Effects of Frequency, Tidal Volume, and Lung Volume on CO₂ Elimination in Dogs by High Frequency (2-30 Hz), Low Tidal Volume Ventilation

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ABSTRACT Recent studies have shown that effective pulmonary ventilation is possible with tidal volumes (V_T) less than the anatomic dead-space if the oscillatory frequency (f) is sufficiently large. We systematically studied the effect on pulmonary CO₂ elimination ($\dot{V}CO_2$) of varying f (2-30 Hz) and V_T (1-7 ml/kg) as well as lung volume (V_L) in 13 anesthetized, paralyzed dogs in order to examine the contribution of those variables that are thought to be important in determining gas exchange by high frequency ventilation. All experiments were performed when the alveolar P_{CO_2} was 40 ± 1.5 mm Hg. In all studies, VCO2 increased monotonically with f at constant V_T . We quantitated the effects of f and V_T on VCO2 by using the dimensionless equation VCO2/ $\dot{V}osc = a(V_T/V_{To})^b(f/fo)^c$ where: $\dot{V}osc = f \times V_T$, V_{To} = mean V_T , fo = mean f and a, b, c, are constants obtained by multiple regression. The mean values of a, b, and c for all dogs were 2.12×10^{-3} , 0.49, and 0.08, respectively. The most important variable in determining VCO₂ was Vosc; however, there was considerable variability among dogs in the independent effect of V_T and f on $\dot{V}CO_2$, with a doubling of V_T at a constant Vosc causing changes in VCO₂ ranging from -13 to +110% (mean = +35%). Increasing V_L from functional residual capacity (FRC) to the lung volume at an airway opening minus body surface pressure of 25 cm H₂O had no significant effect on VCO₂.

INTRODUCTION

Traditional concepts of gas exchange during tidal ventilation are based on the principle that there is a physical distinction between the regions of the lung where gas transport is primarily convective (the deadspace volume) and regions of the lung where molecular diffusion is the predominant gas transport mechanism (the alveolar region). This concept is supported by a large body of experimental data as demonstrated by the single-breath nitrogen washout test. Following an inspiration of pure oxygen, if one plots the nitrogen concentration of expired gas vs. volume expired, at least three distinct phases are evident. Initially, (phase I) the expirate contains little detectable nitrogen and represents exclusively gas expired from the dead-space. As additional volume is exhaled, the nitrogen concentration of the expirate increases rapidly (phase II), representing the interface between the dead-space volume and the alveolar gas compartment. Finally, the end expired gas contains the highest nitrogen concentrations (phase III), representing alveolar gas. If these zones were distinct, one would predict that to achieve effective gas exchange, the V_T^1 must be greater than the dead-space.

Recently, however, this traditional concept has been challenged by experimental observations demonstrat-

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¹Abbreviations used in this paper: f, oscillatory frequency; FACO₂, fractional alveolar CO₂ concentration; fo, mean f; HFV, high frequency ventilation; V_{DA} , measured anatomic dead-space; V_{DE} , measured equipment dead-space; VCO₂, pulmonary CO₂ elimination; V_L , lung volume; V_T , tidal volume; V_{To} , mean V_T .

ing that effective alveolar ventilation can occur with V_T considerably less than dead-space volume provided that the ventilatory frequencies are sufficiently large (1–5). Although this has by now been well established by a number of studies, the physical mechanisms that account for the observed gas exchange are not known with certainty. Moreover, lacking from most of these studies has been a comprehensive experimental data base and a clear interpretation of what the data signify with respect to possible physical mechanisms that could account for gas exchange.

In a previous short publication (5) we presented experimental data showing that the most important variable determining the effectiveness of high frequency ventilation (HFV) with sinusoidal oscillations of small tidal volumes is the flow amplitude of the oscillations imposed. We also presented a simple theoretical model that could explain these results. In the present study we extend this previous work in terms of a much larger data base and present results of HFV performed at different lung volumes.

METHODS

High frequency oscillatory circuit. Our experimental setup is shown in Fig. 1. It consists of a high frequency ventilator, a large animal ventilator (Harvard Apparatus, Ealing Corp., Natick, Mass.), a servo-controlled vacuum source, a screen pneumotachograph connected to a pressure transducer, a high impedance bias flow system, and a carbon dioxide analyzer (LB-2 Beckman Instruments, Inc., Fullerton, Calif.). We used two different methods of generating the high frequency oscillations. The first was a unit consisting of four 12-in. Diam, coated loudspeakers sealed in a special chamber and acoustically coupled in series. These speakers were driven by an amplified signal from a sinewave generator. The system allows the speakers to generate greater pressure than if we had used a single speaker as the oscillating source. When all four speakers were driven in phase, it was possible to generate volumes of ~100 ml at pressures of ± 25 cm H₂O at a frequency of 25 Hz. This setup allowed us to easily vary independently the frequency (f) and V_T of oscillation for the experiments in which (a) we maintained a constant frequency-tidal volume product (\dot{V} osc = f × V_T) at various V_T (series A, below) or (b) we varied V_T at constant frequency (series C, below). To achieve greater reproducibility of V_T in those experiments in which we varied frequency at a constant V_T (series B, below), we used a custom made volume displacement piston pump. This pump has been described in detail previously (6).

The air flow output of the speaker high frequency ventilator was measured by a 7 sq in. 400-mesh screen pneumotachograph connected to a pressure transducer (Validyne DP-45 Validyne Engineering Corp. Northridge, Calif.: 2 cm H₂O). Since this combination is known to exhibit a broad resonance peak near 80 Hz (7) it was necessary to calibrate the pneumotachograph-transducer combination using a motor driven piston pump. A calibration curve was determined for frequencies ranging from 3 to 30 Hz. We used pump stroke volumes between 20 and 100 cm³ and found that for peak flows <10 liter/s, the calibration curve was solely dependent on frequency and independent of V_T. This curve was unchanged by applying elastic loads (2- and 10-liter bottles) to the distal end of the pneumotachograph or by applying steady pressures in the bottles of up to 50 cm H₂O. For the experiments in which we used the piston pump as the high frequency ventilator, we did not use the pneumotachograph transducer combination.

We provided a steady supply of fresh air at 0.75 liter/s via a needle valve, leading from a compressed air source to a tap in the tracheal cannula. Another tap in the cannula connected to a high vacuum source was located directly across from this air source. During an experiment we could adjust the positive and negative pressure needle valves to maintain the mean pressure at the airway opening to within 0.1 cm H_2O of atmospheric pressure. To ensure that the entire flow measured by the pneumotachograph entered the dog, we checked it



FIGURE 1 Schematic diagram of experimental setup.

initially with the bias flow on and subsequently with the bias flow taps closed off. No effect of the bias flow was found on the measured oscillatory flow in the range of 2-30 Hz. As an additional check, we placed an elastic load distal to the bias flow (in place of the dog in Fig. 1) and oscillated this load with a piston pump. The pressure oscillations within the elastic load were unaffected by the bias flow. Thus, the flow measured by the pneumotachograph or generated by the piston pump was the same as the flow entering the dog.

We used CO₂ output as an index of the effectiveness of pulmonary gas exchange. During a short burst of HFV of the dog we measured the percentage of CO2 in the gas in the tubing between the oscillator and the bias flow and found that the CO₂ concentration was <0.02%. Thus, small amounts of gas leakage into the speaker chamber could account for an error of <2-4%. Therefore we assumed that all the CO₂ from the dog was purged by the bias flow. We calculated CO2 output by continuously drawing a small sample of gas from the bias flow, through the CO₂ analyzer, and electrically integrated the CO₂ analyzer output neglecting an initial transient. Since the bias flow was constant, the integral of the CO₂ concentration in the bias flow over time was proportional to CO₂ output. Since we required precise measurements of CO₂ at very low CO_2 concentrations (C_{CO_2}) we tested the accuracy and linearity of the system in the following manner. After calibrating the CO2 analyzer, we measured the $\mathrm{C}_{\mathrm{CO2}}$ using a 0.80% CO₂ test gas and electrically integrated this value over time. We then performed serial dilutions of this test gas to obtain a CO2 gas mixture with a concentration of 0.024% and measured C_{CO_2} and the integral of C_{CO_2} . We found that although the absolute value of C_{CO_2} varied due to analyzer noise, the time averaged value determined from the integral of C_{CO_2} was within 4% of the true value. To confirm that during an experimental run of HFV the oscillations did not introduce an artifact, we measured the integral of the CO₂ concentration from the bias flow using a constant CO_2 source in place of the dog while oscillatory frequency and stroke volume were varied and found this integral to be constant. In dogs 3-6, whose data were presented in part in our previous paper (5), and in dogs 8 and 9, we corrected the integral of CO_2 concentration for a small systematic error (7 ml/min) in our CO_2 analyzer calibration. This problem was eliminated for the experiments in dogs 10-16.

We found that changes in the fractional alveolar CO2 concentration (FACO₂) resulted in a change in $\dot{V}CO_2$ at any $\dot{V}osc$. When the Vosc was such that the VCO_2 was approximately equal to the metabolic CO2 production, the measured endtidal PCO₂ (PetCO₂) before and after HFV were identical. At the higher values of Vosc, VCO₂ was greater than the metabolic CO₂ production and there was a fall in FACO₂. Thus, as time progressed VCO₂ continued to decrease. This was readily apparent on the tracing of integrated CO₂ production, which exhibited a decreasing slope with time, and was accompanied by a fall in PetCO₂ after the period of HFV. To correctly estimate the effectiveness of HFV under these conditions we examined the CO₂ output until $\sim 10-20$ ml of CO₂ was removed. This corresponded to a minimum integration time of $\sim 6-10$ s depending on the value of $\dot{V}CO_2$. At the very low values of Vosc, the oscillations were ineffective at removing CO₂; thus the value of PetCO₂ rose by an amount related to the CO₂ production of the dog, or an average of \sim 2–3 mm Hg over a 30-s period. We confirmed this by measuring PetCO₂ after each HFV run and found that it changed by <3 mm Hg when HFV was relatively ineffective. In this circumstance the errors introduced by assuming a constant FACO₂ instead of a changing FACO₂, during the course of the oscillations would be small and would be in the direction of overestimating VCO2 at very low levels of Vosc. The

magnitude of this error would be roughly proportional to the average percent increase in PetCO₂. If HFV was totally ineffective and PetCO₂ increased by 3 mm Hg in a linear fashion over the 30-s period of HFV, the average increase in PetCO₂ would be 1.5 mm Hg. This would thus introduce an error of about 1.5 divided by 40 (=PetCO₂) representing an error of <5%.

Experimental protocol

We studied 13 mongrel dogs (body wt 9.8-22.5 kg) anesthetized with intravenous sodium pentobarbital (initial dose 50 mg/kg) and supplemented every hour with 10% of the initial dose. A tracheostomy was performed and the trachea cannulated with a tight-fitting metal tube that contained a pressure tap. The cervical vagi were isolated and cut to minimize variations in airway tone. Airway opening pressure minus body surface pressure was measured with a Hewlett-Packard 268B transducer (Hewlett-Packard Co., Palo Alto, Calif.). Catheters were placed in the femoral artery and vein for sampling arterial blood and intravenous administration of solutions and drugs, respectively. Sodium bicarbonate was given intravenously to maintain arterial pH between 7.25 and 7.45. The dogs were ventilated with a conventional piston ventilator at frequencies from 10-15 breaths/min and then paralyzed with a loading dose of succinvlcholine (2 mg/kg) and a continuous infusion of 50 μ g/kg per min. Under these conditions respiratory CO2 output was determined as described above.

In six dogs (3-6, 8, 9) the anatomic dead-space was measured using a modification of the Fowler technique with CO₂ as the test gas. In these measurements, CO₂ concentrations were determined just proximal to where the cannula entered the trachea. This technique has been described in detail previously (8). The mean of three or four determinations was used as an estimate of the anatomic dead-space. The equipment dead-space, from CO₂ sampling site to the bias flow output, was determined by direct measurement in all experiments.

Measurements performed at FRC. After these determinations the ventilator was adjusted to maintain the endtidal CO₂ between 38.5 and 41.5 Torr and base line measurements of CO₂ output were made. Then, the animal was ventilated with the high frequency ventilator for 15–30 s, during which time measurements of $\dot{V}CO_2$ were made. After each measurement, the dog was returned to standard tidal ventilation, and the end-tidal CO₂ concentration was measured. If the CO₂ concentration had changed, the rate of the conventional ventilation was increased or decreased transiently to allow the end-tidal CO₂ concentration to return to its baseline value.

Using this protocol we examined the effectiveness of HFV at two to four fixed values of Vosc in dogs 3–6 over the range of frequencies from 4 to 28 Hz by decreasing V_T as f increased such that the product $f \times V_T$ was held constant. Short bursts of HFV were interspersed with normal tidal ventilation such that PetCO₂ remained within its specified limits. This set of experiments will subsequently be referred to as series A. In addition, in these dogs (3–6) we performed further experiments in which we varied f and V_T over a wide range of values but in which Vosc and V_T were not systematically held constant.

We examined the effectiveness of HFV in seven dogs (10-16) by using the piston pump with fixed stroke volumes ranging from 3 to 5 ml/kg over the range of frequencies, 2–30 Hz. These tests will be referred to as series B.

Measurements at V_L above FRC (series C). We studied the effectiveness of HFV at different V_L in two dogs (8, 9) by

placing the animals in a rigid chamber, similar to an iron lung, in which the mean pressure was controlled by a servo-feedback mechanism. By changing the pressure within the chamber we could change and control V_L . We measured CO_2 output at a number of different values of Vosc, by varying the V_T of oscillation (dog 6: 8–30 ml; dog 9: 8–76 ml) but keeping the frequency constant at 16 Hz. We made measurements at four to six different V_L : FRC and the V_L corresponding to airway opening minus body surface pressures of 5, 10, 15, 20, or 25 cm H₂O. A similar protocol was followed in that short bursts of HFV were interspersed with conventional tidal ventilation.

RESULTS

The weight, anatomic dead-space (V_{DA} —where measured), and equipment dead-space (V_{DE}) for each of the dogs are given in Table I. Mean systemic arterial pressure was not significantly different for the experiments performed during the conventional tidal ventilation and the high frequency ventilation. However, there was a diminution in the respiratory variations in pressure as noted by others (4).

In Fig. 2, results obtained in series A for fixed Vosc are presented for dogs 3 and 6. These two were chosen since the results for dog 3 did not show any substantial effect on $\dot{V}CO_2$ as f was increased and V_T decreased such that Vosc remained fixed, whereas dog 6 showed the greatest such effect observed in series A.

In Fig. 3 results obtained in series B for fixed V_{T} are presented for dogs 12 and 15. These two were chosen since, as will be seen, dog 12 showed the smallest effect of V_T at a fixed Vosc while dog 15 showed the largest such effect (as determined from values of b-c as described below). The results for dogs 3, 6, 12, 15 are presented in Fig. 4 as VCO₂ vs. Vosc. In this form, the data fall in relatively narrow bands; however, there is a tendency in all the dogs for the results obtained at the larger values of V_T to lie above the results for the lower V_{T} . Although there does not appear to be much of a difference between dogs 12 and 15, with regards to the effect of V_T , based on the results when plotted as VCO₂ vs. f (Fig. 3), the plots of VCO₂ vs. Vosc (Fig. 4) clearly show that dog 15 exhibits a greater V_T dependence. Note that there are more data points presented for dogs 3 and 6 in Fig. 4 than in Fig. 2 because in addition to the data obtained in series A, we performed further experiments (as described previously) in which we independently varied f and V_{T} without aiming for a fixed Vosc.

The effects on $\dot{V}CO_2$ of varying V_L (series C) are shown in Fig. 5. For both dogs at a fixed oscillation frequency of 16 Hz, $\dot{V}CO_2$ increased as V_T of oscillation increased, but $\dot{V}CO_2$ remained relatively independent of V_L .

Thus, although the product of $f \times V_T$ is the main

TABLE I HFV Data Summary

Dog no.	Weight	V _{da}	V_{DE}	V _{To}	fo	VCO₂/Vosc (×10⁻³)	a (×10 ⁻³)	b	с	r	n	$\mathbf{b} - \mathbf{c}$
	kg	ml	ml	ml	Hz							
3	22.5	99	45	54	14.3	1.669	1.725	0.393	0.156	0.65	38	0.237
4	12.2	43	39	25	18.0	1.878	2.278	1.022	1.231	0.75	12	-0.209
5	11.2	45	39	41	14.0	1.210	1.219	0.513	0.060	0.67	51	0.453
6	9.8	51	39	45	14.6	1.214	1.368	0.600	0.487	0.69	23	0.113
8	15.0	62	45	18	16.0	2.486	2.575	0.496	_	0.98	51	—
9	14.8	86	45	35	16.0	2.975	2.953	0.039	_	0.94	65	_
10	13.2		39	37	13.5	1.603	1.485		-0.236	0.92	14	
11	11.0	—	39	39	13.3	2.644	2.533	0.423	-0.154	0.93	26	0.577
12	13.2		39	53	14.9	2.313	2.220	0.186	-0.139	0.79	47	0.325
13	12.0		39	49	13.1	2.209	2.091	0.211	-0.277	0.93	20	0.488
14	14.5		45	57	14.4	1.656	1.614	0.490	-0.090	0.97	24	0.580
15	12.2		39	49	12.3	2.426	2.284	0.909	-0.158	0.91	39	1.067
16	15.2	_	45	60	14.5	3.223	3.190	0.612	-0.046	0.90	47	0.658
Mean SD	13.6	64 23.2	41 3.0	43 12.4	14.5 1.5	2.116 0.638	2.118 0.610	0.491 0.270	0.076 0.439	0.85 0.12	35 16.5	0.429 0.344

Summary of data for all dogs based on equation 1:

$$\frac{\dot{V}CO_2}{\dot{V}osc} = a \left(\frac{V_T}{V_{To}}\right)^b \left(\frac{f}{fo}\right)^c$$

where V_{To} and fo are the mean V_T and frequency used for each dog, and the units of $\dot{V}CO_2$ and $\dot{V}osc$ (= $f \times V_T$) are identical. V_{DA} = measured anatomic dead-space; V_{DE} = measured dead-space; r = correlation coefficient; n = number of data points; a, b, c = best fit numerical values for equation 1.

determinant of CO_2 elimination, f and V_T by themselves are of some importance. To quantitate the effects of V_T and frequency individually, we fit the data obtained from the experiments on each dog to a dimensionless equation of the form:

$$\frac{\mathbf{VCO_2}}{\mathbf{Vosc}} = \mathbf{a} \left(\frac{\mathbf{V_T}}{\mathbf{V_{To}}} \right)^{\mathbf{b}} \left(\frac{\mathbf{f}}{\mathbf{fo}} \right)^{\mathbf{c}} \tag{1}$$

where (in contrast to Figs. 2-5) $\dot{V}CO_2$ and $\dot{V}osc$ are expressed in same units, V_{T_0} and fo are the mean V_T and f used for each dog (Table I), and "a, b, c," are constants determined by least squares regression analysis of each data set to this equation. Note that since the dimensions of $\dot{V}CO_2$ and $\dot{V}osc$ are identical in this expression, the parameter "a" is dimensionless. This equation can be rewritten in alternative forms by substituting the quantity $f = \dot{V}osc/V_T$ into equation 1.

$$\dot{\mathbf{V}}\mathbf{CO}_{2} = \mathbf{a} \left(\frac{1}{\mathbf{V}_{To}}\right)^{\mathbf{b}} \left(\frac{1}{\mathbf{fo}}\right)^{\mathbf{c}} \dot{\mathbf{V}} \mathbf{osc}^{1+\mathbf{c}} \mathbf{V}_{T}^{\mathbf{b}-\mathbf{c}}$$
(2a)

$$= a \left(\frac{1}{V_{To}}\right)^{b} \left(\frac{1}{fo}\right)^{c} \dot{V}osc^{1+b}f^{c-b}$$
(2b)



FIGURE 2 Plots of CO₂ elimination ($\dot{V}CO_2$) vs. frequency (f) at fixed values of $\dot{V}osc$ (=f × V_T) for dogs 3 (top) and 6 (bottom).



FIGURE 3 Plots of $\dot{V}CO_2$ vs. f at constant values of V_T for dogs 12 (top) and 15 (bottom).

Table I shows for each dog the best-fit values of a, b and c. The mean correlation coefficient (r) for all the data was 0.85 and the mean value of b – c was 0.429. Note that for any given value of Vosc the exponent b – c is an index of the independent effects of V_T and f on VCO₂. For example, if b – c = 0, then VCO₂ is determined only by Vosc and does not depend upon the individual values of either V_T or f. If, however, b – c is non-zero, then VCO₂ will depend on both Vosc and V_T , or Vosc and f. Suppose that b – c = 0.5 and a given tracheal flow, Vosc, is achieved with two V_T , one twice the other. The same VCO₂ would not be achieved even though the Vosc were equal. The VCO₂ with the higher V_T would be greater by a factor of 2^{0.5}, or ~41%.

Using this type of analysis, we found that the effect of doubling V_T while maintaining the same Vosc varied considerably from dog to dog. The minimum such effect on VCO₂ was in dog 4 (-13%), whereas the maximum effect was in dog 15 (110%). The mean effect for all dogs of doubling V_T at a fixed Vosc was ~35%.

To determine the effect of V_L on $\dot{V}CO_2$ we fit the data from dogs 8 and 9 to the equation:

$$\dot{V}CO_2 = \beta_0 + \beta_1 \dot{V}osc + \beta_2 V_L + \beta_3 \dot{V}osc V_L \qquad (3)$$



FIGURE 4 Plots of VCO_2 vs. Vosc for dogs 3, 6, 12, and 15. Each symbol represents a certain range of V_T for dogs 3 and 6 and a specific V_T for dogs 12 and 15.

where: $\dot{V}CO_2$ is the observed CO_2 elimination for each value of $\dot{V}osc$ and V_L and the β_i (i = 0, . . . 3) are coefficients determined from least squares regression

analysis. The estimated values of β_2 and β_3 were not statistically different from zero (P > 0.05) indicating that V_L had no independent effect on $\dot{V}CO_2$.



FIGURE 5 Plots of VCO_2 vs. Vosc at different V_L corresponding to FRC and the V_L corresponding to FRC plus airway opening minus body surface pressures of 5, 10, 15, 20, and 25 cmH₂O for dogs 8 (left) and 9 (right). The frequency for all experiments was 16 Hz.

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FIGURE 6 Mean results for $\dot{V}CO_2$ vs. $\dot{V}osc$ at constant values of frequency (left) and stroke volume (right). These results were obtained using equation 1 and the mean values of the coefficients a, b and c from Table I.

A plot of $\dot{V}CO_2$ vs. $\dot{V}osc$ based on the mean regression results for all dogs is presented in Fig. 6 for constant values of V_T and f.

DISCUSSION

Previous studies of HFV. Although a number of investigators have used rapid oscillations to achieve gas exchange (9-11), only recently has it been demonstrated that rapid oscillations with volumes less than the anatomic dead-space volume could effect adequate gas exchange (1-5, 12). Lunkenheimer and colleagues (1) while investigating the effect of high frequency oscillation on cardiac performance, fortuitously found that they were able to maintain normal blood gases in dogs without standard tidal ventilation by using ventilatory frequencies of up to 40 Hz and V_T as low as 10-20 cm³. Similar observations were also provided by Bunnell et al. (2) and Custer et al. (3) who, using an asymmetric flow pulse at frequencies of 4-6 Hz, were able to maintain normal blood gases before and after induction of diffuse lung injury with alloxan. Bohn et al. (4) also found that HFV with V_T equal to 25% of the dead-space could produce normal blood gases and suggested that there appeared to be a frequency optimum at \sim 15 Hz that provided the most effective CO₂ elimination. In a recent report we also demonstrated that HFV could support eucapnic gas exchange in anesthetized dogs (5).

Although the observations mentioned clearly document the effectiveness of HFV with small V_T in achieving gas exchange, a comprehensive experimental data base and an understanding of the physical mechanisms responsible for the gas exchange with this technique are necessary before the full potential of this mode of

ventilation can be realized. In this paper we present a larger data base exploring the effects of systematic variations of V_T and oscillation frequency on gas exchange. Further, we explore the effects of changes in V_L on gas exchange achieved by HFV in normal dogs. With regard to all of these observations, we provide a unifying analysis of these results and highlight several potentially important mechanisms.

Comparison with previous results. The new and important feature of our experimental apparatus that allowed us to obtain quantitative data relating VCO₂ to f, V_T , and Vosc was the very high impedance bias flow circuit. This permitted large quantities of fresh air to be delivered to the airway opening without loss of oscillation volume. In this regard, our experimental setup was substantially different from that of Bohn et al. (4) who found that at a fixed stroke volume of the piston pump, arterial PCO₂ passed through a minimum at 15 Hz, thus suggesting an optimum frequency for CO₂ elimination. To deliver fresh air to the animal they used a flow of fresh gas delivered through a long tube that acted as a low pass filter. Consequently, the stroke volume produced by their piston ventilator was not necessarily the same as the volume delivered to the experimental subject since a variable fraction of the stroke volume would be lost to the bias flow, the fraction depending upon the ratio of the subject's impedance to that of the bias flow. Both of these impedances are functions of the frequency of oscillation. Thus, it is possible that as frequency increased above 15 Hz in the experiments of Bohn et al. (4), the fraction of stroke volume lost to the bias flow increased such that the flows actually delivered to the dogs decreased.

In a previous paper (5), we suggested that the effec-

tive gas exchange during HFV might be due to a number of augmentive mechanisms including (a) Taylor laminar (13) and turbulent dispersion (14), (b) mixing due to asymmetrical velocity profiles as proposed by Haselton and Scherer (15) and (c) secondary flows at bifurcations. One of our predictions from this model and that of Fredberg (16) was that V_L should have relatively minor effects on VCO₂ at any given tracheal flow. The reason for this is that increasing V_L produces two competing phenomena: (a) the increasing crosssectional area of the airways tends to increase VCO₂ but (b) at any given tracheal flow as cross-sectional area increases, the velocity in any airway decreases and thus may lead to decreased enhancement of the mixing process. Our results provide evidence in support of this prediction since we found no significant effect of V_L (Fig. 5) on $\dot{V}CO_2$ as a function of \dot{V} osc. It should be noted that all the experiments were performed at V_L at or greater than FRC, in which presumably all airways were open. It is possible that if experiments had been performed at V_L below FRC and if airways were closed at these volumes, VCO2 might decrease. As well, at lower V_{1} , flow limitation might occur and also further decrease VCO₂.

Our previous observations suggested that the magnitude of Vosc achieved during HFV was the critical factor in determining CO₂ elimination. The current experimental data base indicates that although Vosc is the most important factor, V_T and f have independent effects on VCO₂ at any given Vosc. This can be appreciated by comparing the data presented in Figs. 3 and 4. When the data are shown as $\dot{V}CO_2$ as a function of frequency at a given V_T the slope of the nearly linear VCO₂ vs. f relationship obtained varies in magnitude as much as the V_T varies, dog 12, or more than V_T varies, dog 15. Thus in Fig. 4 the V_T dependence is minimal when plotted as a function of Vosc in dog 12 and is quite striking in dog 15. Using equation 1 we quantified the effects of V_T and f and found that, on the average, a doubling in V_T at a given Vosc resulted in an increase in $\dot{V}CO_2$ of ~35% (=2^{0.429}; 0.429 is the mean value of b - c). There is a relatively large variability in this effect, with some dogs showing a 13% decrease in $\dot{V}CO_2$ with a doubling in V_T (dog 4) and others showing $\sim 100\%$ increase in VCO₂. In all but one of the dogs, the value of b - c was positive, indicating that at a given Vosc, greater VCO₂ is achieved with the combination of larger values of V_T and lower values of f. Clearly, this must be the case when V_T exceeds the dead-space volume. The values of the parameters estimated for equation 1 were obtained using data from experiments where f varied from 2 to 30 Hz and V_T was always less than the estimated total (anatomic plus equipment) dead-space. As V_T gets very small, approaching the volume of a single generation of the tracheobronchial tree, one might anticipate that gas

mixing efficiency might decrease even more. However, we do not have data to address this point because we did not systematically study $\dot{V}CO_2$ with very small V_T .

This V_T effect on CO_2 elimination was not predicted by our previous model (5) and most likely relates to the bulk transport of gas both at the airway opening and at the junction of the dead-space and the alveolar region. This convective process would tend to purge the equipment dead-space of CO_2 and enhance gas transport at the alveolar-dead-space interface in a more efficient manner than augmented transport, the only mechanism considered in our previous analysis. Thus, greater V_T would cause greater $\dot{V}CO_2$ at equivalent values of $\dot{V}osc$.

In an attempt to provide an estimate of the effect due to convective purging, we modified our previous theoretical analysis (5) by assuming that the diffusional resistance is reduced to zero in two regions, one adjacent to the bias flow and the other adjacent in the alveolar region. The volume of each of these two regions is taken to be one-half of the V_T . We then applied the equations used previously (equations 1–5 of reference [5]) to obtain estimates of VCO_2 . Theoretical results using this formulation are presented in Fig. 7. These theoretical results provide an approximate upper bound for the purging effect and show that convective purging could represent a reasonable mechanism causing the V_T effect. Further analyses will be required to determine the exact nature of the effect.

In estimating VCO₂ in our experiments we used a relatively short period of HFV (<30 s), so that we would be able to obtain a large number of measurements for any given dog over a relatively short period of time. Our assumption was that data collected in this manner could be extrapolated to predict the values of f and V_{T} that would be required to maintain eucapnia in the dogs during steady-state ventilation. To investigate this question, in three of the dogs, we used the estimated values of f and V_T that would be required to produce a VCO₂ equal to the dogs' measured metabolic CO₂ production and ventilated the dogs for 1-2 h. We measured arterial blood gases at the end of this period and found arterial PCO₂ values were between 38 and 42. This not only confirms the previous findings of Bohn et al. (4), but also demonstrates that the experimental values we determined for VCO₂ over 30 s reflect the steady-state values that would exist over long periods of HFV.

The experimental data presented in this paper, together with our earlier experimental and theoretical findings (5) provide the rule that $\dot{V}CO_2$ is approximately independent of lung size and dependent mainly on Vosc. If we use (Table I) the mean value of $\dot{V}CO_2$ / Vosc for all 13 dogs, namely, 2.12×10^{-3} , (where $\dot{V}CO_2$ and Vosc have the same units), we can estimate the



FIGURE 7 Theoretical results for $\dot{V}CO_2$ vs. \dot{V} osc at various V_T using our previous analysis (5) with the addition of convective purging at the airway opening and alveolar regions (see text for details).

tracheal flows required to produce eucapnia in a given dog. For example, if the metabolic CO₂ production of a dog is about 5 ml/min per kg (17), then one would predict that a value of \dot{V} osc of ~ 0.8 liter/s would be required for eucapnia in a 20 kg dog. Applying the same data to humans, where the metabolic CO₂ production is about 3 ml/min per kg (18), one obtains a Vosc of \sim 1.7 liter/s for eucapnia in a 70 kg man. This is, of course, a predicted value, to be assessed by clinical trials in humans. Since these estimates are based on the average value of VCO₂/Vosc, it is expected that they would be most accurate at the mean frequency used in our experiment, 14.5 Hz. If the frequency of oscillation were much different than 14.5 Hz, then more accurate estimates of Vosc would be obtained using equation 1 with the appropriate mean values of the constants for this equation from Table I. These estimates are probably sensitive to the specific geometry of the experimental setup. A further consideration in applying these data is the fact that the oscillatory peak flow may be near or above flow limitation in many lungs. For example, the calculated Vosc of 1.7 liter/s corresponds to a peak flow rate of 5.3 liter/s and not all patients would be able to support this flow rate at FRC.

The potential benefits of HFV in the clinical setting are substantial. The mean tracheal pressure during HFV may be maintained at zero and the peak transpulmonary pressure is low. Thus, the detrimental effects of positive pressure ventilation, such as barotrauma and impaired hemodynamics, may possibly be diminished or eliminated. In this paper we have presented a relatively comprehensive experimental data base relating CO_2 elimination to the various variables thought to be important during HFV. Our data clearly demonstrate that HFV is an effective method of achieving pulmonary ventilation and that the magnitude of the effective ventilation achieved varies with the amplitude of tracheal volume flow rate. It is hoped that these results will provide a framework on which to base further work, with the aim of making this technique clinically useful in humans.

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