A general dimensionless equation of gas transport by high-frequency ventilation

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VENEGAS, JOSÉ GABRIEL, CHARLES A. HALES, AND DENISE J. STRIEDER. *A general dimensionless equation of gas transport by high-frequency ventilation.* J. Appl. Physiol. 60(3): 1025–1030, 1986.—To identify a general relationship between eucapnic oscillatory flow ($\dot{V}osc$) and frequency (f) in high-frequency ventilation (HFV), we searched the literature for eucapnic HFV data in different mammalian species. We found suitable results for rat, rabbit, monkey, dog, human, and horse, which we expressed in terms of two dimensionless variables, $Q = \dot{V}osc/\dot{V}A$ and $F = f/(\dot{V}A/VD)$, with $\dot{V}A$ the alveolar ventilation and VD the volume of the conducting airways. The experimental HFV data define the linear regression equation $\ln Q = 0.54 \ln F + 0.92$ ($R = 0.94$). Krogh's equation for conventional ventilation (CV), $\dot{V}osc = \dot{V}A + fVD$, in dimensionless terms becomes $Q = 1 + F$, which is valid for low F. The intersection of the CV and HFV equations at $F = 5.0$ defines a transition frequency, $f_t = 5.0$ ($\dot{V}A/VD$). At that point the alveolar ventilation per breath, $\dot{V}A/f$, represents 20% of VD, and tidal volume (VT) equals 1.20 VD. For eucapnia f_t ranges from 5.9 Hz in the rat to 0.9 Hz in the dog. The dimensional form of our HFV equation, $\dot{V}A = 0.13\ (VT/VD)^{1.2}\ (VTf)$ is very similar to other empirical equations reported for dogs in noneucapnic settings. Therefore the dimensionless equation should also be valid within a species at noneucapnic settings.

dimensional analysis; anatomic dead space; mammalian lung; Reynolds number; Womersley parameter; Peclet number; dog; horse; human; monkey; rabbit; rat

CONVENTIONAL VENTILATORS, developed to mimic spontaneous breathing, operate at frequencies (f) of 12–60/min (0.2–1 Hz). At these frequencies gas transport across the conducting dead space volume (VD) occurs primarily by convective bulk flow, and conventional ventilators need to deliver tidal volumes (VT) well in excess of VD. Recently, high-frequency ventilators, operating at frequencies of 1–30 Hz, have been found capable of maintaining a normal alveolar CO_2 concentration (eucapnia), with VT smaller than VD (4, 5, 22). Therefore, as eucapnia is maintained and frequency is increased, the principal mechanism of gas transport should change from that of conventional ventilation (CV) to a different one in high-frequency ventilation (HFV). Experimental measurements of gas transport in HFV have been performed in several mammalian species, representing a wide range of body sizes and metabolic rates. However, the general relationship between gas transport, f, and VT remains controversial, and the transition frequency, at which the mechanism of gas exchange is expected to change from CV to HFV, is undefined.

Dimensional analysis allows one to express experimental results from a model in terms of a minimum number of variables and in a general form that is applicable to systems different in size but similar in geometry. We surmised that dimensional analysis might provide the tools to identify a single functional relationship describing gas exchange in HFV for different mammalian species over a wide range of frequencies. We defined two dimensionless variables that can describe gas transport in CV and found that their use reduces the experimental HFV data published for different species to a single relationship. The intersection between the dimensionless form of the CV gas transport equation, and the HFV relationship, identifies the transition frequency separating the CV and HFV domains.

RATIONALE

Because the classical definition of alveolar ventilation ($\dot{V}A$), as the ratio of CO_2 output ($\dot{V}CO_2$) to alveolar CO_2 concentration in the steady state, implies no assumption with regard to gas transport, it applies to HFV as well as to CV. For both HFV and CV and for healthy lungs, it is accepted that $\dot{V}A$ increases monotonically with VT (23). Therefore, for a given f, there exists a unique VT that produces a desired level of $\dot{V}A$. It follows that, in the full span of the frequency range for a given VD and metabolic CO_2 production, there must exist a functional relationship between f and the oscillatory flow rate ($\dot{V}osc$) = VTf needed to maintain a steady eucapnic alveolar ventilation ($\dot{V}A$). For low frequencies in CV, an appropriate expression of such relationship is the classical equation (16)

$$VTf = \dot{V}A + VDf \qquad (1)$$

based on the assumption that all the gas in VD is replaced by alveolar gas or fresh gas at the end of each expiration or inspiration. *Equation 1*, therefore, is only valid under the condition that $VT \gg VD$. *Equation 1* is often used to define physiological dead space, which in CV, is greater than or equal to anatomic VD and in HFV becomes smaller than anatomic VD (28). In this study, however, we chose to consider VD as the volume of the conducting airways, which remains well defined and constant both in CV and HFV.

A dimensionless form of *Eq. 1* results from dividing both sides by $\dot{V}_A$, which yields

$$Q = 1 + F \quad (2)$$

where $Q = \dot{V}osc/\dot{V}_A$ is the oscillatory flow normalized by the eucapnic $\dot{V}_A$ or the inverse of the efficiency of ventilation ($\dot{V}_A/\dot{V}osc$). $F = f/(\dot{V}_A/V_D)$ is the ratio of the frequency of oscillation to a characteristic turnover rate of the dead space. F can also be viewed as the ratio of V_D to the alveolar ventilation per breath ($\dot{V}_A/f$). A low value of F means a large $\dot{V}_A/f$ in relation to V_D, and conversely. This definition of F is independent of the gas transport mechanism, since V_D, $\dot{V}_A$, and f are measurable quantities in both CV and HFV. V_D and eucapnic $\dot{V}_A$ are characteristics of a given animal and may be regarded as parameters, so that any expression of Q as a function of F represents a relationship between $\dot{V}osc$ and f.

A formal dimensional analysis should include variables such as the kinematic viscosity (ν) and the molecular diffusivity (Dmol) of the respiratory gases, introduced as dimensionless groups such as Reynolds ($Re = ud/\nu$), Womersley ($\alpha = d2\pi f/\nu$), and Peclet ($Pe = ud/Dmol$) numbers, where d is the airway diameter and u a characteristic velocity. We did not include these groups because actual values for Re, Pe, and α, or, alternatively, local airway dimensions and gas velocities have not been published in HFV studies. In addition, experiments in which the composition of respiratory gases was changed to alter Dmol and α, did not show significant effects on gas exchange in HFV at f up to 30 Hz (2, 13, 15).

EXPERIMENTAL DATA

We reviewed published results of HFV for evidence that eucapnia was achieved and for the numerical values of f, $\dot{V}osc$, $\dot{V}_A$, and V_D that are needed to calculate F and Q. We found reports including complete mean values for rats (11), rabbits (7), and dogs (23). Other data on dogs (3), humans (19), and horses (7) did not include eucapnic $\dot{V}_A$, and therefore standard values of $\dot{V}CO_2$ (1, 10, 17) were used to calculate $\dot{V}_A$. Finally, data on Bonnet monkeys (26) and on dogs (24, 25) could be included by solving the reported empirical equations for V_T and f in eucapnia. The selected data include single HFV measurements in rabbits, humans, and horses and two or three measurements at varying V_T and f in rats, monkeys, and dogs (Table 1). Actual calculations in each case are described in the APPENDIX.

In all calculations V_D stands for the total conduction dead space volume, defined as the sum of the anatomic and equipment dead spaces, $V_{D_A} + V_{D_E}$. Using V_D rather than V_{D_A} allows a realistic representation of the experimental conditions. When V_{D_A} was not given, but physiological V_D was or could be calculated during CV (3, 7, 19, 28) with the modified Bohr equation (17), we used the latter value as an approximation acceptable for healthy lungs. In one instance, when no V_D measurement was made (24, 25), we used the V_{D_A} values of Slutsky et al. (23) for dogs.

The studies were carried out in the steady state, with the apparent exception of some dog data (23) and the monkey data (26) that were measured during 10- to 20-s intervals shortly after the onset of HFV. Because in these protocols the animals were ventilated at eucapnia, with CV just prior to HFV, and because we only used HFV data at eucapnic settings, we inferred that the actual $\dot{V}CO_2$ in HFV was equal to the steady-state value, which we then used to calculate $\dot{V}_A$.

In none of the studies under review were the conditions of gas measurement defined in terms of temperature, pressure, or water vapor saturation, with the exception of Fletcher and Epstein (7), who refer to ambient temperature. When in need of correcting STPD data (e.g., predicted metabolic $\dot{V}CO_2$) to experimental conditions, we have used the STPD to ATPS conversion factor for 21°C ambient temperature.

In addition we identified some HFV data for dogs that were obtained by varying V_T and f to yield a wide range of alveolar ventilations (24, 25) ($\dot{V}_A = 0.6$–4.0 ml·s^{-1}·kg body wt^{-1} and $PCO_2 = 60$–25 Torr) or to yield hypocapnia (28) ($\dot{V}_A = 2.6$ ml·s^{-1}·kg body wt^{-1} and $PCO_2 = 30$ Torr). The data were presented as empirical equations that can

TABLE 1. *Summary of experimental data*

Species	Ref. No.	n	Mean Body Wt, kg	V_D, ml	f, Hz	$\dot{V}osc$, ml/s	$\dot{V}_A$, ml/s	F	Q
Rats	11	9	0.37	0.82	20	14.1	1.71	9.6	8.2
					20	10.4	0.96	17.1	11.4
Rabbits	7	7	3.75	6.53	1	15.2	8.67	0.8	1.8
					14	112.6	8.67	10.5	13.0
Monkeys	9	8	7.63	18.7	4.6	68.0	9.44	9.0	7.2
					9.7	97.0	9.44	19.3	10.3
					35.6	178.0	9.44	70.4	18.9
Dogs	23	6	14.25	106	15.5	592	19.9	83	31.0
Dogs	24	6	19.0	85	1.8	140	25.3	5.8	5.5
					7.5	299	25.3	24.7	11.8
Dogs	3	7	21.5	194	0.2	73	37.6	1.0	1.9
					5.8	760	38.6	29.9	19.7
					15	1,260	38.6	75.4	32.6
					30	1,320	38.6	150	34.2
Humans	19	6	82	134	0.2	113	86	0.3	1.3
					14	1,263	75	25	16.9
Horses	6	5	427	1750	3	6,000	862	6.0	7.0

V_D, conducting dead space volume; f, frequency; $\dot{V}osc$, eucapnic oscillatory flow; $\dot{V}_A$, alveolar ventilation; F, $f/(\dot{V}_A/V_D)$; Q, $\dot{V}osc/\dot{V}_A$.

be readily converted into dimensionless form. The equation of Venegas et al. (24, 25) reads

$$\dot{V}_A = 1.9(V_T/V_L)^{1.1}(V_T f)$$

where V_L is the mean lung volume equal to the resting functional residual capacity (FRC), measured with ambient pressure at the airway opening. Actual V_L averaged 44 ml/kg body wt. Since all HFV data were obtained with the mean lung volume equal to FRC, we assumed a constant ratio of V_L to V_D, which we calculated with V_D equal to 4.4 ml/kg (23). Then the experimental equation can be rewritten as $Q = (F/0.18)^{0.524}$. The equation of Weinmann et al. (28), with experimentally determined constants, reads

$$\dot{V}_{CO_2} = 0.19f(V_T/V_D^*)^{2.2}V_D^*F_{A_{CO_2}}$$

where V_D^* is the physiological dead space in CV and $F_{A_{CO_2}}$ is the alveolar CO_2 concentration. If $V_D^* = V_D$, then that equation can be rewritten as $Q = (F/0.25)^{0.545}$.

RESULTS

On a bilogarithmic plot of Q vs. F (Fig. 1), *Eq. 1* is represented by a curve on which the CV data points in this study fall near $F = 1$. HFV data points correspond to $F > 5$; most of them fall below *Eq. 1*, and their scatter suggests that a linear regression analysis of the logarithmically transformed data ($n = 14$) is justified. Such analysis yields the equation

$$\ln Q = (0.543 \pm 0.54)\ln F + (0.92 \pm 0.18) \quad (3)$$

where the two coefficients are given as mean values ± SD (correlation coefficient between ln Q and ln F, $R = 0.94$).

Equation 3 can be written as

$$Q = \left(\frac{F}{0.18 \pm 0.06}\right)^{0.54\pm0.05} \quad (4)$$

By equating *Eqs. 2* and *4* and solving for F, one finds that the two functions intersect at $F = 5.0$ (+3.7 and −2.5), that point marking the transition from CV to HFV. In eucapnia, the transition frequency, $f_t = 5.0$ ($\dot{V}_A/V_D$), varies from species to species proportionally to the ratio of metabolic rate ($\dot{V}_A$ is eucapnic alveolar ventilation) to dead space (Table 2). Because the smaller the animal the higher the relative metabolic rate, one would expect the f_t to be higher for smaller species. Table 2 shows such a trend, but it also shows deviations from expected behavior. The dogs have the lowest f_t because of the large V_{D_A} of the species and the relatively large V_{D_E} used in the experiments. The rabbits, in contrast, have the highest f_t because of their small V_{D_A} and high metabolic rate.

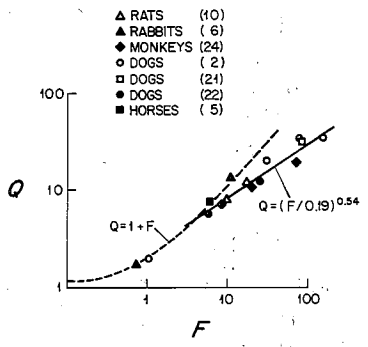

FIG. 1. Bilogarithmic plot of Q vs. F for eucapnic ventilation in 6 species. *Interrupted curve, Eq. 2* (conventional ventilation); *solid line, Eq. 4* (high-frequency ventilation).

TABLE 2. *Transition frequency and frequency for $V_T = V_D$ in eucapnia corresponding to $F = 5.0$ and 7.5, respectively, in six species*

Species	Ref. No.	$\dot{V}_A$, ml·s^{-1}·kg^{-1}	V_D, ml/kg	Transition Frequency, Hz	Frequency at $V_T = V_D$, Hz
Rats	11	2.6	2.22	5.9	8.8
Rabbits	7	2.3	1.74	6.6	9.9
Monkeys	26	1.2	2.45	2.4	3.7
Dogs	23	1.4	7.44	0.9	1.4
Humans	19	0.9	1.63	2.8	4.1
Horse	6	2.0	4.10	2.4	3.7

Eucapnic alveolar ventilation ($\dot{V}_A$) and conducting dead space volume (V_D, per kg body wt) are calculated from experimental data given in Table 1. For dogs, only data of Slutsky et al. (23) are presented here, as these data include actual measurements of anatomic dead space in dogs.

When $V_T = V_D$, $Q = F$. Solving *Eq. 4* for this condition yields $F = 7.5$ (SD = +3.4 and −2.6), from which we can calculate the frequency needed to maintain eucapnia at $V_T = V_D$ (Table 2). The latter is higher than the f_t because the condition $Q = F$ is never satisfied by *Eq. 2*. It follows that the gas transport mechanism characteristic of HFV must come into play when V_T is still greater than V_D. This fact has been experimentally documented by Weinmann et al. (28). Our analysis shows that the transition from CV to HFV occurs when $\dot{V}_A/f$ represents 20% of V_D and $V_T = 1.20\ V_D$.

Finally, *Eq. 4* can be expressed in dimensional terms yielding

$$\dot{V}_A = 0.13(V_T/V_D)^{1.2}V_T f \quad (5)$$

Two equations very similar to *Eq. 5* have been proposed by Venegas et al. (24, 25) for dogs at varying P_{CO_2} and by Weinmann et al. (28) for dogs in hypocapnia. When expressed in dimensionless form, with the actual noneucapnic values of $\dot{V}_A$ used in calculating F and Q, these equations closely approximate the HFV relationship derived from normocapnic data (Fig. 2). This finding demonstrates that, at least in dogs, *Eq. 4* is also applicable to hypercapnic and hypocapnic settings.

DISCUSSION

Using dimensionless variables allowed us to combine experimental data from different species of diverse body size and metabolic rate. The results show that, despite differences in techniques and protocols and despite the need to introduce some predicted rather than experimental values, the HFV data describe a singular relationship between dimensionless eucapnic oscillatory flow and dimensionless frequency. A similar relationship could be presented in terms of the dimensional variables, eucapnic $\dot{V}_{osc}$, and f, but that approach yields a family of curves,

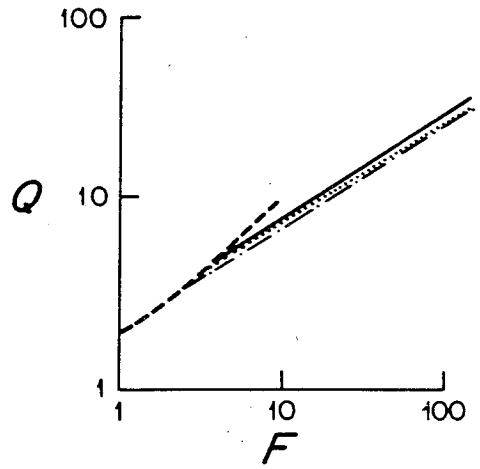

FIG. 2. Regression equation of Venegas et al. (24, 25) for dogs at varying P_{CO_2} (*dotted line*) and regression equation of Weinmann et al. (28) for dogs in hypocapnia (*dashed and dot line*), plotted as Q vs. *F* calculated with actual $\dot{V}_A$. *Solid line, Eq. 4; interrupted curve, Eq. 2.* See *Eqs. 2* and *4* for explanation of Q and *F*.

each characterized by different $\dot{V}_A$ and V_D in different species. In contrast the dimensionless form collapses the curves into a single function. Similarly, the dimensionless *Eq. 2* represents a single relationship for the CV domain. Thus the intersection of the CV and HFV equations marks the region where the transition between the two modes of gas transport occurs.

To achieve these results, we needed to be sure that the data were obtained in physiologically similar conditions, which we defined as steady state, eucapnia, and healthy lungs. The condition of steady state, defined as $\dot{V}_{CO_2}$ equal to the metabolic CO_2 production, was needed because we were seeking a time-independent relationship, which data obtained during transient disturbances may not fit. The condition of eucapnia was chosen because it introduces a minimum of experimental distortion from normal physiology. The condition that the subjects should be healthy was evidently desirable for physiological comparisons to be made. In addition it is known that the effectiveness of HFV, as judged by transient $\dot{V}_{CO_2}$ measurements, falls when frequency exceeds about 10 Hz in vagotomized dogs infused with histamine (20) and 3–6 Hz in respirator-dependent patients thought to have small airway disease (21).

The exponent of *F* in *Eq. 4* (0.543 ± 0.054) predicts that to provide a constant alveolar ventilation at rising frequencies, oscillatory flow must increase approximately with the square root of frequency instead of the first power expected from the asymptotic solution of *Eq. 2* at high frequencies. For comparison with other published equations, it is advantageous to convert *Eq. 4* into dimensional form, which yields $\dot{V}_A \sim V_T^{2.2} f$, in which the exponent of V_T is determined by the exponent of *F* in *Eq. 4* [$2.2 = 1/(1 - 0.54)$]. Using the method of transient $\dot{V}_{CO_2}$ measurements in dogs, Slutsky et al. (23) obtained the experimental relationship $\dot{V}_{CO_2} \sim V_T^{1.5} f^{0.9}$, and in monkeys Watson et al. (26) obtained $\dot{V}_{CO_2} \sim V_T^{1.85} f^{0.99}$. In both equations the exponent of *f* is close to unity but that of V_T is appreciably smaller than the value of 2.2 found in this and other studies (28). The different exponents are most likely attributable to divergence between the transient $\dot{V}_{CO_2}$ and $\dot{V}_A$ because the assumption that alveolar P_{CO_2} remains unchanged during 10- to 20-s bursts of HFV becomes questionable as the measurements are made away from eucapnia. In both studies (23, 25) a relatively large V_{D_E} compared with V_{D_A} could also have contributed to the observed differences.

The transport of CO_2 during HFV has been expressed (8, 14) as

$$\dot{V}_{CO_2} = \text{Deff} A \delta c / \delta x$$

where Deff is an effective diffusivity, *A* a cross-sectional area, and $\delta c/\delta x$ the concentration gradient of CO_2 along the airway. Fredberg (8) theorizes that the mixing due to turbulence and secondary flows in the bronchial tree, as represented by Deff, should be proportional to the product of a characteristic velocity (U) and a characteristic mixing length, the latter assumed to be the diameter of the airways. For an oscillatory flow, $U \sim V_T f$, and therefore Deff $\sim V_T f$. However, the present study and others (24, 25, 28) show that gas transport during HFV depends approximately on the second power of V_T. This suggests that the relevant characteristic mixing length in the estimation of Deff could be the average axial displacement of the gas in each breath (V_T/A), instead of the airway diameter. A model compatible with this interpretation has been proposed by Permutt et al. (18).

The constant 0.18 in *Eq. 4* determines the vertical position of the HFV regression line in Fig. 1 and therefore the efficiency of ventilation at any given frequency. The value of the constant is known with less certainty than that of the exponent in *Eq. 4*, as shown by its relatively large SD, which may reflect the uneven efficiency of devices used in the original experiments. For some dogs (3) and for humans (19), the authors published actual values of the stroke volume of the pump but acknowledged that, at the lower HFV frequencies, V_T might have been smaller than stroke volume. For the horses (6) the use of a jet ventilator implies some uncertainty about actual V_T. The corresponding points in Fig. 1 for those subjects lie above the regression line. For rats (11), monkeys (9), and some dogs (24), different equipment produced greater accuracy of measurement or greater efficiency of ventilation. The corresponding points in Fig. 1 all lie on, or below, the regression equation and parallel to it. It is therefore likely that the true value of the constant could be somewhat larger than 0.18.

The range of validity of *Eq. 4* is limited on the low-frequency end by its intersection with the CV curve (Fig. 1). This intersection appears common to all species reviewed but corresponds to a different *f* in each species, as determined by the ratio $V_D/\dot{V}_A$ (Table 2). No limit at the high-frequency end is defined by the present analysis. One may speculate, however, that such limit may be set by the increasing role of airway wall oscillation at very high frequencies (9). This mechanism is thought to account for the fact that above a critical frequency (f_{cr}), $\dot{V}_{CO_2}$ fails to increase with increasing *f* at constant V_T in chronically ventilated humans (21) and histamine bronchoconstricted dogs (20). At frequencies above f_{cr}, a constant V_T is needed to maintain a constant $\dot{V}_{CO_2}$, and

therefore eucapnic $\dot{V}osc$ rises linearly with f. This behavior would mark the high-frequency limit of validity of *Eq. 4*. In very high-frequency ventilation (VHFV) for $f > f_{cr}$, the Q vs. F relationship would be represented by a line of *slope 1*, intersecting the HFV line at $F = f_{cr}(V_D/\dot{V}_A)$.

Because f_{cr} is likely to be primarily determined by the mechanical properties of the respiratory system, species-specific differences cannot be ruled out a priori. In rabbits Watson and Jackson (27) observed that $\dot{V}CO_2$ fails to increase with increasing frequency at constant V_T, and Fletcher and Epstein (7) observed that physiological dead space fails to decrease with increasing f up to 22 Hz. Both observations differ from other published results for healthy dogs (24, 25, 28). The discrepancy could represent technical difficulties with $\dot{V}osc$ measurements (28), but Watson and Jackson (27) provide evidence that indeed the mechanical properties of the respiratory system are markedly different in dogs and rabbits. In dogs airway resistance varies by no more than ±20% between 2 and 14 Hz. In rabbits it falls by about 60% in the same range of frequencies. It is possible, therefore, the f_{cr} in rabbits is close to or less than f_t and that *Eq. 4* is valid, if at all, only during a narrow transition range from CV to VHFV. However, because the latter analysis is still purely theoretical and because we and others (28) have shown that HFV gas transport mechanism becomes prevalent when V_T is still somewhat larger than V_D, we judged it preferable to keep rather than reject the rabbit 14-Hz data point.

For healthy lungs in steady state, *Eq. 4* predicts eucapnic $\dot{V}osc$ in HFV over a wide range of frequencies, provided that V_D and eucapnic $\dot{V}_A$ are known or can be estimated from published values. Hypocapnia or hypercapnia will be induced if V_T is greater or smaller than that predicted by *Eq. 4* with eucapnic $\dot{V}_A$ as a parameter. However, experimental equations obtained from hypocapnic and hypercapnic data in dogs (24, 25, 28), when expressed in terms of Q and F calculated with the measured noneucapnic $\dot{V}_A$, are very similar to *Eq. 4* (Fig. 2). Therefore we conclude that *Eq. 4*, with noneucapnic $\dot{V}_A$, should be valid for noneucapnic ventilatory settings.

The fact that the dimensionless flow, Q, can be expressed as a function of the dimensionless frequency, F, alone could mean that for a given F and Q, neither Re, Pe, or α differed significantly from species to species. An order of magnitude calculation, however, suggests that for any given eucapnic combination of Q and F and for the same breathing gas, because of different $\dot{V}_A$ and V_D for monkey or rat, Re and Pe should decrease by a factor of 1.6 or 4.1 and α by a factor of 1.3 or 2, respectively, compared with the dog. We must conclude that gas transport during HFV in healthy mammals is insensitive to species-related changes in Re, Pe, and α within the ranges covered experimentally. Regardless of the likely complexity of gas exchange mechanism in HFV, our dimensionless equation is sufficiently accurate to describe the quantitative outcome of actual experiments carried out in diverse species or in any one species for different ventilator settings.

APPENDIX

Calculation of Q and F

Rats. Harf et al. (11) studied rats of 370 g mean body wt, anesthetized, tracheostomized, and placed in a plethysmograph. HFV at 20 Hz was produced by a piston pump, connected either to the tracheal tube or to the plethysmograph, as one purpose of the study was to compare internal and external HFV. Both techniques were found equally effective. Therefore we pooled the internal and external HFV data for each of the two V_T values that closely approached eucapnia [mean arterial CO_2 partial pressure ($PaCO_2$) = 41.8–41.1 Torr and 37.1–36.4 Torr for internal-external HFV]. For the 9 animals Harf et al. (11) estimated mean V_{D_A} as 0.6 ml. V_{D_E} was 0.22 ml and V_D was 0.82 ml. With V_T = 1.4 ml/kg or 0.52 ml, $\dot{V}osc$ was 10.4 ml/s. $\dot{V}_A$ calculated from mean $PaCO_2$ and $\dot{V}CO_2$ averaged 0.961 ml/s. F was 17.1 and Q 11.4. With V_T = 1.9 ml/kg or 0.70 ml, $\dot{V}osc$ was 14.06 ml/s. $\dot{V}_A$, similarly calculated averaged 1.713 ml/s. F was 9.6 and Q 8.2.

Rabbits. Fletcher and Epstein (7) studied rabbits weighing between 3 and 4.5 kg (3.75 kg estimated mean body wt), anesthetized, and intubated. The animals were curarized and ventilated at frequencies of 1–22 Hz. Physiological V_D measured at a frequency similar to that of spontaneous ventilation (1 Hz) averaged 1.74 ml/kg or 6.525 ml. $PaCO_2$ was kept in the range of 34–42 Torr, and $\dot{V}CO_2$ was monitored, but actual data are not reported. Therefore we calculated $\dot{V}_A$ from CV data at 1 Hz ($\dot{V}osc - f V_D$ = 8.67 ml/s). Accepting that eucapnia was maintained at higher frequencies, we used the same value for $\dot{V}_A$ at 14 Hz. At F = 1 Hz, mean $\dot{V}osc$ was 15.2 ml/s and F = 0.75, Q = 1.75. At f = 14 Hz, mean $\dot{V}osc$ was 112.6 ml/s and F = 10.5, Q = 13. Other frequencies were studied, but corresponding $\dot{V}osc$ values are not reported. By numerical trials we determined that changing our estimate of mean body weight within the published range of values had little effect on the values of F and Q at either frequency.

Monkey. Watson and Jackson (26) studied Bonnet monkeys (*Macaca radiata*) (7.63 kg mean body wt), anesthetized, intubated, and ventilated at frequencies of 2–40 Hz. V_T was 5, 10, or 15 ml, mean V_D 18.7 ml (V_{D_E} = 7.5 ml), and mean metabolic $\dot{V}CO_2$ 31 ml/min (personal communication). Eucapnic $\dot{V}_A$ was calculated from $\dot{V}CO_2$ by assuming $PaCO_2$ = 39 Torr, then $\dot{V}_A$ = 9.44 ml/s. For each V_T, one value of frequency should yield $\dot{V}CO_2$ equal to metabolic $\dot{V}CO_2$ and therefore eucapnia. We calculated the eucapnic frequencies by setting $\dot{V}CO_2$ = 31 ml/min in the empirical equation relating $\dot{V}CO_2$, V_T, and f for all experiments. $\dot{V}CO_2$ (ml/min) = $0.046\ V_T^{1.85} f^{0.99}$, with V_T in milliliters and f in hertz. For V_T = 5 ml, eucapnic frequency was 35.6 Hz and F = 70.4, Q = 18.9. For V_T = 10 ml, eucapnic frequency was 9.73 and F = 19.3, Q = 10.3. For V_T = 15 ml, eucapnic frequency was 5.46 and F = 9.0, Q = 7.2.

Dogs. Slutsky et al. (23) studied dogs, anesthetized, tracheostomized, and ventilated at frequencies of 4–28 Hz either with loudspeakers or a piston pump. For six animals (14.25 kg mean body wt) anatomic dead space was measured by the method of Fowler and averaged 64 ml. Equipment dead space averaged 42 ml. Mean values of V_T, f, and $\dot{V}CO_2/\dot{V}osc$, listed for each animal, allowed us to calculate mean $\dot{V}osc$ = 592 ml/s, f = 15.5 Hz, and $\dot{V}CO_2$ = 1.116 ml/s or 4.62 $ml \cdot min^{-1} \cdot min^{-1} \cdot kg$ body wt^{-1}, a value close to the expected metabolic $\dot{V}CO_2$ of 5 $ml \cdot min^{-1} \cdot kg$ body wt^{-1} for dogs (17). PCO_2 was maintained between 38.5 and 41.5 Torr. Assuming a mean PCO_2 of 40 Torr, we calculated mean $\dot{V}_A$ = 19.9 ml/s and F = 83 where Q = 31.

Some of us (24, 25) directly measured alveolar ventilation during HFV from the washout rate of nitrogen-13 in six paralyzed intubated dogs (19 kg mean body wt). The experiments were conducted at constant lung volume equal to FRC or 44 ml/kg. V_T was 40 or 80 ml, and $\dot{V}osc$ varied from 100 to 450 ml/s. V_{D_A} was not measured. We assumed V_{D_A} equal to the value reported by Slutsky et al. (23), 4.4 ml/kg body wt. The equipment had virtually no dead space; therefore, V_D = V_{D_A} or 85 ml. Eucapnic $\dot{V}_A$ was measured at 1.33 ml/s kg body wt or 25.3 ml/s, with PCO_2 = 37 Torr. The original data analysis yielded the empirical equation, $\dot{V}_A = 1.9(V_T/V_L)^{1.1} V_T f$.

We solved that equation for eucapnic f by setting $\dot{V}_A$ = 25.3 ml/s for each V_T. For V_T = 40 ml we found f = 7.48 Hz, $\dot{V}osc$ = 299 ml/s, and F = 24.7 where Q = 11.8. For V_T = 80 ml and f = 1.75 Hz, $\dot{V}osc$ = 140 ml/s; thus, F = 5.8 and Q = 5.5.

Brusasco et al. (3) also studied dogs, anesthetized, intubated, and ventilated with a piston pump at 0.2, 6, 15, and 30 Hz in eucapnia. To calculate $\dot{V}_A$, we used the published mean values of Pa_{CO_2} and assumed a metabolic $\dot{V}CO_2$ of 5 ml $STPD \cdot min^{-1} \cdot kg$ body wt^{-1} (17) or 1.97 ml

ATPS/s for an estimated 21.5 kg mean body wt (actual range 18–25 kg). We estimated total VD as $(\dot{V}osc - \dot{V}A)/f = 194$ ml for $f = 0.2$ Hz in CV. From the given mean VT at each frequency we calculated Q = 2, 20, 33, and 34, and $F = 1.0$, 29.9, 75, and 150, respectively.

Humans. Rehder and Didier (19) studied healthy male volunteers, anesthetized, intubated, paralyzed, and ventilated at frequencies of 0.2 and 14 Hz. VT averaged 566 or 90 ml, and mean $\dot{V}osc$ was 113 or 1,263 ml/s. To calculate $\dot{V}A$ we used the published mean values of Pa_{CO_2} of 38 Torr in CV and 44 Torr in HFV and assumed a metabolic $\dot{V}CO_2$ of 3.6 ml (STPD)·min^{-1}·kg^{-1} (1) or 325 ml (ATPS)·min^{-1} for 82 kg mean body wt. We estimated mean VD as $(\dot{V}osc - \dot{V}A)/f = 133.5$ ml for $f = 0.2$ Hz in CV. We then calculated Q = 1.3 and 16.9, and $F = 0.3$ and 25.

Horses. Dunlop et al. (6) studied horses, anesthetized, intubated, and ventilated with a jet ventilator at a frequency of 3 Hz. For five animals (427 kg mean body wt), VT was estimated as 2,000 ml, VD was 1,750 ml, and mean Pa_{CO_2} 39 Torr (FASEB presentation). $\dot{V}CO_2$ was not measured. To calculate $\dot{V}A$, we assumed a metabolic $\dot{V}CO_2$ of 6 ml STPD·min^{-1}·kg body wt (10) or a mean value of 47 ml ATPS/s for the given mean body weight. Then, mean $\dot{V}osc$ = 6,000 ml/s, $\dot{V}A$ = 862 ml/s, $F = 6$, and Q = 7.

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