JM 1981 Effects of frequency, tidal volume, and lung volume on CO_2 elimination in dogs by high frequency (2–30 Hz), low tidal volume ventilation. J Clin Invest 68:1475–1484
4. Watson JW, Jackson AC, Gillespie JR 1984 CO_2 elimination and airway opening pressure during high frequency oscillation in dogs. Respir Physiol 58:235–244
5. Boynton BR, Fredberg JJ, Buckley BG, Frantz ID 1989 Gas exchange in healthy rabbits during high-frequency oscillatory ventilation. J Appl Physiol 66:1343–1351
6. Permutt S, Mitzner W, Weinmann G 1985 Model of gas transport during high-frequency ventilation. J Appl Physiol 58:1956–1970
7. Brusasco V, Rehder K, Beck KC, Crawford M 1985 Gas volume delivered by high frequency ventilation. Fed Proc 44:1383(abstr)
8. Fredberg JJ, Keefe DH, Glass GM, Castile RC, Frantz ID 1984 Alveolar pressure nonhomogeneity during small-amplitude high-frequency oscillation. J Appl Physiol 57:788–800
9. Simon BA, Weinmann GG, Mitzner W 1984 Mean airway pressure and alveolar pressure during high-frequency ventilation. J Appl Physiol 57:1069–1078
10. Allen JL, Fredberg JJ, Keefe DH, Frantz ID 1985 Alveolar pressure magnitude and asynchrony during high frequency oscillation of excised rabbit lungs. Am Rev Respir Dis 132:343–349
11. Yamada Y, Venegas JG, Strieder DJ, Hales CA 1986 Effects of mean airway pressure on gas transport during high-frequency ventilation in dogs. J Appl Physiol 61:1896–1902
12. Kolton M, Cattran CB, Kent G, Volgyesi G, Froese AB, Bryan AC 1982 Oxygenation during high-frequency ventilation compared with conventional ventilation in two models of lung injury. Anesth Anal 61:323–332
13. Wright K, Lyrene RK, Truog WE, Standaert TA, Murphy J, Woodrum DE 1981 Ventilation by high-frequency oscillation in rabbits with oleic acid lung disease. J Appl Physiol 50:1056–1060
14. Boynton BR, Buckley BG, Villanueva D, Vreeland P, Kamitsuka MD, Frantz ID 1988 Effect of mean airway pressure on gas exchange during high frequency oscillatory ventilation. Pediatr Res 23:499A(abstr)
15. Lachmann B, Robertson B, Vogel J 1980 In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol 24:231–236
16. Frantz ID, Close RH 1985 Alveolar pressure swings during high frequency ventilation in rabbits. Pediatr Res 19:162–166
17. Allen JL, Frantz ID, Fredberg JJ 1987 Heterogeneity of mean alveolar pressure during high-frequency oscillations. J Appl Physiol 62:223–228
18. Fredberg JJ, Ingram RH, Castile RG, Glass GM, Drazen JM 1985 Nonhomogeneity of lung response to inhaled histamine assessed with alveolar capsules. J Appl Physiol 58:1914–1922
19. Bohn DJ, Miyasaka K, Marchak BE, Thompson WK, Froese AB, Bryan AC 1980 Ventilation by high-frequency oscillation. J Appl Physiol 48:710–716
20. Korvenranta H, Carlo WA, Goldthwait DA, Fanaroff AA 1987 Carbon dioxide elimination during high-frequency jet ventilation. J Pediatr 111:107–113