Role of Molecular Diffusion in Conventional and High Frequency Ventilation[1-3]

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SUMMARY The influence of molecular diffusion on gas-mixing during conventional mechanical ventilation (CMV) and high frequency ventilation (HFV) was studied by observing the wash-in of six poorly soluble, inert gases in arterial blood. Anesthetized dogs were ventilated either with CMV or HFV. Following a step change in inspired gas composition, the increase in arterial concentrations of hydrogen, helium, methane, ethane, isobutane, and sulfur hexafluoride was determined by gas chromatography. The relative gas diffusivities encompassed a range of almost one order of magnitude. Propane, present in inspired gas during both the control and wash-in phases, served as an internal reference for calculation of blood tracer concentrations. The wash-in of all six inert gases followed a single exponential time course during both CMV and HFV. The rate of wash-in of each gas decreased with increasing molecular weight (MW). The relationship of rate constants to a measure of relative diffusivity ($MW^{-0.5}$) was significantly different than zero for both types of ventilation. The slope of this relationship was three times larger for CMV than HFV, indicating that molecular diffusion has a greater role in gas mixing during ventilation with large tidal volumes. Diffusion has a minor role in gas mixing during high frequency ventilation with small tidal volumes. Demonstration of the presence of gas separation secondary to molecular diffusion during HFV is enhanced by measuring wash-in, rather than wash-out, of inert gases because gas separation is likely to be obscured as exhaled gases pass through the well-mixed central airways during gas wash-out.

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Introduction

Ventilation accomplished with tidal volumes similar to or less than anatomic dead space requires augmentation of intrapulmonary gas mixing in a manner usually not addressed in classic descriptions of gas exchange. Chang (1) and Slutsky and coworkers (2) have summarized potential mechanisms for gas transport occurring during high frequency ventilation (HFV). Direct ventilation of alveoli located relatively close to the airway opening is possible, but there is no evidence that this actually takes place. Pendelluft, exaggerated far beyond that seen in conventional ventilation, appears to be an important factor in intrapulmonary gas mixing in HFV (3, 4). Asymmetry of flow profiles, both during the ventilatory cycle (5) and in different portions of the airways (6), can improve mixing but is difficult to quantitate. Taylor dispersion in turbulent flow within the airways is one of the major factors responsible for improved gas mixing in HFV (7, 8). The role of molecular diffusion is thought to be small, if present at all, during high frequency ventilation (1, 9, 10). Diffusion can affect gas mixing in two possible ways. First, as a result of decreasing convective flow associated with increasing airway cross-sectional area, gas mixing in the last few generations of the tracheobronchial tree is accomplished predominantly by axial diffusion (11). Second, with laminar flow in airways, Taylor dispersion can occur as a result of radial diffusion of gases out of the parabolic convective front. This mode of Taylor dispersion probably is far less important than convective mixing in HFV (1).

Knopp and colleagues (9) could find no effect of molecular diffusion during HFV when comparing simultaneous washout of helium and sulfur hexafluoride. Later work demonstrated a minimal effect of diffusion on the slope of phase III of single-breath exhalations obtained at different points during steady-state wash-out of tracer gases during HFV (10). Investigation of gas exchange occurring in the lung periphery using washout techniques during HFV is complicated by the presence of the central airways in series with the more peripheral airways and alveoli. With high frequency ventilation, the central airways exhibit properties of a well-mixed compartment (9, 12), which obscures distal processes producing gas separation. Furthermore, subtle peripheral events often are reflected in the terminal portion of the wash-out curve, which is most affected by signal/noise discrimination (13). To avoid these problems, we investigated wash-in of tracer amounts of six poorly soluble, inert gases having almost a ninefold span in diffusivity. Tracer gas wash-in was measured in arterial blood rather than expired gas. With this approach, separation of gases occurring in the periphery of the lung is not obscured because the observations are made without the tracers being exhaled through the well-mixed central compartment.

Methods

Anesthesia initially was induced in dogs with 4% thiamylal (6 mg/kg) by intravenous injection. This was immediately followed by injection of α-chloralose (120 mg/kg) in sodium tetraborate buffer. Anesthesia was maintained by a continuous intravenous infusion of α-chloralose (43 mg/kg/h) throughout the duration of the experiment. Pancuronium bromide (0.1 mg/kg) was utilized for muscle paralysis only after demonstration of effective, deep anesthesia with α-chloralose. Supplemental fluids and drugs were administered via a catheter placed in a femoral vein. anticoagulation was achieved with an initial intravenous dose of 7,000 U of heparin, supplemented by hourly doses of 3,000 U, to avoid clotting of catheters and the need to heparinize blood samples. A large-bore (2.7 mm ID) polyethylene catheter was introduced through

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the right carotid artery and advanced into the aortic arch. The arterial catheter was connected to a stopcock that permitted either monitoring pressure with a strain gauge (Model P23Db; Gould Inc., Cleveland, OH) or sampling aortic blood through a multiple port manifold.

The animal was intubated with a cuffed No. 10 endotracheal tube (34.5 cm long, 1.0 cm ID) connected to a No. 3 Fleisch pneumotachograph. The differential pressure across the pneumotachograph was measured with a Validyne MP-45 (± 2 cm H_2O) variable reluctance transducer (Validyne Corp., Northridge, CA). The system was calibrated by injecting air from a 3-L syringe at a rate approximately equal to peak airflow and numerically integrating the digitized flow signal over the time of injection. Airway pressure, monitored with a Validyne MP-45 (±50 cm H_2O) transducer, and instantaneous O_2 and CO_2 concentrations, obtained by mass spectrometry (Model MA-1100; Perkin-Elmer Corp., Pomona, CA), were measured proximal to the pneumotachograph. The dead space of the connectors and pneumotachograph placed between the ventilator and endotracheal tube was 55 ml.

Animals received either conventional mechanical ventilation (CMV) or HFV with an inspiratory gas mixture of 0.1% propane, 30% oxygen, balance nitrogen obtained from a premixed gas cylinder. The propane served as an interval reference for determining concentrations of tracer gases. CMV was provided with a dual piston, constant volume ventilator (Model 618; Harvard Apparatus, Inc., South Natick, MA). Tidal volume was constant at 15 ml/kg; ventilator frequency was adjusted initially to maintain $Paco_2$ at 40 mm Hg. No subsequent changes were made in respirator settings. Prior to wash-in, the animal was ventilated with the baseline propane reference gas with one piston of the ventilator. At end-expiration, a sliding valve with low dead space (11 ml) was activated to switch ventilation to the second piston, which previously had been flushed with the inspired mixture containing the tracer gases. This mixture was stored in a nondiffusing gas bag (Hans Rudolph, Inc., Kansas City, MO). Prior to the experiment, the gas bag was filled with the propane, oxygen, and nitrogen mixture, and pure tracer gases (table 1) were added individually by syringe. The quantity of each tracer in the mixture was chosen on the basis of its solubility in blood (14 , 15) and the sensitivity of the chromatographic detector used to quantify gas concentration. The exact concentration of tracer gases in the inspirate was inconsequential, but it was essential that the reference propane concentration was the same prior to and during the wash-in. Therefore, a calculated quantity of pure propane was added to the mixture by syringe to correct for the slight dilution caused by addition of the tracer gases to the original reference gas. Propane concentration in the premixed gas and the tracer gas mixture, measured by gas chromatography, was determined

TABLE 1

CHARACTERISTICS OF INERT GASES

Gas	Molecular Weight	Relative Diffusivity	Solubility ($ml_{STPD}/ml/atm$)	Percentage in Mixture
Hydrogen	2.0		0.0170*	1.65
Helium	4.0		0.0094*	4.92
Methane	16.0		0.0378*	0.62
Ethane	30.1		0.1076*	0.17
Propane	44.1		0.0483†	0.10
Isobutane	58.1		0.0126†	0.12
Sulfur hexafluoride	146.1		0.0074*	0.01

* Average of values of solubility in blood at 37° C from (14).

† Solubility in blood not available. Calculated from aqueous solubility at 17° C from (15) assuming that solubility changes −1%/° C.

with each experimental run and did not differ significantly ($p > 0.8$). HFV was administered with an oscillator consisting of a 2.5-inch ID Teflon® piston within a machined brass cylinder (figure 1). A Plexiglas® cap with a 0.5-inch outlet was attached to the end of the brass cylinder. The piston was driven with a ¼ hp motor with speed adjusted (zero to 28 Hz) by a solid-state controller. Stroke volumes could be varied between zero and 100 ml by altering the position of the drive shaft on the motor-driven cam. A stroke volume of 3 ml/kg administered at 20 Hz was used for the HFV experiments. A flexible gas bag enclosed the rear of the brass cylinder to prevent minimal contamination across the piston, which occurred despite closely machined tolerances. Bias flow was introduced at the port of the oscillator where it was connected to the No. 3 Fleisch pneumotachograph and endotracheal tube. Bias flow (6.5 ± 0.7 L/min), entering and leaving through high impedance connections to prevent loss of oscillatory volume, was measured with No. 00 Fleisch pneumotachographs and Validyne MP-45 (±2 cm H_2O) transducers. The pneumotachographs were calibrated with constant flow, measured with a 9-L water-filled spirometer (Warren E. Collins, Inc., Braintree, MA). Less than 5% of oscillatory volume was lost in the bias flow pathway. This volume was not reflected in the measured tidal volume because bias flow was administered proximal to the pneumotachograph, which measured stroke volume. Airway pressure was adjusted by utilizing a positive pressure source for bias flow and applying variable negative pressure to the exhausted bias flow. Bias flow was provided from a premixed gas cylinder during the control state. The presence of flammable and explosive gases in the tracer mixture precluded use of a premixed gas cylinder. Therefore, a gas bag containing the tracer mixture was placed inside a 30-gal drum that was pressurized with air to the same setting as the gas regulator used to administer the control bias flow. The bias flow could be changed rapidly from the control gas to the tracer mixture with a respiratory stopcock. Because the dead space of the stopcock and associated connections was only 65 ml, the composition of the bias flow could be changed within 1 to 2 s.

After 20 to 30 min of either CMV or HFV, an arterial blood sample was drawn for blood gas analysis and determination of baseline tracer gas concentrations. The latter were always negligible. Then wash-in of the tracer gas mixture was initiated and aortic blood (10 ml) was sampled at approximately 12, 24, 36, 48, 60, 90, 180, and 240 s. Blood blow through the aortic catheter was initiated just prior to each sampling to clear the catheter of stagnant blood. The timed midpoint of the sampling period was used for subsequent calculations.

Data were recorded on both an eight-channel chart recorder (Model 2800; Gould, Inc.) and an eight-channel FM tape recorder (Model 3968A; Hewlett-Packard, Waltham, MA). Recorded variables were systemic blood

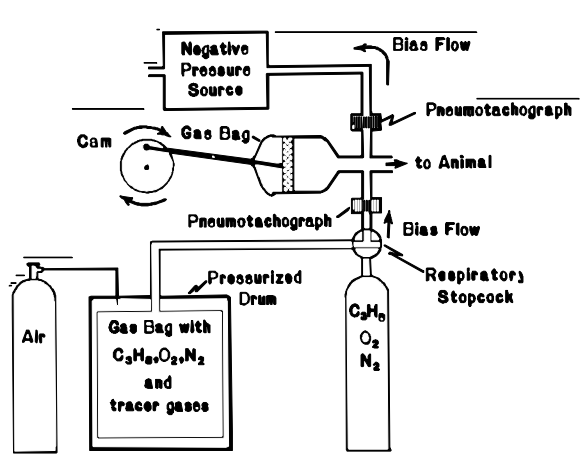

Fig. 1. Oscillator circuit used for HFV experiments.

pressure, time of blood sampling, mean airway pressure, airflow at the proximal end of the endotracheal tube, bias inflow and outflow, and airway CO_2 concentration. Tidal volume was obtained by integrating airflow digitally off-line. Data analysis was performed by digitizing (Model DT2801; Data Translations, Inc., Marlboro, MA) the tape-recorded signals in a personal computer (Model 4885; Kaypro, Inc., Solana Beach, CA). Data was sampled at 200 Hz in CMV experiments and 500 Hz in HFV experiments.

Inert gas concentrations were measured with a variation of the technique of Wagner and coworkers (16). Approximately 10 ml of nitrogen was added to the 10-ml blood sample and the syringe was agitated in a water bath at 37° C for 30 min to extract tracer gases from blood. The gaseous phase was aspirated into another syringe and injected into three constant volume sampling loops (Model 2018; Carle Instruments, Inc., Fullerton, CA and Model LOV; Condyne Instruments, Inc., La-Canada, CA) connected to a single manifold. The samples were then injected into three separate chromatographs. Hydrogen and helium were separated at 27° C on a 6-ft column of activated charcoal (Analabs, Inc., North Haven, CT) purged with nitrogen carrier gas and measured by thermal conductivity (Model 100; Carle Instruments, Inc.). The other tracer gases were not present in sufficient quantities to be detected by this system. Organic gases (methane, ethane, propane, and isobutane) were separated on a 12-ft column of Porasil B (Waters Associates, Inc., Milford, MA) at 50° C and measured by flame ionization (Model GC 72-5; Beckman Instruments, Fullerton, CA). Sulfur hexafluoride was analyzed with an 8-ft column of 5A molecular sieve (Matheson Co., Inc., E. Rutherford, NJ) maintained at 15° C and a linear electron capture detector with a scandium source (VALCO Instrument Co., Houston, TX).

Calculations of tracer gas concentrations were referenced to the constant propane standard. Arterial blood was in equilibrium with 0.1% propane prior to and throughout the wash-in. Changing inert gas concentrations were expressed as a fraction of the constant propane value. This avoided the requirement of precise measurements of the volume of the blood sample and the nitrogen added to extract the tracer gases.

Comparison of physiologic variables (table 2) was accomplished with analysis of variance with repeated measures design (17). Data from the wash-in curves were fitted to a first-order exponential by the least-squares criterion for each of the six tracer gases. Analysis of covariance was used to test for a relation between the fitted exponential rate constants and the relative diffusivities of the gases and whether any possible relation was affected by the type of ventilation (17).

Results

A total of 13 pairs of wash-in experiments were conducted in five dogs. Each pair included a tracer wash-in during both types of ventilation. Hemodynamics and respiratory variables are included in table 2. Arterial blood gases were identical during both types of ventilation. Heart rate was slightly lower during the CMV experiments. By design, there were significant differences in respiratory rate and tidal volume. Mean airway pressure however, did not differ significantly between CMV and HFV.

TABLE 2

RESPIRATORY AND HEMODYNAMIC VARIABLES*

	CMV	HFV
pH	7.32 ± 0.01	7.32 ± 0.01
P_{CO_2}, mm Hg	39.7 ± 0.9	39.0 ± 0.01
P_{O_2}, mm Hg	108 ± 4	108 ± 3
Hb, g/dl	12.7 ± 0.6	12.5 ± 0.7
HR, beats/min	142† ± 5	156 ± 6
P_{Airway}, cm H_2O	3.5 ± 0.4	6.3 ± 0.9
f, breaths/min	21.7† ± 0.9	1,255 ± 4
VT, ml_{BTPS}	315† ± 5	63 ± 1
BP, mm Hg	160/120 ± 2/2	164/112 ± 3/4

Definition of abbreviations: CMV = conventional mechanical ventilation; HFV = high frequency ventilation; Hb = hemoglobin; HR = heart rate; P_{Airway} = mean airway pressure; f = respiratory frequency; BP = systemic blood pressure.

* All values mean ± standard error.

† Significantly different from HFV value ($p < 0.001$).

The appearance of tracer gases in aortic blood in a single experiment during conventional mechanical ventilation following a step-change in inspired gas composition is shown in the left panel of figure 2. Gas concentrations are expressed as the ratio of each tracer to the propane reference and are normalized to the ratio achieved at equilibrium. The gas/propane ratio, R_G, for each tracer was fitted to an exponential function

$$R_G = R_{G\infty}[1 - e^{-k_G(t-d_G)}] \quad (1)$$

where $R_{G\infty}$ indicates the equilibrium value of the ratio, k_G is the rate constant describing the kinetics of the wash-in of the tracer, t is time, and d_G is a constant describing the delay in appearance of the tracer in blood following the change in inspired gas composition. This delay reflects the time required for transfer of the gas from the endotracheal tube to the alveoli as well as the transit of blood from the lung to the sampling site in the aorta. Values of R_G and t were obtained experimentally as described previously. The constants $R_{G\infty}$, k_G, and d_G were computed by assuming initial values for each and calculating the values of R_G at each experimental time. These calculated values of R_G were compared to the observed data and the residual sum of squares computed. The three constants were adjusted to minimize the residual sum of squares using a Newton technique incorporated into data-processing software (Systat Inc., Evanston, IL). Data were fitted to the single exponential process indicated in equation (1); addition of a second exponential did not reduce the computed residual sums of squares signi- ficantly. The appearance of the same tracers in the paired experiment utilizing high frequency ventilation is plotted in the right panel of figure 2. Two features are obvious from inspection of

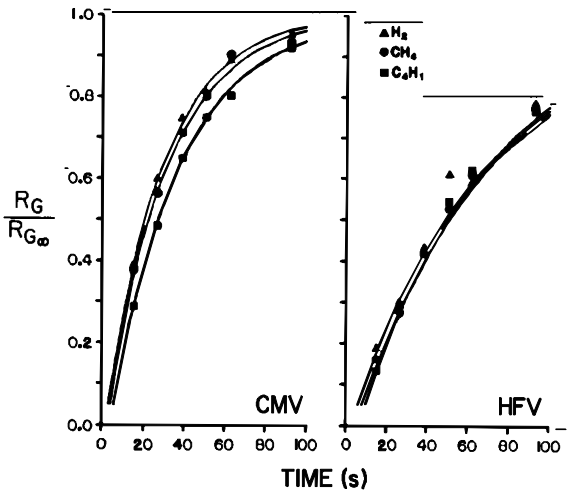

Fig. 2. Ratio of tracer/propane concentrations, expressed as a fraction of the ratio at infinite time, plotted as a function of the time of wash-in. For clarity, only hydrogen, ethane, and isobutane data are plotted. Helium, ethane, and sulfur hexafluoride data occupy intermediate positions. Data obtained at 180 s and 240 s are not shown in the graph but were included in the procedure to fit the rate constants to the data. *Left panel*: wash-in during CMV; *right panel*: wash-in during HFV.

the figure. First, a steady state is reached more rapidly with CMV, reflecting the larger tidal volumes used with this mode of ventilation. Second, there is a greater disparity between the rates of wash-in of the different gases with CMV compared to HFV.

The mean rate constants for each gas in the 13 paired experiments are listed in table 3. The rate constants are plotted in figure 3 as a function of the inverse square roots of the molecular weights of the gases. This variable provides an approximation of the relative diffusivity of each gas. Regression lines are fitted to each set of rate constants obtained during the two modes of ventilation. The rate constants obtained during CMV have greater absolute values, indicating the more rapid attainment of the steady state in these experiments. The slope of the relation between the rate constants and relative diffusivities is significantly greater for the CMV experiments compared to the HFV data. However, the slope of both regression lines differs significantly from zero, indicating that diffusivity of the tracer affects the rate of wash-in in both CMV and HFV.

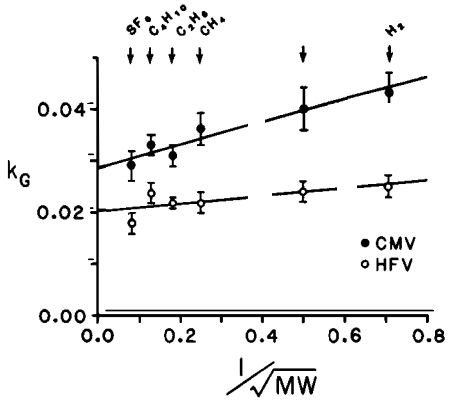

Fig. 3. Relation between the rate constants of wash-in and the reciprocals of the square roots of molecular weights of the tracers. Filled circles represent data from CMV experiments; open circles indicate HFV data. The coefficients from the analysis of covariance that represent the slopes of the regression lines are 0.0218 ± 0.0029 (standard error of the estimate) and 0.0206 ± 0.0020 for CMV and HFV experiments, respectively. The CMV slope is significantly greater than zero ($p < 0.0001$) and the HFV slope ($p < 0.002$). The HFV slope is also significantly greater than zero ($p < 0.001$).

Discussion

These experiments demonstrate that molecular diffusion has less importance in gas exchange during high frequency ventilation compared to conventional ventilation with large tidal volumes. This occurs despite a slower approach to equilibrium during HFV, a finding that intuitively might be expected to emphasize the role of diffusion. Interestingly, wash-in of inert gases into arterial blood with both ventilatory modes is described by single exponentials, whereas washout measured at the airway opening is usually a multiexponential process (9, 10, 12, 13). Observations made in blood leaving the lung have the advantage of reflecting events occurring near the alveolar surface without subsequent distortion that can be present in measurements performed in the gas phase. However, inert gas concentrations in blood are influenced by gas solubility, a factor absent in measurements made in expired gas.

The tracer gases utilized in these experiments were chosen because of their physical properties, chiefly solubility and molecular weight. Although the gases are relatively insoluble in blood (table 1), they do have a finite solubility that could affect the data in two ways.

The method of extraction from blood assumes that the reference propane and the tracer gases behave identically during the extraction procedure. Differences in solubility (14, 15) will lead to different fractions of gas extracted. The partitioning of a gas between equal volumes of blood and nitrogen is proportional to its solubility. Comparing sulfur hexafluoride and ethane, the two gases with the greatest discrepancy in solubility, the percentage of gas extracted from blood is 99.26% and 89.24%, respectively. This discrepancy would pose a serious problem except for the fact that each tracer/propane ratio is normalized to its equilibrium value in equation (1). Therefore, a constant discrepancy in extraction will not affect the computed rate constant of tracer wash-in.

The second effect of differing gas solubility is to distort relative alveolar gas concentrations through different rates of uptake by blood and saturation of peripheral tissues. During the course of a breath, the alveolar fraction of a gas with greater solubility will decrease more than that of a less soluble gas because of greater uptake. However, with the ventilatory parameters used in these experiments, we calculated that the wash-in rate constant would change only by a maximum of 4% over the range of Ostwald solubility coefficients of the gases used in these experiments (table 1). The influence of gas uptake by peripheral tissues is mediated through an effect on venous blood concentrations. This process is inconsequential because gases of differing solubilities are completely extracted during perfusion of peripheral tissues in these short-term experiments.

The reciprocal of the square root of molecular weight was chosen as an index of diffusivity because data reported in the literature for the tracer gases were not obtained under uniform conditions. Optimally, each diffusivity should be measured under the conditions of the experiment in question because the value of a diffusion coefficient is influenced by the presence of other gases. Fortunately, diffusivities of the tracer gases in the present work are affected minimally as a result of their low concentrations (18).

Mean airway pressure in the HFV experiments was slightly greater than that present during wash-in with CMV despite attempts to match the pressures, but this difference was not statistically significant. However, alveolar pressure may be higher than airway pressure during high frequency ventilation (19), and it is possible that lung volume may have been slightly greater during HFV. With the respiratory settings utilized in our experiments, there is little or no difference between mean airway and alveolar pressures (19). Small differences in lung volumes are unlikely to account for the difference in wash-in rate constants seen in the two types of ventilation. The deeper penetration of the inspired tidal volume in CMV is responsible for the faster attainment of equilibrium.

Wash-in of inert gases with high frequency ventilation is characterized by at least two phases when monitored at the

TABLE 3

RATE CONSTANTS OF GAS WASH-IN*

Gas	CMV	HFV
Hydrogen	0.043 ± 0.004	0.025 ± 0.002
Helium	0.040 ± 0.004	0.024 ± 0.002
Methane	0.036 ± 0.003	0.023 ± 0.002
Ethane	0.031 ± 0.002	0.023 ± 0.001
Isobutane	0.033 ± 0.002	0.024 ± 0.002
Sulfur hexafluoride	0.029 ± 0.003	0.018 ± 0.002

Definition of abbreviations: CMV = conventional mechanical ventilation; HFV = high frequency ventilation.

* All values are mean ± standard error and are expressed in units of s^{-}

proximal end of the endotracheal tube (9, 10). The rapid first phase of the wash-out is completed within a few seconds and the volume of this compartment is 60 to 70% of total lung volume (9, 12). This represents the wash-out of a large proximal compartment, encompassing most conducting airways. Support for this conclusion lies in the data of Berdine and coworkers (13). These investigators demonstrated a two-phase wash-out of ethane during HFV. The volume of the rapid compartment decreased in magnitude as the sampling catheter was advanced down the tracheobronchial tree. Sampling of peripheral lung units via an alveolar capsule yielded monoexponential wash-out curves. The presence of a large, well-mixed compartment in series with the peripheral compartment in which gas separation occurs secondary to diffusive processes limits the ability to detect these processes by observations made proximally at the endotracheal tube. This accounts for the failure of Knopp and others (9) to demonstrate gas separation during wash-out with HFV. These authors did not perform experiments during CMV, so it is not possible to compare their work to our studies of conventional ventilation. Kaethner and colleagues (10) did demonstrate separation of helium and SF_6 during HFV wash-out using a different technique. After a variable period of HFV, a slow maximal expiration was used to reflect gas concentrations along the tracheobronchial tree. Less turbulent flow with slow exhalation compared to conditions during HFV wash-out is likely to preserve the gas pattern present in the periphery. Kaethner and colleagues (10) appeared to observe similar separation of helium and SF_6 in both CMV and HFV in contrast to our finding of much greater separation during CMV. Unfortunately, they were unable to quantify the degree of separation, so it is not possible to accurately compare their data to the present work. One drawback of our wash-in technique stems from the wash-in of gases to an equilibrium value. A small, second compartment with a slower rate of wash-in could be difficult to detect. Small, slow compartments are most prominent in the terminal phase of a wash-in or wash-out curve. In the latter case, gas concentrations are approaching zero and small changes in concentration can be detected. With wash-in, gas concentrations are increasing to an equilibrium value, and detection of small changes is much more difficult.

The relative importance of molecular diffusion in gas exchange can be estimated by comparing the observed rates of wash-in with that expected on the basis of relative diffusivities (12). Using the regression equations fitted to the experimental data, the computed ratio of rate constants for hydrogen and SF_6 is 1.45 for CMV and 1.20 for HFV. The theoretical bounds on the ratios are 1.0 for a complete lack of any diffusive effect and 8.55 for complete dependence on molecular diffusion. This suggests that molecular diffusion plays a small role in both types of ventilation but is more important in CMV than HFV. Berdine and coworkers (12) measured a ratio of rate constants of helium and SF_6 during wash-out by jet ventilation of 1.16. This is similar to the computed ratio (1.14) we observed for these two gases during HFV.

If laminar Taylor dispersion was a dominant factor in gas mixing during HFV, tracers with less diffusivity would have greater wash-in rate constants because smaller molecules would tend to diffuse radially out of the flow profile. We reasoned intuitively that there could be an intermediate maximum in the relation between wash-in rate and relative diffusivity if both laminar Taylor dispersion and axial diffusion played a role in exchange. However, we observed a linear relationship compatible with an axial diffusive effect only. In a model of HFV, including both axial and radial diffusion, Gavriely and Butler (20) calculated that the rate of exchange would plateau for tracers in the range of diffusivities of respiratory gases and would exhibit only slight curvilinearity in the span used in these expeirments. The accuracy of these computations and the present data are not sufficient to reach any conclusion regarding the role of laminar Taylor dispersion. Axial and radial diffusion would have opposite effects on the rate of wash-in and gas separation dependent on diffusion. It is possible, but unlikely, that the two processes could play greater roles than apparent because the effect of one diffusive process would offset that of the other. Turbulent Taylor dispersion (7, 8) and interregional convection (3, 4) are much more likely to dominate gas mixing during HFV, but quantitative evidence is needed to confirm this impression.

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References

1. Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. J Appl Physiol 1984; 56:553–63.
2. Slutsky AS, Kamm RD, Drazen JM. Alveolar ventilation at high frequencies using tidal volumes smaller than the anatomical dead space. In: Engel LA, Paiva M, eds. Gas mixing and distribution in the lung. New York: Marcel Dekker, 1985; 137–76.
3. Schmid ER, Knopp TJ, Rehder K. Intrapulmonary gas transport and perfusion during high-frequency oscillation. J Appl Physiol 1981; 51: 1507–14.
4. Lehr JL, Butler JP, Westerman PA, Zatz SL, Drazen JM. Photographic measurement of pleural surface motion during lung oscillation. J Appl Physiol 1985; 59:623–33.
5. Haselton FR, Scherer PW. Bronchial bifurcations and respiratory mass transport. Science 1980; 208:69–71.
6. Chang HK, El Masry OA. A model study of flow dynamics in human central airways. Part I: axial velocity profiles. Respir Physiol 1982; 49: 75–95.
7. Fredberg JJ. Augmented diffusion in the airways can support pulmonary gas exchange. J Appl Physiol 1980; 49:232–8.
8. Slutsky AS, Drazen JM, Ingram RH Jr, *et al.* Effective pulmonary ventilation with small-volume oscillations at high frequency. Science 1980; 209: 609–11.
9. Knopp TJ, Kaethner T, Meyer M, Rehder K, Scheid P. Gas mixing in the airways of dog lungs during high-frequency ventilation. J Appl Physiol 1983; 55:1141–6.
10. Kaethner T, Kohl J, Scheid P. Gas concentration profiles along airways of dog lungs during high-frequency ventilation. J Appl Physiol 1984; 56: 1491–9.
11. Chang HK. Convection, diffusion and their interaction in the bronchial tree. Adv Exp Med Biol 1988; 227:39–52.
12. Berdine GG, Lehr JL, Strollo PJ. Multiple gas washout during jet ventilation. J Appl Physiol 1988; 65:2075–9.
13. Berdine GG, Lehr JL, McKinley DS, Drazen JM. Nonuniformity of canine lung washout by high-frequency ventilation. J Appl Physiol 1986; 61: 1388–94.
14. Weathersby PK, Homer LD. Solubility of inert gases in biological fluids and tissues: a review. Undersea Biomed Res 1980; 7:277–96.
15. Braker W, Mossman AL. Matheson gas data book. East Rutherford, NJ: Matheson Gas Products, 1971; 331–8, 489–96.
16. Wagner PD, Naumann PF, Laravuso RB. Simultaneous measurement of eight foreign gases in blood by gas chromatography. J Appl Physiol 1974; 36:600–5.
17. Snedecor GW, Cochran WG. Statistical methods. 7th ed. Iowa City, IA: Iowa Press, 1980; 267–9.
18. Chang HK. General concepts of molecular diffusion. In: Engel LA, Paiva M, eds. Gas mixing and distribution in the lung. New York: Marcel Dekker, 1985; 1–22.
19. Simon BA, Weinmann GG, Mitzner W. Mean airway pressure and alveolar pressure during high frequency ventilation. J Appl Physiol 1984; 57: 1069–78.
20. Gavriely N, Butler JP. Radial and longitudinal compartmental analysis of gas transport during high-frequency ventilation. J Appl Physiol 1986; 60:1134–44.