Quantification of Regional Ventilation in Humans Using a Short-Lived Radiotracer—Theoretical Evaluation of the Steady-State Model

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The accuracy of the steady-state measurement of ventilation by means of a short-lived insoluble inert gas tracer rests with the validity of the steady-state flow equation. This has previously been applied to the qualitative assessment of regional ventilation using krypton-81m, but may potentially be used for the calculation of regional alveolar ventilation per unit alveolar gas volume—$(\dot{V}_A/V_A)_{cal}$—from measurements of the alveolar concentration of the tracer. The steady-state alveolar tracer concentration was calculated for the course of a breathing cycle, using a lung model featuring airways dead space and tidal gas flow. The calculations were made by computer simulations of a lung, characterized by predefined values of parameters describing the lung structure and the mode of ventilation. In the normal lung of supine man at rest (specific alveolar ventilation, ranging from 1.0 to 3.5 min^{-1}) the errors of $(\dot{V}_A/V_A)_{cal}$ relative to the predefined true values range from an overestimation by some 3% in the low ventilation regions to an underestimation by 8% in the best ventilated regions. The errors mainly result from ventilation of the airways dead space, which will influence the distribution of tracer in the lung by the transfer of tracer between regions by way of the common dead space and by the decay of tracer during its transport through the bronchial tree.

J Nucl Med 28: 1144–1154, 1987

Positron emission tomography (PET) allows the regional concentration of radioactive tracers to be measured quantitatively. Using the appropriate models to depict the physiological conduct of the tracers, the regional tracer concentrations measured may be converted into quantitative physiological parameters. In this way, regional organ function can be accurately analyzed in vivo. However, the models applied often involve simplifications which may affect the accuracy of the parameters derived. This paper addresses the accuracy of regional alveolar ventilation as derived from the steady-state concentration in the lung of a short-lived radiotracer inhaled.

Received Apr. 23, 1986; revision accepted Jan. 30, 1987.

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Theory

The steady-state alveolar concentration of a short-lived radioactive tracer during its continuous administration by inhalation, is determined by the balance between the rates of tracer delivery and elimination. The lung model used to assess regional ventilation (*1*) is based on the following assumptions. (For definition of symbols related to parameters, see Appendix.)

1. The delivery and clearance of tracer by ventilation is provided by a constant time independent flow ($\dot{V}_A$).
2. All regions are ventilated in parallel, no gas transfer between regions is considered.
3. Tracer transit through the airways dead space does not affect the tracer concentration in the lung.
4. The distribution volume equals the alveolar gas volume (V_A), which is invariable and constitutes a well mixed compartment.

The concentration of tracer in the pulmonary gas phase

will reach a steady-state level (C_A) given by

$$C_A = \frac{\dot{V}_A/V_A}{\dot{V}_A/V_A + \lambda} C_I, \quad (1)$$

where λ is the radioactive decay constant of the tracer and C_I represents the tracer concentration of inspired air. This concept was introduced by Fazio and Jones (*2*) for the assessment of regional ventilation using ^{81m}Kr ($T_{½}$ = 13.4 s) and the gamma camera. Although the true ventilatory conduct of the lung does not entirely comply with the model used to derive Eq. (1), the steady-state method has proved useful for the qualitative estimation of the relative regional distribution of ventilation in health and disease.

A similar approach can be taken with positron emission tomography and the short lived ($T_{½}$ = 17.4 s) positron emitting isotope 19-neon (*3*). Using PET, the regional concentration of positron emitters can be obtained quantitatively in absolute units in tomographic sections (*4*). In the chest, regional concentration refers to activity per unit volume of the thorax, but a second measurement of the regional pulmonary gas volume allows the tracer concentration to be expressed relative to its volume of distribution. This volume can be obtained from a measurement of regional lung density, using an external radiation source (*5*). Subsequently, Eq. (1) can be rearranged such,

$$\frac{\dot{V}_A}{V_A} = \frac{\lambda}{\frac{C_I}{C_A} - 1}, \quad (2)$$

to provide ventilation per unit alveolar gas volume, i.e., the specific ventilation, in absolute units (min^{-1}). The accuracy of the result is subject to the extent to which the model used to derive Eq. (2) complies with the features of ventilation. Deviations between this model and the lung are as follows.

1. The ventilatory flow rate varies during the breathing cycle and both delivery and clearance of tracer by ventilation are tidal phenomena
2. The airways dead space constitutes a mixing chamber for expired gas and a route for transfer of tracer between regions
3. The tracer decays with time during the transit through the airways dead space
4. The distribution volume of the tracer, i.e., the pulmonary gas volume, changes during a breath in accordance with the ventilatory flow rate

The objective of this paper is to investigate the errors introduced by the assumptions involved in the derivation of Eq. (2). For this purpose a lung model featuring airways dead space and a tidal breathing pattern has been used for the simulation of external measurements of radioactivity within the chest.

METHODS

Lung Model

Three homogenous regions are synchronously ventilated (Fig. 1). Each region comprises gas and tissue, in proportions expressed by the regional lung density (D_L – g lung/cm^3 of the thorax). The pulmonary gas volume constitutes both alveolar gas and gas contained in the airways.

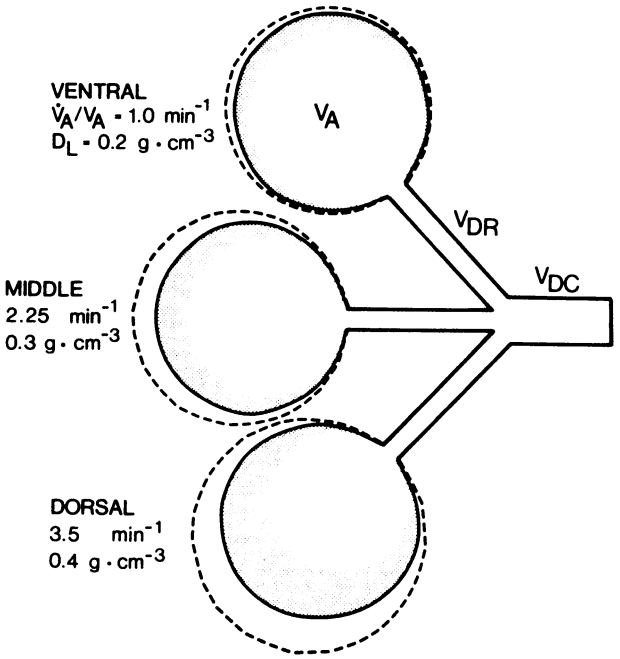

FIGURE 1
The alveolar regions comprise gas (V_A) and tissue (shaded areas). The specific alveolar ventilation ($\dot{V}_A/V_A$) and lung density (D_L) increase from ventral to dorsal regions according to data from normal resting subjects in the supine posture (*5,6*). The difference between end inspiratory (interrupted lines) and end expiratory volume (solid lines) represents both fresh gas reaching the alveolar regions and alveolar gas reinspired from the airways dead space.

The airways dead space V_D includes the common dead space (V_{DC}) shared by all regions and, for each region individually, a regional dead space (V_{DR}). The dead space volumes are regarded as constant throughout the breathing cycle, while the alveolar gas volume will vary with the ventilatory gas flow. The gas flow varies sinusoidally during both inspiration and expiration and has a blunt velocity profile, no longitudinal mixing of gas has been considered. The mode of ventilation can be changed with respect to tidal volume, breathing frequency and the inspiratory/expiratory time ratio (T_I/T_E).

The tidal gas flow to any alveolar region comprises three consecutive fractions with respect to the tracer concentration: (a) gas from the regional dead space, in which the tracer concentration at end expiration equals the regional alveolar concentration; (b) gas from the common dead space, including the mouth piece, with a tracer concentration representing a flow (ventilation) weighted average of gas expelled from all compartments during the previous breath; When inspired, this gas is distributed to all regions, in proportion to the regional flow rate; and (c) fresh gas with a tracer concentration of C_I, as measured at the airway opening.

The model takes into account the decay of tracer during its passage through the airways. The transit time varies during the breath with the flow rate and differs between regions due to the regional differences in ventilation. The amount of gas reaching the alveolar space comprises all three portions inhaled, while only the fresh gas represents alveolar ventilation. The ratio of the regional alveolar ventilation to the regional

alveolar gas volume at mid-inspiration (FRC + 0.5 × tidal volume) defines the regional specific alveolar ventilation $\dot{V}_A/V_A$.

At the onset of expiration, each alveolar region is assumed to represent a well mixed compartment with respect to the tracer concentration. Hence, in each instance, the tracer concentration of the gas expired equals the alveolar concentration. centration of the gas expired equals the alveolar concentration.

Simulation of Regional Measurements

Any regional measurement of radioactivity in the lung, based on external detection, relates to the tracer content of a fixed volume element of the thorax—the study volume (V_S) (Fig. 2). The tracer content of the study volume will vary during the breathing cycle, owing to tidal changes of both the alveolar tracer concentration (C_A) and the pulmonary gas volume in V_S (V_{SG}). Hence, to simulate the result of regional measurements, the time course of both C_A and V_{SG} must be obtained. The regional pulmonary gas volume is related to the regional lung density (D_L), such that

$$V_{SG}(t) = V_S \left(1 - \frac{D_L(t)}{\rho}\right) \quad (3)$$

where ρ is the density of solid lung tissue (1.04 g/cm^3) and t denotes time. $D_L(t)$ is calculated from the predefined values of regional lung density at mid-inspiration and regional alveolar ventilation, assuming that the tissue mass of the lung region is constant throughout the breathing cycle, e.g., neglecting any tidal variations of the vascular pool.

It should be noted that $V_{SG}(t)$ has been considered to include part of the regional airways dead space. Likewise, the study volume tracer content was derived considering both alveolar and airway contributions to tracer within the study volume.

Computer Simulations

The number of lung regions, breathing frequency, and inspiratory/expiratory time ratios (T_I/T_E) are selected. For each region its volume (tissue + gas) at mid-inspiration,

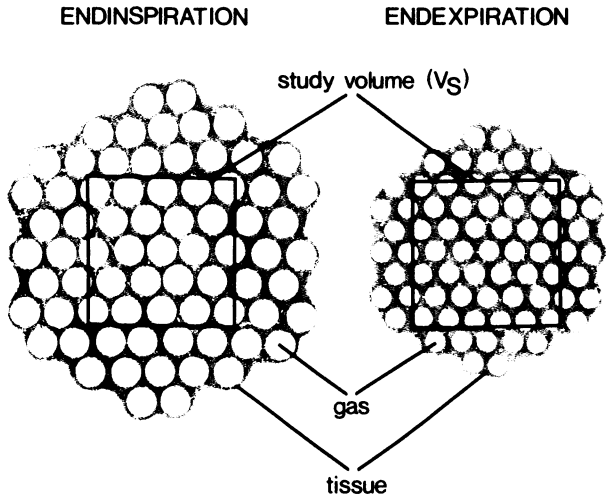

FIGURE 2
The study volume contains gas and tissue and when the lung is inflated both gas and tissue will be displaced from V_S. The gas volume held by V_S is, in each instance, determined by the regional lung density.

specific alveolar ventilation, lung density at mid-inspiration, and the various dead space volumes must be defined.

To obtain the alveolar tracer concentration, the calculations are performed as a stepwise iterative process. The breathing cycle is divided into 800 time increments (Δt). During each of these, the response to alveolar tracer concentration to decay and gas volume displacements is calculated according to simple mass balance equations. Hence, the regional alveolar content of tracer at time $t + \Delta t$ equals the amount of tracer at time t (taking the radioactive decay into account) in addition to the quantity of tracer inhaled (or expired) during the time Δt:

$$C_A(t + \Delta t)\, V_A(t + \Delta t) = C_A(t)\, V_A(t)\, e^{-\lambda \Delta t} + \int_t^{t+\Delta t} C_T(\tau)\dot{V}(\tau)d\tau, \quad (4)$$

where $C_A(t)$ = alveolar tracer concentration at time t;
$V_A(t)$ = alveolar gas volume at time t;
λ = radioactive decay constant of the tracer;
$C_T(t)$ = concentration of tracer in gas entering (or leaving) the alveolar space at time t; and
$\dot{V}(t)$ = ventilatory flow rate at time t.

The initial alveolar and airways dead space tracer content equals zero and the breathing cycle is repeated until a steady-state is reached, i.e., until the end expiratory alveolar tracer concentration differs from the pre-inspiratory level by less than 0.001% in all compartments. Subsequently, to simulate regional measurements extending over numerous breathing cycles, the time weighted average of the study volume tracer content and gas volume are derived. The ratio of tracer content and gas volume corresponds to the regional tracer concentration per unit thoracic gas volume. Regional estimates of specific alveolar ventilation $(\dot{V}_A/V_A)_{cal}$ are then calculated according to Eq. (2). The errors of $(\dot{V}_A/V_A)_{cal}$ are expressed in percent of the true predefined specific alveolar ventilation.

A basic set of model parameters describing the lung and mode of ventilation (Fig. 1), which are typical for a normal resting adult man in the supine posture, are used. The lung is divided into three regions of equal volume (tissue + gas) at mid-inspiration, considered to represent the ventral, middle, and dorsal parts of the lung. The breathing frequency is 12 min^{-1} and T_I/T_E = 0.75. The decay constant of the tracer (2.39 min^{-1}) is chosen to comply with the half-life of 19-neon.

The dead space fractions are defined in terms of the airways generations included (Fig. 3). The volumes have been estimated from Weibel's morphometric model of the airways (*7*). Thus, the total dead space volume (V_D) has been chosen to be 250 ml, of which 220 ml approximates the gas volume of airways generations 1-17 and 30 ml represents the dead space introduced by the tracer gas dispensing system. The common dead space (V_{DC}) extends to include airway generation 5 (85 ml), whilst the regional dead space (V_{DR}) comprises airways generation 6-17, in total 165 ml, i.e., 55 ml for each region. Part of the gas volume observed within the study volume constitutes gas contained in the distal airways (V_{DS}), which is assumed to constitute airways distal to the ninth generation.

Converted into total lung performance, the basic set of parameters yields a total ventilation of 10.5 l/min, of which 28.6% (3.0 l/min) constitutes dead space ventilation. The pulmonary gas volume at mid-inspiration is equal to 3.5 l.

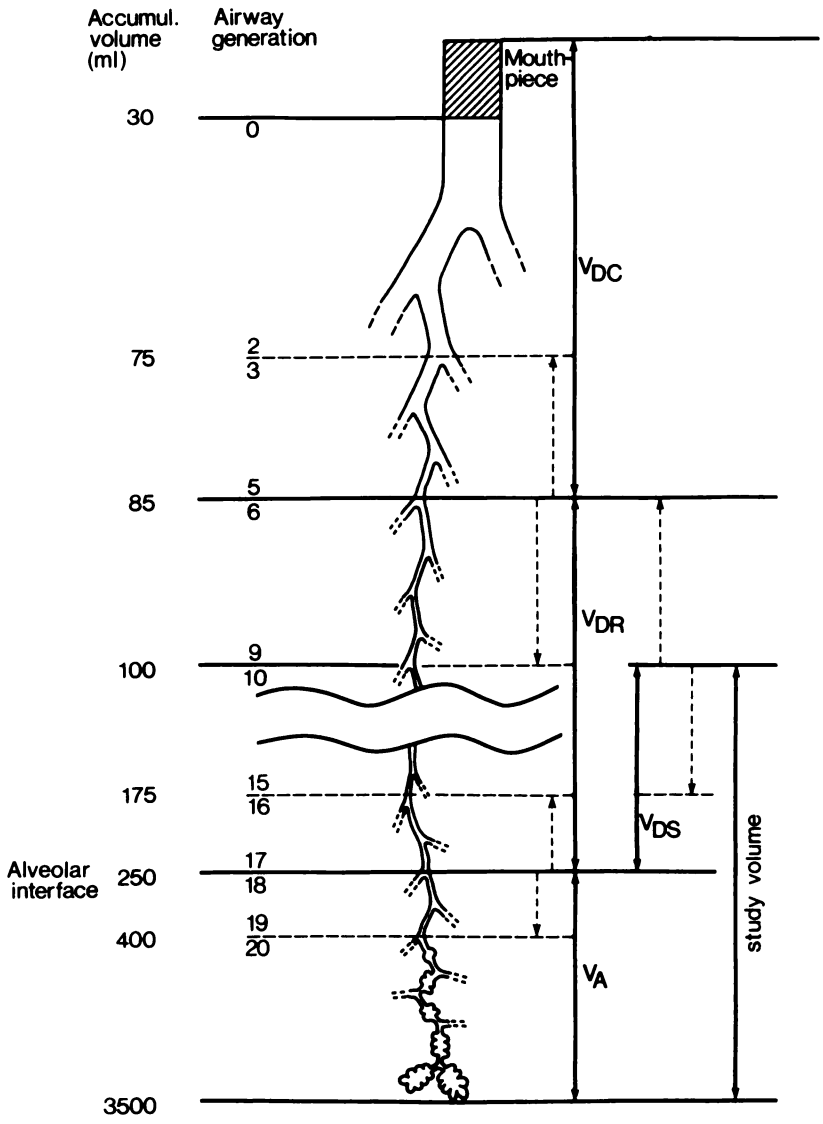

FIGURE 3
Partitioning of the lung in common dead space (V_{DC}), regional dead space (V_{DR}) and alveolar gas volume (V_A). The study volume comprises V_A and part of the regional dead space (V_{DS}). The volumes chosen for the basic set of model parameters are indicated by solid arrows; interrupted arrows indicate the variations considered.

Deviations from the basic set of parameters are described later.

RESULTS

Lung Model at Steady-State

The response of the model during a breathing cycle is illustrated in Figure 4, for the ventral and dorsal parts of the lung, using the basic set of model parameters.

Gas entering or leaving the alveolar space has the tracer concentration C_T (Fig. 4, upper left panel). During inspiration, C_T represents three successive fractions of gas springing from V_{DR}, V_{DC} and fresh gas, respectively. The decay of tracer during transit through the airways dead space serves to reduce C_T in all three fractions inspired. The transit times are influenced by regional differences in ventilation and by the sinusoidal flow pattern. During expiration C_T equals the alveolar tracer concentration (C_A), which will decrease in parallel to the radioactive decay. The fall in C_A continues during inspiration of gas from V_{DR} (Fig. 4, lower left panel) and is accelerated in the dorsal region as gas from V_{DC} enters the alveolar space. Only when fresh gas arrives, does C_A start to increase. The peak concentration is reached slightly before the end of inspiration, as the low final flow rate does not compensate for the decay.

The tidal variations of the alveolar gas volume in a given lung region follow the regional ventilatory gas flow. The amount of gas in the corresponding study volume, however, varies considerably less during the breathing cycle (Fig. 4, upper right panel), since alveoli are displaced as the inflation of the lung changes during tidal breathing (Fig. 2). This is also reflected in the tracer signal attainable by means of external detection techniques, which relate to the amount of tracer within the study volume, and not within a specific set of alveolar units. Together with the tracer held by part of the regional dead space, the displacement of alveoli

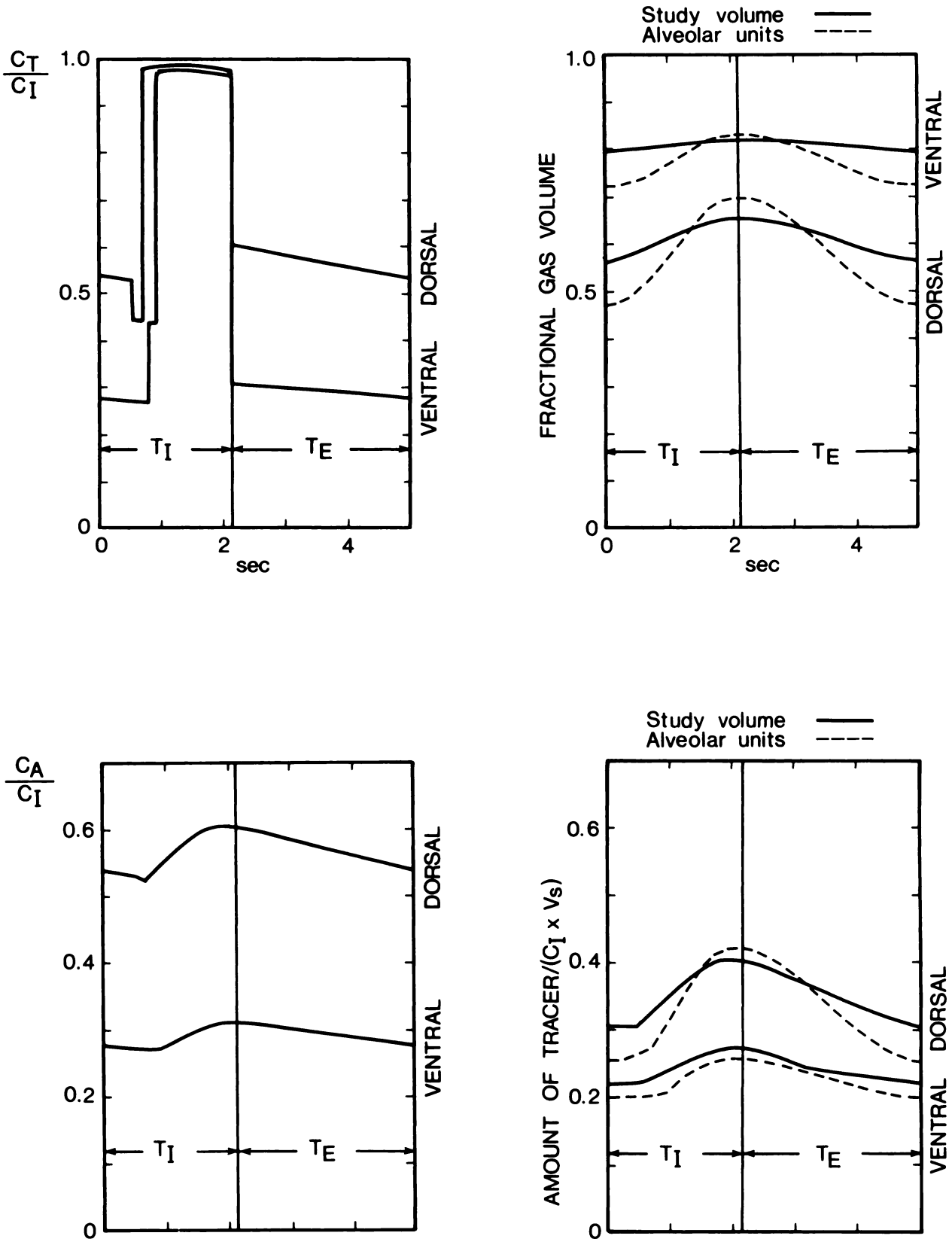

FIGURE 4
Response of ventral and dorsal regions of the lung model at steady-state—symbols are defined in the text. The gas volumes and the amount of tracer have been normalized to the size of the study volume.

TABLE 1
Calculated Estimates of $\dot{V}_A/V_A$ (min^{-1}) for Different Sets of Model Parameters

Model parameters*		$(\dot{V}_A/V_A)_{cal}$ Region			Relative errors (%) region		
		Ventral	Middle	Dorsal	Ventral	Middle	Dorsal
Basic model		1.025	2.166	3.230	+2.5	−3.8	−7.7
V_{DS}=0	a. V_{DC}=85 ml	0.980	2.100	3.158	−2.0	−6.7	−9.8
	b. V_{DC}=0	0.933	2.115	3.268	−6.7	−6.0	−6.6
V_D=0	a. f=12 min^{-1}	1.000	2.254	3.516	<0.1	+0.2	+0.5
	b. f=24 min^{-1}	1.000	2.250	3.503	<0.1	<0.1	+0.1
Alveolar sampling		0.979	2.090	3.126	−2.1	−7.1	−10.7

* The predefined values of $\dot{V}_A/V_A$ amounts to 1.0, 2.25 and 3.50 min^{-1} in the ventral, middle and dorsal region, respectively. See text for details.

accounts for the differences in tracer activity between the study volume and the corresponding alveolar units (Fig. 4, lower right panel).

Regional Specific Alveolar Ventilation

Using the basic set of model parameters, the errors of $(\dot{V}_A/V_a)_{cal}$ were +2.5%, −3.8%, and −7.7% in the ventral, middle, and dorsal compartment, respectively, (Table 1).

When the distal airways within the study volume are eliminated (V_{DS} = 0), gas within the study volume represents alveolar gas only. This results in slightly lower values of $(\dot{V}_A/V_A)_{cal}$ in all regions (Table 1, section 2a). If the different regions are ventilated strictly in parallel and the transfer of gas between regions is neglected, V_D constitutes regional dead space only. This corresponds to V_{DR} of 83 ml for each region and V_{DC} = 0, which results in an almost uniform underestimation (~6–7%) of $\dot{V}_A/V_A$ (Table 1, Section 2b).

In a lung model without any dead space, i.e., without gas mixing and without transport tracer decay, the errors are <0.5% (Table 1, section 3a). Increasing the breathing frequency, further reduces the differences between true and calculated specific alveolar ventilation (Table 1, Section 3b).

The simulation of an invasive method that allows sampling of alveolar gas is represented by the time weighted average of the alveolar concentration of tracer. This gives values of $(\dot{V}_A/V_A)_{cal}$ close to those obtained for V_{DS} = 0 (Table 1, Sections 4 and 1, Section 2a), since the tracer present in the airways plays no role in either of these measurements.

The accuracy of $(\dot{V}_A/V_A)_{cal}$ in regions with alveolar ventilation and lung density outside the range considered for the basic set of data, was calculated by the inclusion of a fourth compartment in the model. $\dot{V}_A/V_A$ in this additional region, comprising ¼ of the lung, was varied from 0.1 min^{-1} to 6.0 min^{-1} with D_L equal to 0.1 g/cm^3 and 0.6 g/cm^3. All other features of the model were unchanged compared with the basic set. $(\dot{V}_A/V_A)_{cal}$ in the additional region is shown in Figure 5. Although the relative errors are substantial in regions with very low ventilation (Table 2), the errors in absolute numbers are small over the whole range. The inclusion of a fourth compartment will slightly affect $(\dot{V}_A/V_A)_{cal}$ in the primary regions, due to the interregional transfer of tracer by way of the common dead space (Table 2).

Influence of Model Assumptions

The basic assumptions concerning the position of the alveoli-to-airways stable interface and the position of

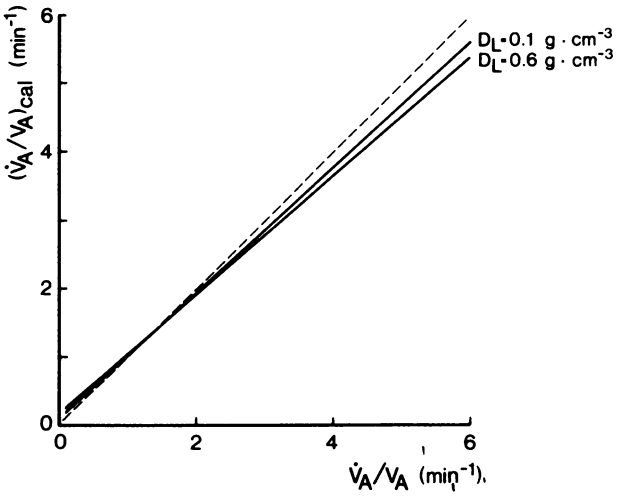

FIGURE 5
$(\dot{V}_A/V_A)_{cal}$ for different values of true specific alveolar ventilation ($\dot{V}_A/V_A$) and lung density (D_L). The region considered comprises ¼ of the lung; the remaining ¾ are depicted by the basic set of model parameters. The line of identity is indicated (– – –).

TABLE 2
Accuracy of $(\dot{V}_A/V_A)_{cal}$ Following Inclusion of a Region with Ventilation and Density Widely Outside the Normal Range

Model parameters*		Relative errors (%) region			Added region
		Ventral	Middle	Dorsal	
Basic model		+2.5	−3.8	−7.7	—
Added region:	D_L=0.6 g cm^{-3}	+2.3	−4.8	−9.5	+109
V_A/V_A=0.1 min^{-1}	D_L=0.1 g cm^{-3}	+2.1	−4.9	−9.5	+50
Added region:	D_L=0.6 g cm^{-3}	+3.5	−1.7	−5.0	−10.1
V_A/V_A=6.0 min^{-1}	D_L=0.1 g cm^{-3}	+3.0	−1.0	−3.5	−6.8

* The basic three-compartment models (1) has been extended by the inclusion of a fourth region, which comprises ¼ of the lung.

the branching point between common and regional dead space were modified (Fig. 3), keeping all other parameters constant. Extending V_D in the distal direction, the errors of $(\dot{V}_A/V_A)_{cal}$ slightly increase (Fig. 6). Similarly, there is a progressively small increase in the errors as the branching point between V_{DC} and V_{DR} is displaced distally (Fig. 7).

$(\dot{V}_A/V_A)_{cal}$ will change with the number of airways generations included in the study volume. Gas and tracer held by the airways serve to increase $(\dot{V}_A/V_A)_{cal}$ in all regions (Fig. 8); more so in the ventral region because of its low alveolar tracer concentration (low ventilation).

The influence of the breathing pattern was studied by assigning different values to the breathing frequency and to T_I/T_E with the alveolar ventilation maintained at constant level in each region. High breathing frequency leads to a considerable increase in the errors of $(\dot{V}_A/V_A)_{cal}$, while changes in T_I/T_E have small effects (Fig. 9).

To the extent that a sequential pattern of ventilation may prevail, regions with a relatively high flow rate during the early parts of the inspiration will receive a higher proportion of the dead space ventilation than they would if ventilation was strictly synchronous. An attempt to assess the effects of sequential ventilation was made by assigning the first 50% of V_{DC} inhaled to one of the regions. The residual gas from V_{DC} was then divided between all regions in proportion to the ventilation. If the early part of the inspiratory gas flow is directed to the ventral region, alveolar ventilation in this region is further overestimated, and the errors increase from +2.5% to +6.0%. When directed to the dorsal part $(\dot{V}_A/V_A)_{cal}$ will decrease, and the underesti-

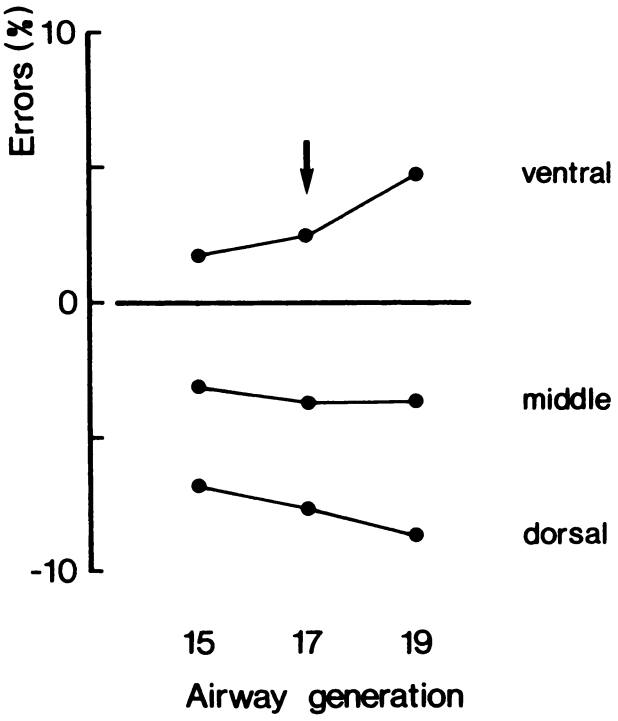

FIGURE 6
Relative errors of $(\dot{V}_A/V_A)_{cal}$ for different positions of the alveoli-to-airways interface. Arrow indicates the distal delineation of V_D, chosen for the basic model (generation 17).

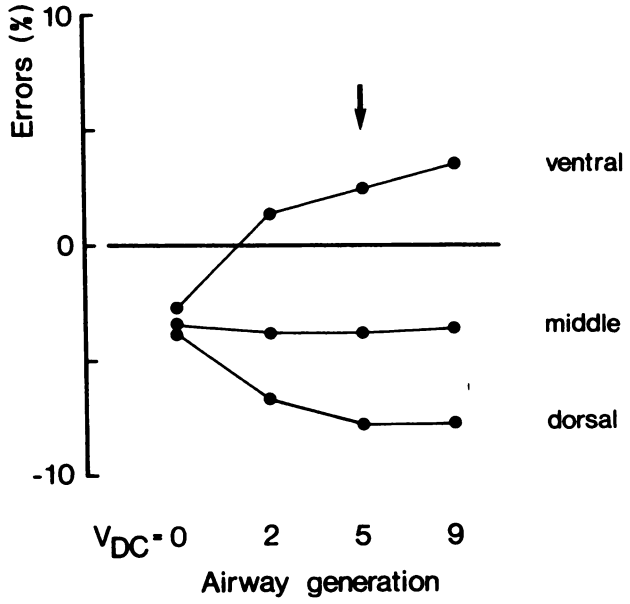

FIGURE 7
Relative errors of $(\dot{V}_A/V_A)_{cal}$ for different positions of the distal delineation of the common dead space (V_{DC}). V_{DC} = 0 corresponds to parallel ventilation. The arrow indicates V_{DC}, chosen for the basic set of model parameters.

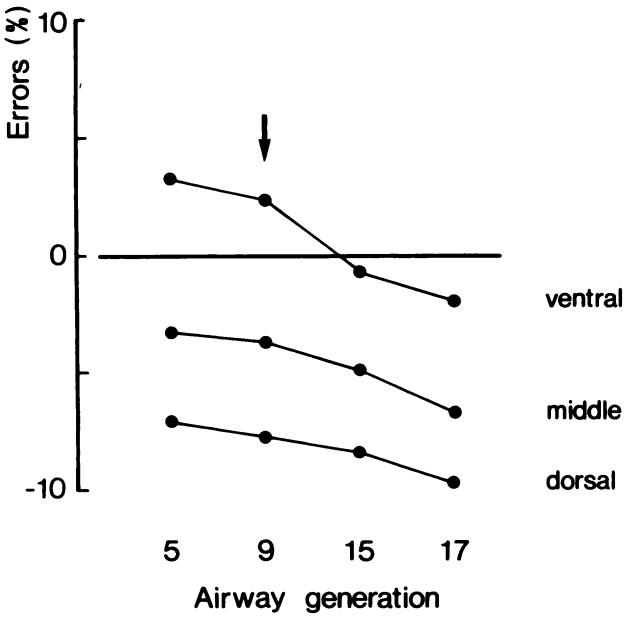

FIGURE 8
Relative errors of $(\dot{V}_A/V_A)_{cal}$, for different number of airway generations included in V_{DS}. The dead space volume included (V_{DS}), comprises airways distal to the generations indicated, extending to the alveolar interface at the 17th generation. Airway generation 17, as indicated, corresponds to $V_{DS} = 0$. The arrow denotes V_{DS}, as chosen for the basic model.

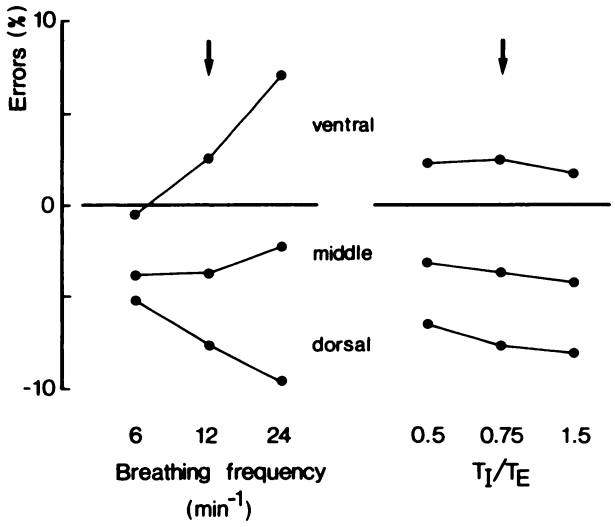

FIGURE 9
Relative errors of $(\dot{V}_A/V_A)_{cal}$ for different breathing patterns. The arrows indicate the pattern chosen for the basic set of model parameters.

mation of specific alveolar ventilation goes from −7.7% to −10.6%. The middle region is little affected by the based distribution of the dead space ventilation, the errors going from −3.8% to −4.6%.

DISCUSSION

Earlier use of the steady-state method for the measurement of ventilation has been associated with qualitative techniques of obtaining the regional distribution of the tracer. Thus, the operational equation, based mainly on the assumption of a constant, time independent ventilatory flow to parallel compartments, has largely been used in a qualitative way. However, with the development of positron emission tomography, the regional tracer concentration can be measured in absolute units. This enables the operational equation to be solved and ventilation to be derived quantitatively. In this context, when the use of the method is no longer confined to qualitative measurements of tracer concentration, the validity of the model itself becomes the limiting factor for the accuracy of the steady-state method. There are obvious differences between the model used to derive the steady-state equation and features of ventilation in man. The extent to which these affect the quantitation of regional alveolar ventilation has been appraised by means of an extended model featuring airways dead space and tidal breathing.

Parameters describing the lung and mode of ventilation have been chosen from a range that is physiologically plausible. It should be noted that the predefined values of alveolar ventilation refer to the volume of fresh gas transferred to the alveolar compartment in each breath, i.e., to the mechanical aspects of ventilation rather than to gas exchange. As the dead space volumes are the most critical factors, we have preferred to use values that may imply a slight overestimation, in that the Weibel data (*7*) relate to the airways system at ¾ of maximal inspiration. The volume of the airways dead space, smaller airways in particular, is likely to change slightly during the breathing cycle. For a given alveolar ventilation, this may result in a small distortion of the time course of the volume flow of gas to the alveolar region. The influence of the flow pattern per se, however, is insignificant (see below).

Factors Affecting Accuracy of $(\dot{V}_A/V_A)_{cal}$

The errors of $(\dot{V}_A/V_A)_{cal}$ result from the combined influence of different features of gas transport in the lung, the relative importance of which can be assessed by changing the conditions of tracer transport in the model.

Airways Dead Space

The importance of the airways dead space follows from the reinspiration of alveolar gas. Total elimination of the airways dead space ($V_D = 0$) results in a trivial difference between $(\dot{V}_A/V_A)_{cal}$ and the true specific alveolar ventilation in all regions. The small residual errors are caused by the sampling technique. Using external detection of radiation, higher weight will be given to the alveolar tracer concentration at high (end inspiratory) alveolar gas volumes that at low (end expiratory) volumes, and the true time weighted average

of the alveolar tracer concentration will be slightly overestimated. Increasing the breathing frequency, the tidal changes of the pulmonary gas volume get smaller and the errors of $(\dot{V}_A/V_A)_{cal}$ are further reduced, reflecting a progressive approach of the model to the prerequisites of the steady-state flow equation.

Implementing the airways dead space in the model, parallel ventilation ($V_{DC} = 0$) results in an almost uniform underestimation of the true specific alveolar ventilation by 6–7%. The magnitude mainly reflects the influence of tracer decay during transport through the bronchial tree.

Gas mixing and the subsequent exchange of tracer between regions are attributable to the common dead space, and results in a substantial scatter of the errors between regions. For high ventilation regions, the gas inhaled from V_{DC} holds lower tracer concentration than the gas expelled. Hence, the net transport of tracer to high ventilation regions will be reduced, resulting in a further underestimation of $\dot{V}_A/V_A$. The opposite is true for regions of low ventilation, which tends to cancel the errors caused by tracer decay during transport.

Breathing Pattern

The influence of the inspiratory/expiratory time ratio was found to be negligible. This implies that the assumption of a specifically sinusoidal flow pattern does not significantly affect $(\dot{V}_A/V_A)_{cal}$. Changes in the breathing frequency, however, have a direct effect on the dead space ventilation. With constant alveolar ventilation, higher breathing frequency serves to increase the dead space ventilation relative to the alveolar ventilation. Thus, the tracer transport between regions will be enhanced, with a progressive divergence of the relative errors of $(\dot{V}_A/V_A)_{cal}$.

Sampling Technique

The application of external sampling techniques results in measurements which include parts of the tracer held by the airways. During most of the inspiration, the airways tracer concentration, being just slightly below C_I, exceeds the alveolar concentration. Thus, tracer held by the airways within the study volume, contributes to and serves to increase the study volume tracer content. $(\dot{V}_A/V_A)_{cal}$, will therefore be higher than if the study volumes represented alveolar gas only ($V_{DS} = 0$) or if direct sampling of alveolar gas could be applied. This is of special importance in regions of very low alveolar ventilation (Fig. 5), where the amount of tracer held by the alveolar compartment is small by virtue of the small amounts of tracer delivered.

Model Assumptions

The distribution of tracer within the airways during expiration equals the flow weighted average of the alveolar concentration of the regions subtended. This will deviate considerably from the concentration of the individual regions only in parts of the bronchial tree subtending regions of widely different ventilation. In the distal parts mixing will have little influence, at least in the normal lung, where adjacent regions are likely to have a similar alveolar ventilation. The result of the continuous process of gas mixing in the bronchial tree, has been approximated by a step distribution of the tracer concentration at end expiration. In the model, each compartment is subtended by airways which constitute the regional dead space (V_{DR}). The tracer concentration in V_{DR} at end expiration equals the regional alveolar concentration. In the common dead space (V_{DC}), comprising the proximal part of the airways, all regions will contribute to the tracer content in relation to the regional gas flow. The volume of V_{DC}, i.e., the position of its distal delineation, will determine the extent of gas transport between regions. The distal delineation of V_{DC} defines the airways generation, distal to which the full range of $\dot{V}_A/V_A$ considered, is represented. For the basic set of model parameters used, this corresponds to a $\dot{V}_A/V_A$ range of 1.0–3.5/min distal to airways generation 5, i.e., well below the segmental level. In the normal lung, this is probably an overestimation of V_{DC}. However, extending V_{DC} from the distal end of generation 2 to the distal end of generation 9, i.e., increasing V_{DC} by some 30%, does not appreciably affect the corresponding differences between calculated and true alveolar ventilation.

Tracer Transport

The assumption that tracer transport is related to volume flow only—that is, disregarding diffusion—needs further consideration. The interaction between convective and diffusive transport during inspiration results in an axial concentration gradient—the stationary alveolar interface. This extends mainly from airways generation 15 to 19 (*8*) in the normal lung. Proximal to the interface, convective transport dominates and the regional distribution of gas transport will follow the volume flow (*9*). Hence, insofar as the branching points between the regions considered are located proximal to generation 15, tracer transport to the different regions will largely follow the volume flow. In parts distal to the alveolar interface diffusive transport dominates and only minor concentration gradients exist. This could be regarded as the physiological limitation of the spatial resolution of the steady-state method. Volume flow can not be resolved within a region where different parts are in diffusion equilibrium with regard to the tracer concentration. The sloping concentration profiles in the distal part of the airways system have been approximated by a step alveolar interface located at the distal end of generation 17. The gas volume distal to this is considered as a well mixed alveolar compartment. The location of the alveolar interface is by no means critical, a shift in the position of the interface has little effect on the accuracy of $(\dot{V}_A/V_A)_{cal}$ (Fig. 6).

In airways where convective gas flow prevails a non-uniform velocity profile results in the longitudinal mixing of gases. Longitudinal mixing serves to smooth the tracer concentration gradients between the different fractions of gas inspired (c.f. Fig. 4, upper left panel) and to slightly modify the arrival of tracer to the alveolar regions. The result of this is similar to that of changes in the inspiratory flow pattern, which were found not to influence $(\dot{V}_A/V_A)_{cal}$ significantly.

The exchange of physiological gases at the alveolar level slightly affects the transport of tracer. The amount of oxygen extracted from a lung region generally differs from the amount of carbon dioxide expelled, as expressed by the respiratory quotient. For the normal lung, with respiratory quotients in a narrow range around 0.8, the gas volume expired is slightly smaller than the volume inspired. The lung model, thus, imposes a small overestimation of the expiratory clearance of tracer. This is, however, partly balanced by small amounts of tracer being cleared by blood flow for tracers with a small but finite solubility in blood. The overall effect is small and has been neglected in the analysis.

Sequential Gas Flow

The assumption of synchronous ventilation may not be met in all circumstances (*10*). To the extent that different regions of the lung are inflated in sequence, this will affect the regional dead space ventilation. Regions receiving most of the volume inhaled during the early part of the inspiration, will therefore get most of the gas inhaled from the common dead space. In addition, sequential deflation of different regions will cause a stratification of the tracer concentration in the common dead space during expiration. Both factors may contribute to a variable and unpredictable degree of tracer transport between regions. However, the calculations made should provide a reasonable assessment of the magnitude of the influence of sequential differences on the measurement of alveolar ventilation. Not even a gross distortion of the distribution of the dead space ventilation between different regions causes a substantial detraction from the basic results in the normal lung.

SUMMARY

The accuracy of the steady-state method, as applied to the derivation of ventilation from quantitative measurements of the regional distribution of a short-lived radiotracer (19-neon, $T_{½}$ = 17.4 sec) and of the regional pulmonary gas volume, is subject mainly to the influence of the airways dead space.

The decay of tracer during its passage through the bronchial tree will cause an underestimation of the true specific alveolar ventilation on the order of 6–7% during normal conditions. The interaction between regions, in terms of the transfer of tracer from regions of higher to regions of lower than average ventilation—via the common dead space—results in a further underestimation of specific alveolar ventilation in high $\dot{V}_A/V_A$ regions. (3.5 min^{-1}) of some 3–4% and an overestimation of almost 5% in low $\dot{V}_A/V_A$ regions (1.0 min^{-1}).

The effect of external detection, i.e., sampling a fixed thoracic volume element, is to overestimate the true values of $\dot{V}_A/V_A$ by ~3–5%. This results in a reduction of the errors associated with the airways dead space—providing an overall distribution of errors in the normal lung ranging from an overestimation of 3% to an underestimation of 8%.

The breathing pattern, per se, will not appreciably affect the accuracy. However, for a given ventilation, the dead space ventilation and, therefore, the transfer of tracer between regions is directly related to the breathing frequency. Hence, the divergence of the errors between regions progressively increases with increasing breathing frequency.

APPENDIX

Summary of Symbols

If not indicated otherwise, symbols relate to regional values of the parameters.

C_A,$C_A(t)$: alveolar concentration of the radioactive tracer;
C_I: tracer concentration in inspired air;
$C_T(t)$: concentration of tracer in gas entering (or leaving) the alveolar space at time t;
D_L,$D_L(t)$: lung density;
λ: radioactive decay constant of the tracer;
ρ: density of gas free lung tissue (1.04 g/cm^3);
$T_E(T_I)$: duration of the expiratory (inspiratory) part of the breathing cycle;
V_A,$V_A(t)$: alveolar gas volume;
V_D: total volume of the airways dead space;
V_{DC}: total volume of the common dead space;
V_{DR}: volume of the regional dead space;
V_S: study volume referring to a fixed volume element of the thorax;
V_{SG},$V_{SF}(t)$: gas volume of the study volume;
$\dot{V}_A$: alveolar ventilation (breathing frequency · alveolar tidal volume);
$\dot{V}(t)$: ventilatory flow rate;
$(\dot{V}_A/V_A)_{cal}$: specific alveolar ventilation (turnover of alveolar gas) as calculated from the literature model (Eq. 2), using simulated values of the alveolar concentration of tracer.

For the time dependent parameters the value at time t has been indicated by inclusion of "(t)" after the symbol.

ACKNOWLEDGMENTS

This study was jointly supported by the Swedish National Association against Chest and Heart Diseases, the Swedish Medical Research Council (grant number 02872) and the Medical Research Council of the United Kingdom.

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