Alveolar slope and dead space of He and SF_6 in dogs: comparison of airway and venous loading

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MEYER, MICHAEL, KLAUS-DIETER SCHUSTER, HOLGER SCHULZ, MICHAEL MOHR, AND JOHANNES PIIPER. *Alveolar slope and dead space of He and SF_6 in dogs: comparison of airway and venous loading.* J. Appl. Physiol. 69(3): 937–944, 1990.—Series (Fowler) dead space (VD) and slope of the alveolar plateau of two inert gases (He and SF_6) with similar blood-gas partition coefficients (~0.01) but different diffusivities were analyzed in 10 anesthetized paralyzed mechanically ventilated dogs (mean body wt 20 kg). Single-breath constant-flow expirograms were simultaneously recorded in two conditions: *1*) after equilibration of lung gas with the inert gases at tracer concentrations [airway loading (AL)] and *2*) during steady-state elimination of the inert gases continuously introduced into venous blood by a membrane oxygenator and partial arteriovenous bypass [venous loading (VL)]. VD was consistently larger for SF_6 than for He, but there was no difference between AL and VL. The relative alveolar slope, defined as increment of partial pressure per increment of expired volume and normalized to mixed expired-inspired partial pressure difference, was larger by a factor of two in VL than in AL for both He and SF_6. The He-to-SF_6 ratio of relative alveolar slope was generally smaller than unity in both VL and AL. Whereas unequal ventilation-volume distribution combined with sequential emptying of parallel lung regions appears to be responsible for the sloping alveolar plateau during AL, the steeper slope during VL is attributed to the combined effects of continuing gas exchange and ventilation-perfusion inequality coupled with sequential emptying. The differences between He and SF_6 point at the contributing role of diffusion-dependent mechanisms in intrapulmonary gas mixing.

alveolar plateau; breath holding; continuing gas exchange; diffusion limitation; functional inhomogeneities; inert gases; intrapulmonary gas mixing; respiratory flow; washout methods

INTRAPULMONARY GAS MIXING has traditionally been analyzed by single-breath or multiple-breath washout procedures that use the respiratory gases O_2 and CO_2 or virtually insoluble inert gases. In particular, the poorly soluble inert gases He and SF_6, which exhibit a sixfold diffusivity difference, have been applied to assess the significance of the incomplete axial diffusive mixing generally referred to as stratification. Incomplete intrapulmonary mixing is reflected by the presence of series or anatomic dead space and the sloping alveolar plateau (phase III) of the expirogram observed late in expiration. Substantial experimental evidence from insoluble test gas washout points at the importance of convection-dependent mechanisms, i.e., parallel inequality of the ventilation-to-volume ratio ($\dot{V}A/VA$), with low $\dot{V}A/VA$ units expiring preferentially late in expiration and contributing to alveolar gas inhomogeneity; however, stratification is generally believed to have a minor role in normal lungs.

The use of virtually insoluble inert gases supplied to inspired gas does not, however, address gas exchange-related mechanisms that become important when gas species that undergo continuous exchange with pulmonary capillary blood are considered. Of the additional mechanisms, continuing gas exchange and inequality of the ventilation-to-perfusion ratio ($\dot{V}A/\dot{Q}$), combined with sequential emptying, can be expected to exert marked effects on the time course of alveolar gas partial pressures.

An important contribution to the understanding of the role of diffusion and convection in intrapulmonary gas mixing and, in particular, of the mechanisms underlying the sloping alveolar plateau has been the infusion of inert gases into mixed-venous blood (1, 7, 12). De Vries et al. (1, 2) have demonstrated that the relative importance of various mechanisms that produce a sloping alveolar plateau varies with the blood-gas partition coefficient of the inert gas species. The importance of continuing gas exchange and distribution of diffusion properties throughout the lung has been addressed by single-breath washout of intravenously infused He and SF_6 (12).

The present study extends our previous work on mechanisms of the alveolar slope in anesthetized mechanically ventilated dogs, which was based on single-breath washout of the insoluble gases He and SF_6 (6, 7). The present study utilizes a novel experimental approach in that the same pair of inert test gases, He and SF_6, was analyzed after equilibration of lung gas with the inert test gases (airway loading) and, alternatively, during continuous venous infusion (venous loading). Whereas in the former case He and SF_6 behave as virtually insoluble gases and remain confined to the gas phase, in the latter the two test gases undergo continuous net transfer across the alveolar capillary membrane and are eliminated almost completely from pulmonary capillary blood on single pulmonary transit. The alveolar slope and the series dead space were the main parameters underlying the present analysis. A side issue of the present data base, which features a quantitative analysis of cardiogenic oscillations of the two test gases, is discussed in a separate

communication (8). Part of the material has been presented in abstract form (9).

METHODS

Simultaneous single-breath washout of He (mol wt 4) and SF_6 (mol wt 146) was performed in 10 mechanically ventilated supine dogs (mean body wt 19.5 ± 2.3 kg). The animals were anesthetized with pentobarbital sodium (3 $mg \cdot kg^{-1} \cdot h^{-1}$ iv, initial dose 20 mg/kg) and paralyzed by alcuronium dichloride (0.055 $mg \cdot kg^{-1} \cdot h^{-1}$ iv, initial dose 0.25 mg/kg). They were intubated by a cuffed endotracheal tube (Charrière 42) and connected to a computerized servo-ventilator, which performed the constant-flow single-breath procedures and provided for steady mechanical ventilation with a normoxic gas mixture between the test runs. The functional characteristics of the ventilator and its use in lung-function testing have been described previously (7, 10). Before the single-breath measurements, ventilation was adjusted to an end-tidal P_{CO_2} of ~35 Torr. Functional residual capacity was determined to have a mean value of 0.92 ± 0.23 (SD) liters (n = 10) by closed-circuit He dilution. No differences were observed between measurements at the beginning and end of the experiment.

After heparinization (heparin sodium 300 IU/kg iv, ~30% contained in the priming solution of the extracorporeal perfusion circuit), a vinyl catheter was placed in the femoral artery, and arterial blood was routed through a roller pump to a disposable Sci-Med 200-2A membrane oxygenator at a flow rate of 60 ml/min. A blood-return catheter was maintained in the ipsilateral femoral vein. Gas flow rate through the oxygenator was 1 l/min of either N_2 during airway loading or 50% He-50% SF_6 during venous loading. Heparin was continuously infused (65 $IU \cdot kg^{-1} \cdot h^{-1}$) to prevent thrombogenesis (partial thromboplastin time was decreased from >5 min to ~75 s) and antagonized by protamine sulfate at the end of the measurements. The animals were allowed to recover on completion of the experiment.

Single-Breath Test

Venous loading. Gas flow through the membrane oxygenator was switched from N_2 to the He-SF_6 gas mixture while the animal was ventilated with compressed air. When end-tidal partial pressures of He and SF_6 had reached steady levels, a constant-flow single-breath maneuver was performed by the servo-ventilator starting at end-expiratory lung level (Fig. 1). To account for differences in lung volume between animals, inspired (V_I) and expired volumes (V_E) of the single breath were adjusted to fixed fractions of the individual's functional residual capacity. The following set of standard respiratory parameters was selected as control: V_I = 0.5 volume at functional residual capacity (V_{FRC}), $V_E = 0.75 \times V_{FRC}$, inspiratory flow ($\dot{V}_I$) = 0.5 l/s, expiratory flow ($\dot{V}_E$) = 0.1 l/s, breath hold 0 s. The 3:2 ratio of V_E to V_I was selected to provide a phase III curve segment that was sufficiently long for calculation of the alveolar slope and was clearly distinguishable from the early portion of the expirogram (phase II). Compressed test gas-free air was used instead of room air because, in the course of the experiment, the room air contamination by He and SF_6 from expired gas gradually approached the trace level of end-tidal partial pressures of He and SF_6 observed during venous loading. For the purpose of the present study, no precise absolute calibration of the gas analyzer was required. End-tidal partial pressures were ~0.05 Torr for He and ~0.085 Torr for SF_6 during venous loading. Venous loading by a membrane oxygenator was preferred over venous infusion of test gas-equilibrated saline because it facilitated unlimited measuring periods without compromising the animal by a large fluid load.

Airway loading. After equilibration of lung gas by open-circuit washin of trace concentrations (~100 parts per million) of He and SF_6, a constant-flow single breath of a test gas-free mixture (compressed air) was performed (Fig. 1). The single-breath procedure was essentially identical to that used during venous loading. The inspired He-SF_6 concentrations during test gas washin were adjusted to approximate the end-tidal levels encountered during venous loading. Thus the experimental conditions, except for the method of administration of the inert test gases, were essentially identical.

Gas Analysis

Partial pressures of He and SF_6 were continuously recorded from the endotracheal tube by a variable-collector magnetic-sector respiratory mass spectrometer (modified Varian M3). Gas sampling rate through a 1-m heated steel inlet capillary was 6 ml/min. The delay time was 190 ms, and 5–95% response time was 70 ms. Special procedures were required (gas-tight ion source, thorium-coated cathode operated at enhanced current) to tune the mass spectrometer for high sensitivity to produce a signal-to-noise ratio of ~200:1 at ~0.03 Torr of He and SF_6.

The output signals for He and SF_6 and the volume recording obtained from the ventilatory servo system were recorded on a direct-writing ink recorder (Gould 2800S) and, after correction for lag time, were stored in a laboratory computer (MINC 11, Digital Equipment) for subsequent analysis. Gas volumes and flow rates were corrected and expressed for BTPS conditions. A representative example of the single-breath measurements during airway and venous loading is presented in Fig. 2.

Slope of the Alveolar Plateau and Dead Space

The slope of the alveolar plateau was defined and calculated in two different ways.

Relative slope referred to volume. The relative slope with reference to volume [$S(v)$] is defined as the change of partial pressure (ΔP) normalized to the difference between mixed expired ($P\bar{E}$) and inspired partial pressure (P_I) per unit of expired volume: $S(v) = \Delta P/(P\bar{E} - P_I)/\Delta V_E$ ($liters^{-1}$).

Relative slope referred to time. The relative slope with reference to time [$S(t)$] is defined as the change of partial pressure normalized to mixed expired-inspired partial pressure difference per 10 s of expiratory time: $S(t) = \Delta P/(P\bar{E} - P_I)/\Delta t_E$ [$(10\ s^{-1})$] where $\Delta t_E = \Delta V_E/\dot{V}_E$. For

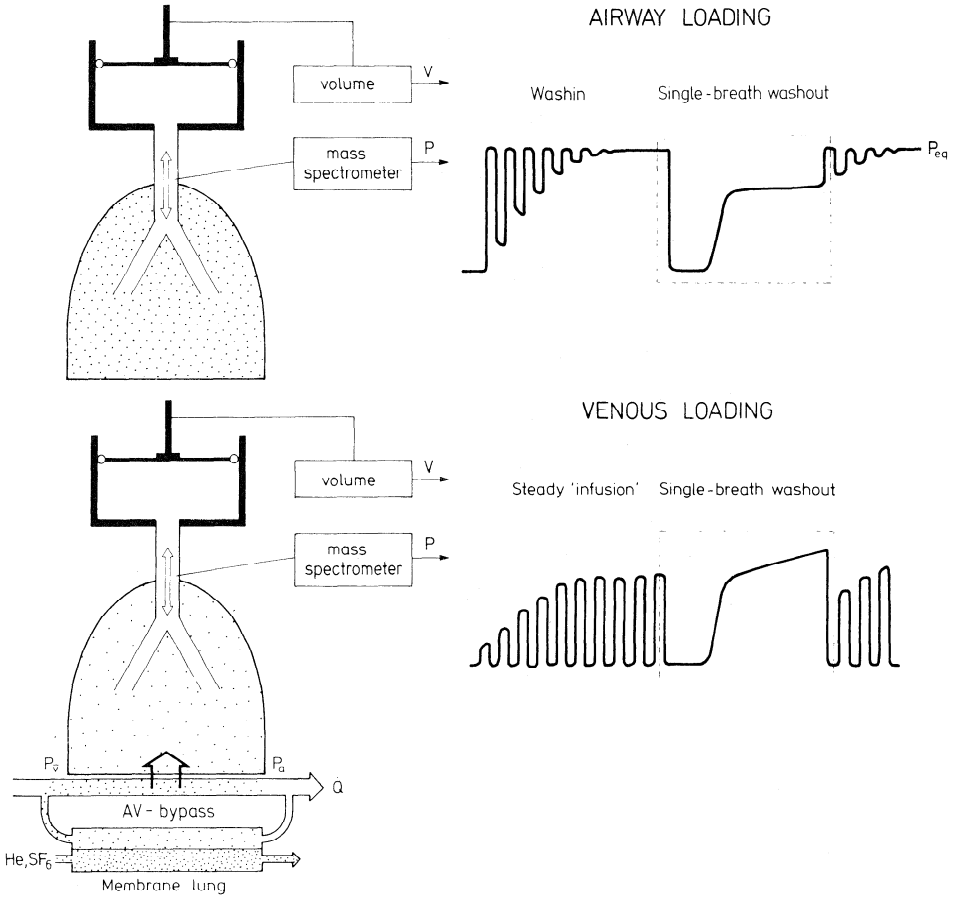

FIG. 1. Experimental setup for airway and venous loading.

control conditions (expiratory flow rate 0.1 l/s) the numerical values of the $S(v)$ and $S(t)$ are identical.

The slope of the alveolar plateau was calculated from the linear curve segment of phase III by least-squares linear regression, typically in the interval between 40 and 80% of the expired volume. These boundaries were chosen to exclude the effects of both series dead space (VD) and low lung volume that resulted from expiration well into the reserve volume. Generally, the alveolar slopes were close to linear beyond these boundaries and were thus insensitive to the curve segment selected (cf. Fig. 2). Mixed-expired partial pressure was obtained by integration of the expirogram to the point where VE was equal to VI. The conventional Fowler method was used to calculate VD from the phase II curve segment of the expirogram.

Experimental Protocol

Typically, a total of 86 single-breath measurements were completed in each of the 10 animals. The sequence of measurements and the conditions of test gas loading are shown in Table 1. In addition to control measurements, the effects of fast (0.3 l/s) and slow (0.05 l/s) expiratory flow rate and end-inspiratory breath holding (4, 8, and 12 s) were analyzed. In any condition, except for the initial control measurements in venous loading and airway loading, where 10 successive measurements were performed in either condition, measurements were completed in triplicate. To eliminate delays attributable to the time required for complete test gas washout or washin, which would otherwise have impeded rapid progression of the experiment, the experimental protocol was not strictly randomized. Instead, any intervention or change of test gas-loading procedure was bracketed by control measurements, and the effects of a given intervention were related to the average values of $S(v)$ [or $S(t)$] or VD obtained from corresponding controls before and after the intervention.

Analysis of variance and unpaired t test were used for statistical treatment of data. Results were considered significant at $P < 0.05$. The coefficient of variation of $S(v)$ in control conditions for both He and SF_6 was 15% during venous loading and 6% during airway loading.

RESULTS

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Overall mean values in control conditions (no breath hold, expiratory flow 0.1 l/s) during airway loading and venous loading are summarized in Table 2. VD was essentially the same during airway or venous test gas loading. This finding was preserved during breath holding and varied expiratory flow rate, as demonstrated by the venous-to-airway loading ratio, which was not statistically different from unity (Table 3). Moreover, the independence of single-breath VD from the route of test gas administration applies equally to He and SF_6. VD for He was consistently smaller than for SF_6 (Table 4). The He-to-SF_6 ratio was slightly increased during breath holding ($P < 0.01$), which indicated a small increase in the relative difference between the VD values for He and

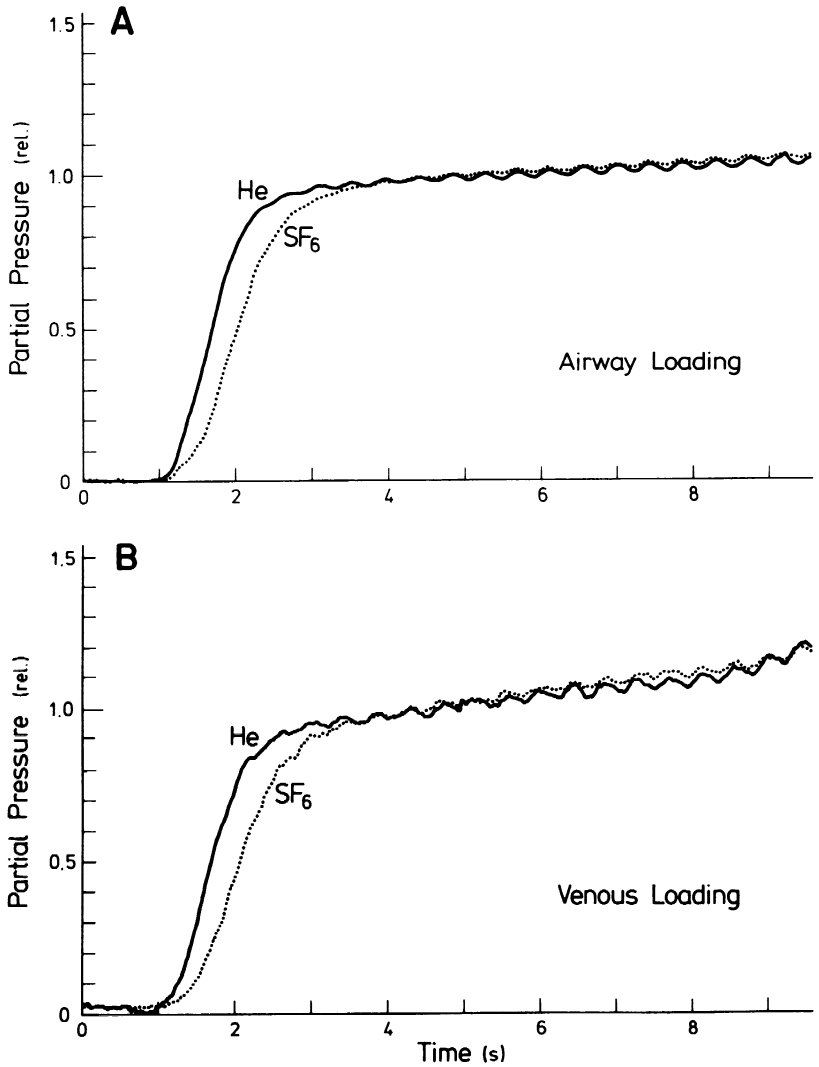

FIG. 2. Experimental record of simultaneous single-breath washout of He and SF_6 during airway and venous loading (lines were redrawn by eye with enhanced line width; actual signal-to-noise ratio is ~200:1).

TABLE 1. *Experimental protocol*

VL	C*										
AL	C*	$\dot{V}_{E}(f)$	C	$\dot{V}_{E}(s)$	C						
VL	C	$\dot{V}_{E}(f)$	C	$\dot{V}_{E}(s)$	C	BH(4)	C	BH(8)	C	BH(12)	C
AL					C	BH(4)	C	BH(8)	C	BH(12)	C

$n = 3$ measurements per condition except as noted. Mode of test gas application: VL, venous loading; AL, airway loading. C, control conditions ($\dot{V}_I = 0.5 \times V_{FRC}$, $\dot{V}_E = 0.75 \times V_{FRC}$, $\dot{V}_I = 0.5$ l/s, $\dot{V}_E = 0.1$ l/s, breath hold 0 s); $\dot{V}_E(f)$, fast expiration (0.3 l/s); $\dot{V}_E(s)$, slow expiration (0.05 l/s); BH, breath holding for no. of s in parentheses. * $n = 10$.

TABLE 2. *V_D and relative slope of alveolar plateau of He and SF_6 during airway and venous loading*

	V_D, liters		$S(v)$, liters^{-1}	
	He	SF_6	He	SF_6
Airway loading	0.130±0.025	0.153±0.028	0.24±0.06	0.26±0.06
Venous loading	0.131±0.023	0.151±0.025	0.50±0.20	0.59±0.17

Values are means ± SD of individual means from 10 experimental animals in control conditions. Relative alveolar slope is referred to volume [$S(v)$], but for control conditions the numerical values apply equally to time reference [$S(t)$, (10 s)$^{-1}$].

SF_6, but was unaffected by varying expiratory flow rate. After breath holding, V_D was decreased ~32% for He and 25% for SF_6 with 4 s of breath holding, but breath holding beyond 4 s had only minor additional effects (Table 5). V_D increased with fast expiration and decreased with slow expiration and the effects were essentially the same for the two test gases.

Slope of the Alveolar Plateau

Overall mean values for $S(v)$ in control conditions during airway loading and venous loading are summarized in Table 2. $S(v)$ is about twice as high in venous loading as it is in airway loading for both He and SF_6. During breath holding, the venous-to-airway loading ratio does not appear to be different from control, although an insignificant tendency for lower values becomes apparent with short breath-holding time (Table 3). Because of the considerable interindividual variability (of unknown origin), the data may be interpreted to reflect trends rather than clear-cut effects. With fast expiration, the relative slopes in venous loading are smaller than those in airway loading (ratio less than unity), whereas the reverse occurs with slow expiration rate.

In airway loading, $S(v)$ for He was consistently lower

TABLE 3. *Venous loading vs. airway loading*

	VL/AL			
	VD		S(v)	
	He	SF_6	He	SF_6
Control [BH(0)]	1.01±0.08	1.00±0.07	2.16±0.77*	2.26±0.61*
BH(4)	0.98±0.09	0.99±0.07	1.38±2.05†	1.20±1.67†
BH(8)	1.00±0.12	0.99±0.10	2.04±1.68‡	1.89±1.48‡
BH(12)	1.02±0.11	1.01±0.13	2.56±1.88‡	2.48±1.29§
$\dot{V}_E$(f)	0.99±0.07	0.98±0.07	0.54±0.57†	0.82±0.54‡
$\dot{V}_E$(s)	0.98±0.10	1.00±0.09	4.47±2.56§	3.90±1.79*

Values are means ± SD of individual means of venous-to-airway loading ratio (VL/AL) from 10 experimental animals. See footnote of Table 1 for definitions of abbreviations. All data for VL/AL of VD are not different from unity. Difference from unity for S(v): not significant († $P > 0.05$); significant (* $P > 0.001$, ‡ $P < 0.05$, § $P < 0.01$).

TABLE 4. *He-to-SF_6 ratio of relative alveolar slope and VD*

	VD		Relative Alveolar Slope	
	Venous loading	Airway loading	Venous loading	Airway loading
Control [BH(0)]	0.87±0.02	0.86±0.02	0.83±0.12	0.90±0.06
BH(4)	0.78±0.06	0.79±0.04	1.13±0.45*	0.93±0.03
BH(8)	0.79±0.06	0.78±0.03	1.06±0.30*	0.92±0.05
BH(12)	0.81±0.05	0.80±0.03	0.87±0.26*	0.90±0.05
$\dot{V}_E$(f)	0.87±0.02	0.87±0.02	0.64±0.16	0.79±0.10
$\dot{V}_E$(s)	0.85±0.05	0.87±0.04	0.93±0.21*	0.92±0.08

Values are means ± SD of individual means of He-to-SF_6 ratio of relative alveolar slope or VD from 10 experimental animals. See footnote of Table 1 for definitions of abbreviations. * $P > 0.05$; in all other cases the He-to-SF_6 ratio was less than unity at $P \leq 0.001$ (t test).

TABLE 5. *Effect of breath holding and varying $\dot{V}_E$ on VD*

	Venous Loading		Airway Loading	
	He	SF_6	He	SF_6
BH(4)	0.68±0.08	0.76±0.04	0.68±0.06	0.74±0.04
BH(8)	0.63±0.08	0.71±0.06	0.60±0.06	0.66±0.05
BH(12)	0.63±0.08	0.69±0.07	0.57±0.06	0.62±0.05
$\dot{V}_E$(f)	1.15±0.03	1.15±0.04	1.15±0.02	1.14±0.03
$\dot{V}_E$(s)	0.85±0.09	0.87±0.05	0.88±0.02	0.87±0.03

Values are means ± SD of ratios relative to control from 10 dogs. See footnote of Table 1 for definitions of abbreviations.

than S(v) for SF_6 (Table 4). The separation of the test gases reflected by the He-to-SF_6 ratio was unaffected by breath holding but was inversely related to expiratory flow rate. During venous loading, the He-to-SF_6 ratio of slopes was less than unity in four of six experimental conditions, but the data were biased by sizable interindividual variability.

The effects of breath holding on the relative alveolar slopes of He and SF_6 are summarized in Table 6. In venous loading, the effects were inconsistent because of widely varying responses among individuals. The average decrease at 4 s of breath holding and the subsequent increase cannot be considered significant. During airway loading, there was a small but steady increase of S(v) for both He and SF_6 with progressing breath-holding time ($4 > 6$ s, $P < 0.01$).

The effects of varying expiratory flow rate are compiled in Table 7. In venous loading, S(v) is inversely correlated with $\dot{V}_E$, whereas $S(t)$ is practically unaffected. In airway loading, only insignificant changes of S(v) with increasing $\dot{V}_E$ were observed, but a marked increase of $S(t)$ with increasing $\dot{V}_E$ was apparent. With slow expiration, $S(t)$ was clearly decreased.

TABLE 6. *Effect of breath holding on relative alveolar slope*

	Venous Loading		Airway Loading	
	He	SF_6	He	SF_6
BH(4)	0.29±1.04	0.38±0.69	0.87±0.06	0.85±0.06
BH(8)	0.85±0.70	0.70±0.56	0.82±0.09	0.80±0.10
BH(12)	1.01±0.70	0.92±0.43	0.74±0.08	0.74±0.09

Values are means ± SD of ratios relative to control from 10 dogs. BH, breath hold for no. of s in parentheses.

TABLE 7. *Effect of varying $\dot{V}_E$ on S(v) and S(t)*

	Venous Loading		Airway Loading	
	He	SF_6	He	SF_6
		S(v)		
$\dot{V}_E$(f)	0.22±0.34	0.38±0.28	0.96±0.15	1.06±0.15
$\dot{V}_E$(s)	2.15±0.72	1.92±0.75	1.18±0.05	1.13±0.06
		S(t)		
$\dot{V}_E$(f)	0.66±1.02	1.14±0.84	2.88±0.45	3.18±0.45
$\dot{V}_E$(s)	1.08±0.36	0.96±0.38	0.59±0.09	0.57±0.03

Values are means ± SD from 10 experiments. Effects of varying $\dot{V}_E$ on S(v) and $S(t)$ are expressed as relative changes from control. $\dot{V}_E$(f), fast expiration (0.3 l/s); $\dot{V}_E$(s), slow expiration (0.05 l/s).

DISCUSSION

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The differences in VD derived from measurements using gases of different diffusivities are well documented by previous work (7, 11). In a previous study on anesthetized artificially ventilated dogs, the VD He-to-SF_6 ratio was 0.84 and was only slightly affected by changes of ventilatory parameters (7), in accordance with the range of values (0.79–0.87; Table 4) observed in the present study. The larger dead space for the less diffusible gas is generally interpreted to reflect the different position of the inspired-resident gas interface that is displaced to more proximal airways for the more diffusible gas. This concept is further supported by the fact that VD is essentially the same during airway or venous loading (Table 3) and hence is unaffected by the route of test gas administration.

The decrease of VD with breath holding constitutes a well-known phenomenon (3, 7). The changes of VD by breath holding or varying expiratory flow rate may be considered to represent time effects. In Fig. 3, VD is plotted against "effective time," i.e., the time from the end of inspiration to the point where phase II is intersected by a line perpendicular to the x-axis according to Fowler's dead-space calculation procedure. The following features become apparent: *1*) VD of He and SF_6 decreases with time according to a similar pattern; *2*) the He-to-SF_6 ratio of VD slightly increases with time. This behav-

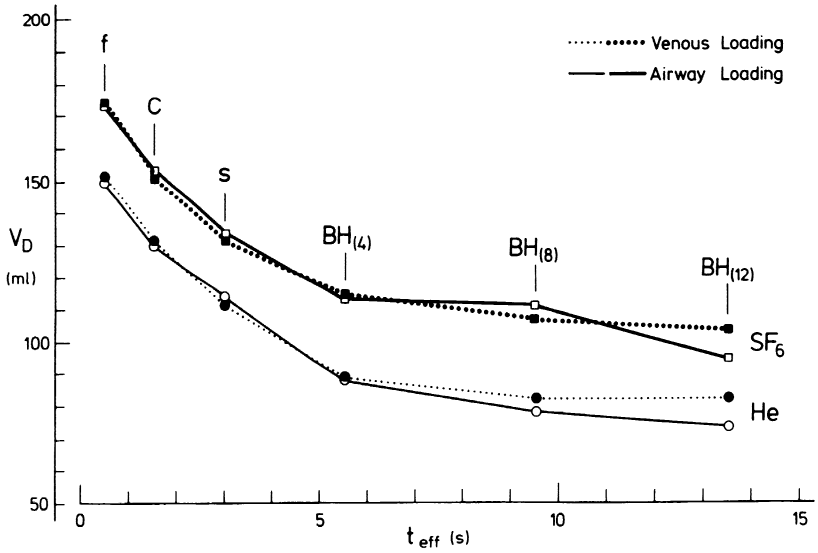

FIG. 3. VD of He and SF_6 during airway and venous loading plotted against effective time (t_{eff}). f, fast expiration; C, control; s, slow expiration; BH, breath hold for no. of s in parentheses.

ior may in part result from a combination of the location of the tidal-residual gas interface, more proximal for He than for SF_6, and its displacement by diffusion, also different for both gases. However, the changes of the He-SF_6 ratio were strikingly small and unexpected of diffusion alone. It appears that additional mechanisms counteracting diffusional equilibration must have been involved; and *3*) the decrease of VD with time is essentially the same with airway and venous loading.

Alveolar Slope: Venous Loading vs. Airway Loading

Although the same test gases, He and SF_6, are used in identical dogs in the same experimental conditions, ventilated in the same manner, there is a fundamental difference in gas transport conditions between steady venous loading and airway loading.

During airway loading, He and SF_6 behave as essentially insoluble gases because of their low blood-gas partition coefficients (λ 0.0080 for He, 0.0068 for SF_6; cf. Ref. 5), and uptake into pulmonary capillary blood can be neglected as a mechanism that produces the sloping alveolar plateau. Calculations show that during 12 s of breath holding only ~0.4% of the amount of He would be absorbed by a cardiac output of 2 l/min and would thus lead to an $S(t)$ of only −0.004/(10 s).

Somewhat more important are the lung volume changes brought about by the gas exchange ratio continually decreasing to below unity during a slow expiration (gas exchange effect due to volume shrinkage). Given an O_2 uptake of 100 ml/min (assumed for the anesthetized dog), a mean gas exchange ratio of 0.5, and a lung volume of 1 liter, the lung volume would decrease by ~1% in 12 s, which corresponds to an $S(t)$ of 0.01/10 s. The relative contribution of this mechanism to the overall slope, which is similar for He and SF_6 and equally applies to both airway and venous loading, is ~8% in control conditions, which is in close agreement with the value (14%) previously determined experimentally in similar conditions (cf. Ref. 7).

The basic difference between airway and venous loading concerns the effect of continuing gas exchange on the relative alveolar slope.

For an ideal lung model (single homogeneous compartment, no gas-phase diffusion limitation), continuing gas exchange during apnea leads to an increase of alveolar pressure (PA) due to continuous supply by mixed-venous blood according to the relationship

$$\frac{dP_A}{dt} = \frac{\dot{Q}\lambda}{V_A} \cdot (P\bar{v} - P_A) \qquad (1)$$

where VA is alveolar volume, $\dot{Q}$ is pulmonary blood flow, and $P\bar{v}$ is mixed venous pressure. During venous infusion of poorly soluble inert gases the difference between $P\bar{v}$ and PA is much higher than the difference between PA and PI as demonstrated by the relationship derived by Farhi (4)

$$\frac{P\bar{v} - P_A}{P_A - P_I} = \frac{\dot{V}_A}{\dot{Q}\lambda} \qquad (2)$$

In airway loading, starting from the equilibrated state ($P_A = P\bar{v}$), PA after a single-breath washout with test gas-free air is determined by the relationship

$$\frac{P_A - P_I}{P\bar{v} - P_I} = \frac{V_A + V_D}{V_A + V_T - V_D} \qquad (3)$$

where VA is the end-expired alveolar volume and VT is tidal volume. Because VT − VD is smaller than VA, (PA − PI)/($P\bar{v}$ − PI) is not far below unity and ($P\bar{v}$ − PA) is smaller than (PA − PI). It follows that the relative alveolar slope standardized to PA − PI[$S(t) = (dP_A/dt)/(P_A - P_I)$] due to continuing gas exchange, for inert gases exhibiting identical low λ, is expected to be considerably higher for venous loading than for airway loading.

Additional mechanisms that could produce an alveolar slope are *1*) axial mixing deficit (stratification) and *2*) $\dot{V}_A/V_A$ and $\dot{V}_A/\dot{Q}$ inequality combined with sequential emptying, with relatively poorly ventilated lung regions emptying last. Whereas the first factor should depend on the diffusivity of the test gas species, the second may be assumed to be primarily diffusion independent.

In airway loading, the inhomogeneity to produce al-

veolar slopes has been demonstrated to be due to unequal distribution of $\dot{V}A/VA$ with sequential expiration of parallel lung regions, in which relatively poorly ventilated units expire last (7). In venous loading, $\dot{V}A/\dot{Q}$ inequality combined with sequential emptying is expected to contribute to the alveolar slope. The larger relative slopes of He and SF_6 in venous loading compared with airway loading would be interpreted to be due to continuing gas exchange and $\dot{V}A/\dot{Q}$ inhomogeneity, in addition to $\dot{V}A/VA$ inhomogeneity, associated with sequential emptying.

Alveolar Slope: Effects of Breath Holding and Expiratory Flow Rate

In airway loading, the alveolar slope for He and SF_6 decreased with breath holding in a manner similar to the behavior of VD. In venous loading, the effects of breath holding were highly variable. In part, the variability may be due to the somewhat arbitrary selection of the proper phase III curve segment because the alveolar slopes during venous loading were not strictly constant, and sometimes negative slopes were encountered, particularly for short breath-holding times. The changes of the relative slopes (and of the interindividual variability) as a result of breath holding may have been due to a combination of factors influencing the inhomogeneity of intrapulmonary gas distribution: *1*) breath holding is expected to improve homogeneity by diffusive and cardiogenic mixing, and *2*) unequal distribution of blood flow to lung compartments emptying sequentially could enhance inhomogeneity.

The changes of the alveolar slope with varying $\dot{V}E$ may in part reflect changes in the emptying pattern of compartments with differing gas composition. In part, however, breath-holding effects would also be expected. In airway loading, the changes in $S(v)$ with $\dot{V}E$ are small and those of $S(t)$ are large (Table 7). Because the effects of continuing gas exchange must have been negligible in airway loading, the marked dependence of $S(t)$ on $\dot{V}E$ must be attributed to other factors. Of the remaining factors, $\dot{V}A/VA$ inequality coupled with sequential emptying is expected to be the most important mechanism for the alveolar slope, which may furthermore be modified by diffusion-dependent (time-dependent) mixing processes. In venous loading, the relationships are reversed compared with airway loading; $S(v)$ displays large changes with $\dot{V}E$, whereas $S(t)$ is relatively constant. The relative constancy of $S(t)$ is expected of continuing gas exchange, which thus sems to be the main factor producing the alveolar slope in venous loading.

Alveolar Slope: He-to-SF_6 Ratio

The He-to-SF_6 ratio of alveolar slopes was consistently less than unity in airway loading. In venous loading, the He-to-SF_6 slope ratio was not statistically different from unity in most conditions but appeared to decrease with fast expiration and to increase with slow expiration (Table 4). This behavior could be explained by time effects similar to those that cause changes of VD.

It should be emphasized that none of the mechanisms considered so far, continuing gas exchange and unequal distribution of $\dot{V}A/VA$ or $\dot{V}A/\dot{Q}$ combined with sequential emptying, by their inherent convective nature, would account for differences between the alveolar slopes of He and SF_6. The He-to-SF_6 ratios are much higher than expected on the basis of Graham's law. If all the alveolar slopes are assumed to be attributable to diffusion limitation, assuming that the resistance to gas transport is confined to a single boundary, the ratio of slopes based on the ratio of relative diffusivities is estimated at 0.17. Even when it is taken into account that the initial location of the tidal-residual gas interface is different for the two gases whereby the expected He-to-SF_6 ratio would be 0.33 (cf. Ref. 12), the present experimental values appear to be far outside the expected range. Interestingly, Scherer et al. (12) found close agreement with the predicted value of the He-to-SF_6 slope ratio determined during venous infusion in humans, which is in striking contrast to our findings in anesthetized dogs. The mechanisms for this apparent discrepancy remain unclear but likely result from differences in species, methodology, and experimental conditions. Notably, Scherer et al. (12) calculated the alveolar slope from two discrete alveolar samples, which could result in directional errors if the alveolar slope was not constant during expiration.

Nonetheless, the finding of a He-to-SF_6 ratio smaller than unity points at the contribution of diffusion-dependent mechanisms to intrapulmonary gas mixing, but the importance of diffusion limitation in normal lungs is expected to be minor.

Conclusions

The alveolar slopes of He and SF_6 administered intravenously (venous loading) or by inspired gas (airway loading) in anesthetized artificially ventilated dogs were interpreted to be mainly attributable to the following mechanisms. *1*) During airway loading, unequal distribution of $\dot{V}A/VA$ combined with sequential emptying was responsible for the alveolar slope; *2*) during venous loading, continuing gas exchange and unequal distribution of $\dot{V}A/\dot{Q}$ combined with sequential emptying were the most important mechanisms underlying the alveolar slope; and *3*) the difference between He and SF_6 reflects the contribution of diffusion-dependent mechanisms, but the limiting role of diffusion limitation in normal lungs is expected to be of minor importance.

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