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ORIGINAL ARTICLE

A. C. M. Schrikker · H. Wesenhagen · S. C. M. Luijendijk

Intrapulmonary gas mixing and dead space in artificially ventilated dogs

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Abstract In this study we have investigated the effects of breath holding and of the physical properties of gases on four different respiratory dead spaces (V_D): the Fowler, the physiological, the washout and the inert gas dead space. The experiments were performed with dogs which were ventilated artifically with breathing patterns with different post-inspiratory breath holding times (t_a) of 0, 0.5, 1.0 and 2.0 s. Tracer amounts of acetone, ether and enflurane were infused continuously into a peripheral vein and a bolus of a mixture of krypton, Freon12 and SF_6 was introduced into the peritoneal cavity. After reaching steady state, samples of arterial blood, mixed venous blood and mixed expired air were taken simultaneously. From the partial pressures (P_a, $P_{\bar{V}}$ and $P_{\bar{E}}$ respectively) we determined the excretion ($\bar{E} = P_{\bar{E}}/P_{\bar{V}}$), retention ($R = P_a/P_{\bar{V}}$) and the physiological dead space fraction ($V_{D,phys}/V_T = (1 - P_{\bar{E}}/P_a)$) for each gas, where V_T is tidal volume. Further, we recorded the expirograms of the six tracer gases and of CO_2 from which the Fowler dead space fractions ($V_{D,Fowler}/V_T$) of the different gases were determined. Also the washout dead space fractions ($V_{D,washout}/V_T$) for He and SF_6 were determined as well as the inert gas dead space fraction ($V_{D,MIGET}/V_T$) with the use of the multiple inert gas elimination technique (MIGET).

With the exception of $V_{D,phys}/V_T$ for SF_6, all dead space fractions decreased with increasing t_a. $V_{D,phys}/V_T$ for the poorly soluble gas SF_6 was considerably larger than $V_{D,phys}/V_T$ for the remaining gases. For the highly soluble acetone V_{Fowler}/V_T was considerably smaller than $V_{D,Fowler}/V_T$ for the other gases. $V_{D,washout,SF6}/V_T$ was always larger than $V_{D,washout,He}/V_T$ and $V_{D,Fowler,SF6}/V_T$. Further, $V_{D,phys}/V_T$ was larger than $V_{D,Fowler}/V_T$ for SF_6 and acetone. However, for gases with intermediate solubility in blood $V_{D,phys}/V_T$ tended to be smaller than $V_{D,Fowler}/V_T$. We conclude that the respiratory dead spaces are affected by the breathing pattern and by the physical properties of gases, i.e. their diffusivity in alveolar gas and their solubility in blood or lung tissue.

Key words Gas transfer · Diffusion · Expiratory concentration volume curves · Dead space · Blood solubility · Multiple inert gas elimination technique

A. C. M. Schrikker
Department of Medical Physiology and Sports Medicine, University of Utrecht, P.O. Box 80043, 3508 TA, Utrecht, The Netherlands

H. Wesenhagen
Department of Anaesthesiology, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

S. C. M. Luijendijk (✉)
Department of Pulmonology, University Hospital Maastricht, University of Limburg, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands

Introduction

The tidal nature of breathing in mammals is the consequence of the morphology of their lungs where inspired air and expired gas are conducted through the same airways. The effects of the tidal nature of breathing on pulmonary gas exchange are closely related to the physical properties of the gases involved. The present paper focusses on the dead space.

During inspiration mixing of inspired air with residual gas in the conducting airways is poor. As a result, a transition zone between inspired air and residual gas is formed in the regions of the respiratory bronchioles where diffusive mixing of inspired air with residual gas takes place. During a post-inspiratory apnoea this mixing process is continued and, accordingly, the dead space volume decreases with increasing duration of the post-inspiratory apnoea [1, 12, 15, 18]. The aims of the present study were twofold. First to extend this observation to different types of dead space – Fowler, physiological, inert gas and washout dead space – all

measured under the same conditions for gases with different solubility in blood and lung tissue, ranging from poorly to highly soluble gases, and for gases with different diffusivity in alveolar gas so as to obtain a more complete picture of the effects of diffusion-limited gas mixing in the lung on dead space. Second, to use these data and further observations made in the study to obtain a better insight into the properties of the gas exchange processes that take place in the lung during tidal breathing.

Materials and methods

Experiments were carried out on eight mongrel dogs weighing 11.5–18.5 kg (mean 14.2 kg) fasted for at least 16 h. After premedication with ketaminehydrochloride (10 mg·kg^{-1} i.m.) and induction with 50–100 mg thiopental i.v., anaesthesia was maintained by continuous i.v. infusion of 0.5–1.0 mg·kg^{-1}·h^{-1} midazolamhydrochloride combined with 0.15–0.30 mg·kg^{-1}·h^{-1} of the muscle relaxant vercuronium bromide and 0.01–0.02 mg·kg^{-1}·h^{-1} fentanyl. The supine dogs were intubated with a cuffed endotracheal tube connected to a piston pump controlled by a microcomputer (MCZ1/05, Zylog). This microcomputer also controlled the inlet and outlet valves of the breathing circuit and the valve between the pump and the experimental animal (Fig. 1). The respiratory rate was fixed at 15 breaths/min, and the tidal volume (V_T, about 20 ml·kg^{-1}) was adjusted so that the end-tidal partial pressure of CO_2 was about 4 kPa. The instrumental dead space between the valves 2 and 3 and the distal end of the endotracheal tube was 35.5 ml (Fig. 1). The computer program further allowed the use of four preselected breathing patterns which differed with regard to the duration of the post-inspiratory apnoea (t_a = 0, 0.5, 1.0 and 2.0 s; Fig. 1). Further details concerning the operation of the piston pump have been reported previously [17].

Expired air was conducted through a heated metal tube to a mixing box that was kept at 40 °C to prevent condensation of water vapour. The outlet of the mixing box was connected to a Fleisch flow transducer head (No. 3). The integrated flow signal ($\int \dot{V} dt$) from the pneumotachograph was sampled with a PDP11/73 computer (Fig. 1).

The femoral artery was catheterized to permit sampling of blood and monitoring of blood pressure and heart rate. An angiographic balloon catheter (Berman) was introduced via the jugular vein and positioned in the pulmonary artery to obtain mixed venous blood samples. The catheters were kept patent during the experiment with the aid of a pressure infuser (Tycos) filled with physiological salt solution. The tracer gases enflurane (0.04 vol%), ether (0.6 vol%) and acetone (1.25 vol%) in physiological salt solution were infused into the femoral vein at 1.4 ml · min^{-1} using an infusion pump. The less soluble tracer gases were administered as a bolus of gas into the peritoneal cavity (50 ml of SF_6 together with 30 ml of Krypton and 30 ml of Freon12). Further details concerning the choice of these tracer gases and their blood/gas partition coefficients (λ) have been reported previously (see discussion in [17]). The signal for argon was used to monitor the constancy of the performance of the MSM during the measurements.

Washout dead space fraction

Each experiment started with the determination of the end-expiratory lung volume ($V_{L,E'}$) and the specific ventilation ($\dot{V}_A/V_{L,E'}$). For this purpose a 190-ml syringe containing He (2 vol%), SF_6 (2 vol %) and air was connected to a port in the metal tube which connected the pump with the endotracheal tube (Fig. 1). After stopping the pump at the end of an expiration, and with all valves closed, rebreathing was started with the aid of the syringe, i.e. the content of the syringe was emptied into the system (tubes and end-expiratory lung volume) and subsequently the same volume was withdrawn again. This manoeuvre was repeated 10 times over about 20 s to allow He and SF_6 to equilibrate between the gas mixtures in the syringe and in the lung of the dog. Immediately thereafter the pump was restarted and the subsequent washout of He and SF_6 recorded for 1.5 min. The partial pressures of both He and SF_6 in inspired and expired gas were measured with a mass spectrometer (MSM) (Fig. 1, port 7). Argon was measured as a reference gas during this procedure to allow corrections to be made for changes in the partial pressures of He and SF_6 resulting from the decreasing lung volume during the rebreathing manoeuvre due to continued gas exchange. The rebreathing manoeuvre and the washout were carried out subsequently for each of the selected breathing patterns.

During the washout the decrease in the partial pressures of He and SF_6 in residual gas for a single breathing cycle is equal to: $V_{L,E'}/(V_{L,E'} + V_{T,A})$, where $V_{T,A}$ is the volume of tidal air that mixes with residual gas. For N subsequent breathing cycles, the decrease in partial pressure is equal to:

$$P_N/P_o = [V_{L,E'}/(V_{L,E'} + V_{T,A})]^N \quad (1)$$

where P_O and P_N are the partial pressures of the tracer gas in end-tidal gas at the beginning and at the end of the N breathing cycles respectively. From this equation the specific ventilation can be calculated:

$$\dot{V}_A/V_{L,E} = f \cdot V_{T,A}/V_{L,E'} = f \cdot [(\sqrt[N]{P_O/P_N}) - 1] \quad (2)$$

where f is the respiratory frequency. The value of N used to determine the specific ventilation was 15, usually cycles 2 through 16. $\dot{V}_A$ was obtained from the product of $V_{L,E'}$ and $\dot{V}_A/V_{L,E'}$. The washout dead space fraction was calculated from: $V_{D,washout}/V_T = (\dot{V}_E - \dot{V}_A)/\dot{V}_E$, where $\dot{V}_E = f \cdot V_T$.

Fowler dead space fraction

About 1 h after the start of the infusion of the tracer gases, when the partial pressures of these gases in mixed expired air measured

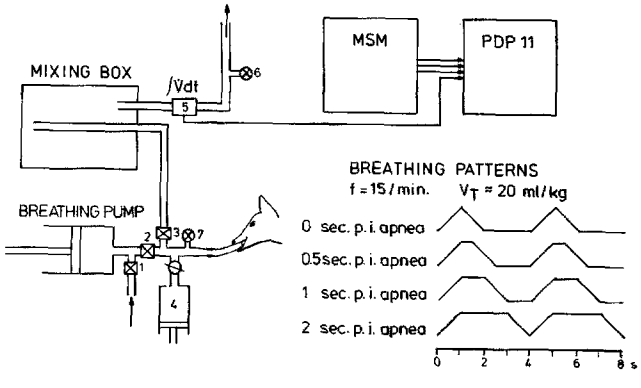


Fig. 1 Schematic representation of the experimental set-up. *1*, *2* and *3* are the inlet valve, the valve between pump and experimental animal and the outlet valve respectively. Valves *1*, *2* and *3* and the breathing pump were operated by a microprocessor. *4* Syringe (190 ml), used for the determination of the end-tidal lung volume. *5* Fleisch flow transducer head (No. 3), *MSM* Quadrupole mass spectrometer (Balzers, QMG511), used to measure the partial pressures of the tracer gases in mixed expired air (*6*) or in inspired and expired air (*7*). *PDP11* A PDP11/73 microcomputer (DEC) used for on-line data sampling. The inset shows the breathing patterns for the different durations of the t_a, period of post-inspiratory apnoea (f breathing frequency, V_T tidal volume)

at Fig. 1 port 6, were stable, expirograms were recorded one-by-one for all tracer gases and for CO_2, and successively for each breathing pattern, by the PDP11/73 computer. Each recording took 75 s and the sampling frequency was 100 Hz. From the expirograms the Fowler dead space ($V_{D,Fowler}$) was determined [5]. In computing $V_{D,Fowler}$ corrections were made for the transit time of the sample capillary (90 ms) and for the time constant of the MSM (ca 15 ms). For each tracer gas $V_{D,Fowler}/V_T$ was calculated from ten expirograms per breathing pattern.

Physiological dead space fraction

Finally, blood and gas samples for the determination of the excretion (E) and retention (R) were collected. The catheters used for blood sampling were first flushed with a few millilitres of blood. Samples were collected in dry heparinized, 100-ml glass syringes. A 100-ml sample of mixed expired air was collected at the same time as the arterial and mixed venous blood samples. A second sample of mixed expired air was taken 1 min later. The samples of mixed expired air were kept in an oven at a temperature of 40 °C until analysis, along with the headspaces of the blood samples. The exact volumes of the 10-ml blood samples were determined gravimetrically using the specific weight of the blood. The samples were then equilibrated with 30 ml air in a shaking water bath at the same temperature as measured in the experimental animal. A headspace volume of 30 ml was chosen in order to have enough gas to measure the partial pressures of the tracer gases for at least 0.5 min. The sample flow of the MSM was 20 ml · min^{-1}. After at least 30 min equilibration the first sample of mixed expired air was analysed with the MSM. After that the headspaces of the mixed venous and arterial blood samples were analysed and finally the second sample of mixed expired air of the series. With the aid of the λ values (Table 1) and the ratio of the volumes of headspace and blood the partial pressures of the tracer gases in the arterial (P_a) and mixed venous ($P_{\bar{v}}$) blood samples were calculated: $P = P_{eq}\,[1 + V_g/(V_{bl} \cdot \lambda)]$, where P_{eq} is the partial pressure of the tracer gas measured in the gas phase after equilibration and (V_g/V_{bl}) is the ratio of the headspace volume to blood volume (≈ 3). From the results of the two mixed expired air samples per series the mean value ($P_{\bar{E}}$) was calculated and from the collected data E ($= P_{\bar{E}}/P_{\bar{v}}$) and R ($= P_a/P_{\bar{v}}$) of the tracer gases determined. The data for E and R were then used to compute the physiological dead space fractions of the different tracer gases according to: $V_{D,phys}/V_T = (1 - P_{\bar{E}}/P_a)$, where $P_{\bar{E}}/P_a = E/R$.

Inert gas dead space fraction

The ventilation/perfusion distribution was determined from the E and R data for each breathing pattern according to the method of Wagner et al. [20, 21], and $V_{D,MIGET}/V_T$ (MIGET, multiple inert gas elimination technique) was calculated from the results of this fitting procedure.

Table 1 Physical properties of the inert gases. Data are means ± SD (M molecular weight, λ, blood/gas partition coefficient, m/e, mass-to-charge ratio at which the gases were measured, *determined in this laboratory according to the method described by Wagner et al. [21])

	M	λ	Reference	m/e
SF_6	146	0.007	[9]	127
Krypton	84	0.06	[6, 8, 22]	84
Freon12	121	0.24 ± 0.05	*	85
Enflurane	184	3.0 ± 0.1	*	117
Ether	74	11.9 ± 0.7	*	59
Acetone	58	312	[21, 23]	58

With the measurements of $V_{D,washout}$, $V_{D,phys}$ and $V_{D,MIGET}$ the total instrumental dead space of 35.5 ml was included, whereas for $V_{D,Fowler}$ the instrumental dead space was only 17 ml (the volume of the endotracheal tube up to port 7, (Fig. 1). To compare the different dead space fractions, 18.5 ml was added to $V_{D,Fowler}$.

The results for the different types of dead space fractions were analysed by fitting them with the following equation:

$$V_D/V_T = A - B \cdot t_a^{\beta} \quad (3)$$

where $A = V_D/V_T$ for $t_a = 0$, and B and β are parameters determining the decrease of V_D/V_T with increasing t_a.

In the first three experiments, three different breathing patterns were applied with $t_a = 0$ s, 1 s and 2 s respectively. In the remaining five experiments a fourth pattern with a post-inspiratory apnoea of 0.5 s was added to the protocol. After completion of the measurements the dogs were allowed to recover.

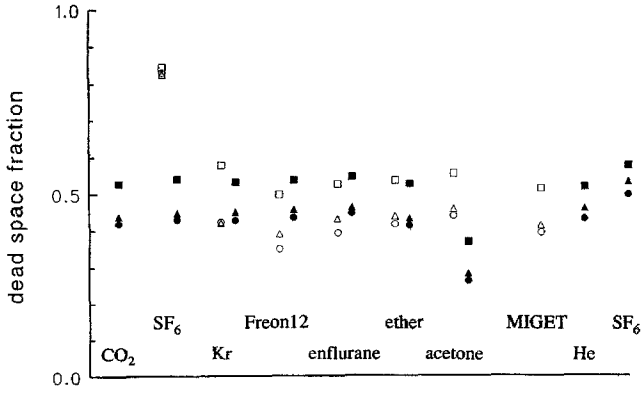
Student's t-test for paired observations was applied to compare the results for the different types of dead space fractions.

Results

In Fig. 2 the mean values of the different dead space fractions are displayed. These were obtained from eight dogs with three breathing patterns and durations of the post-inspiratory apnoea of 0, 1 and 2 s respectively. In Fig. 3, in addition to the mean values for V_D/V_T for 0-, 1- and 2-s apnoea, the values for 0.5-s apnoea are given. This figure, however, shows results obtained from only five dogs. These figures show that, in general, V_D/V_T decreases with increasing t_a. The different dead space fractions ranged from about 0.55 for $t_a = 0$ to about 0.35 for $t_a = 2$ s. Exceptions were $V_{D,phys}/V_T$ for SF_6 (> 0.8) and $V_{D,Fowler}/V_T$ for acetone (between 0.35 and 0.25) (Figs. 2 and 3).

The relationship between V_D/V_T and t_a was further analysed using Eq. 3. In Table 2 the values of the

Fig. 2 Mean values of four different dead space fractions obtained from the results with eight dogs at three different values of t_a. The Fowler dead space fractions are displayed with *solid* symbols for CO_2 and for the six tracer gases in order of increasing blood solubility (from *left* to *right*). The physiological dead space fractions for the six tracer gases are depicted with *open* symbols. In the right part of the figure the results of the dead space fractions obtained with the multiple inert gas elimination technique (*MIGET*) and those for the washout dead space fractions for He and SF_6 are shown. □, ■ $t_a = 0$ s; △, ▲ $t_a = 1$ s; ○, ● $t_a = 2$ s. Data files are available on request



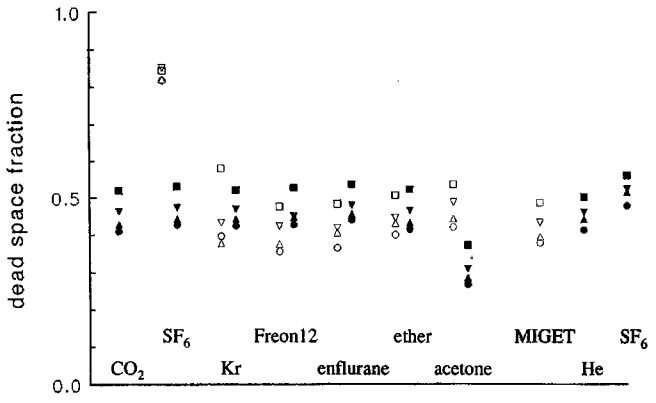


Fig. 3 Mean values of four different dead space fractions obtained from the results with five dogs at four different values of t_a. For further explanation see Fig. 2. □, ■ t_a = 0 s; ▽, ▼ t_a = 0.5 s; △, ▲ t_a = 1 s; ○, ● t_a = 2 s. Data files are available on request

parameters A, B and β calculated for the different types of dead space fractions and for the different gases are given. A corresponds to the fitted value of V_D/V_T for $t_a = 0$, and B corresponds to the decrease in V_D/V_T when a post-inspiratory apnoea of 1 s is used. β reflects the behaviour of V_D/V_T as a function of t_a.

Most of the β values in Table 2 are around 0.5. For $V_{D,Fowler}/V_T$ the values of the parameters B and β for the different gases were all about 0.083 and 0.36 respectively. All values for B and β were significantly different from zero (Table 2). Hence, $V_{D,Fowler}/V_T$ decreased similarly for all gases with increasing t_a.

The values of B and β obtained for $V_{D,phys}/V_T$ for the different gases varied more widely than the values of these parameters for $V_{D,Fowler}/V_T$ (Table 2). For enflurane, ether and acetone the values for B and β were almost in the same ranges as for $V_{D,Fowler}/V_T$. For SF_6, Krypton and Freon12, however, B and β were considerably different from those for $V_{D,Fowler}/V_T$. For less soluble gases $V_{D,phys}$ and $V_{D,Fowler}$ thus behave differently with regard to t_a.

For $V_{D,MIGET}/V_T$ B and β were close to those for $V_{D,phys}/V_T$ for enflurane, ether and acetone and close to those for $V_{D,Fowler}/V_T$ (Table 2).

In general, for $V_{D,washout}/V_T$ for He and SF_6 B was smaller and β was larger than the corresponding values for the other types of dead space fractions (Table 2). In summary, the four types of dead space fractions investigated do not behave uniformly as functions of t_a. The best agreement for B and β was found between $V_{D,Fowler}/V_T$ and $V_{D,MIGET}/V_T$, and $V_{D,phys}/V_T$ for well-soluble gases.

The quantitative differences between the different dead space fractions for the four breathing patterns are shown in Table 3. Except for SF_6 and acetone, the values obtained for $V_{D,phys}/V_T$ corresponded well with the values obtained for $V_{D,Fowler}/V_T$ for all values of t_a (Table 3, upper part). For both SF_6 and acetone $V_{D,phys}/V_T$ was considerably larger than $V_{D,Fowler}/V_T$ for all t_a. For SF_6 $V_{D,washout}/V_T$ was significantly larger than $V_{D,Fowler}/V_T$ for $t_a = 0$, 1 and 2 s (Table 3, middle part). For $t_a = 0.5$ the significance level ($P = 0.05$) was not reached, probably due to the smaller number of observations, (five instead of eight dogs, see Materials and methods). The $V_{D,washout}/V_T$ for SF_6 was significantly larger than that for He for all values of t_a (Table 3, lower part). It appeared further that the difference $V_{D,washout,SF6}/V_T - V_{D,washout,He}/V_T$ was not related to t_a.

Discussion

Dependence of V_D on t_a

The volume of the alveolar space is many times larger than that of the conducting airways. The transport of

Table 2 Parameter values for A, B and β (see Eq. 3 in text) for the different types of dead space and gases. Data are means (SEM) of all experiments (eight dogs) ($V_{D,Fowler}$ Fowler dead space, $V_{D,phys}$ physiological dead space, $V_{D,MIDGET}$ dead space determined by the multiple insert gas elimination technique, $V_{D,washout}$ washout dead space)

Types of dead space fraction and gas	A	B [$s^{-\beta}$]	β
$V_{D,Fowler}$			
CO_2	0.528 (0.012)	0.084 (0.004)	0.393 (0.027)
SF_6	0.540 (0.011)	0.087 (0.006)	0.343 (0.058)
Krypton	0.532 (0.014)	0.078 (0.006)	0.407 (0.044)
Freon12	0.537 (0.010)	0.079 (0.006)	0.328 (0.059)
Enflurane	0.546 (0.011)	0.080 (0.006)	0.312 (0.036)
Ether	0.527 (0.012)	0.088 (0.004)	0.380 (0.025)
Acetone	0.369 (0.021)	0.085 (0.005)	0.342 (0.046)
$V_{D,phys}$			
SF_6	0.841 (0.024)	0.006 (0.009)	3.693 (2.031)
Krypton	0.576 (0.030)	0.142 (0.031)	1.440 (1.226)
Freon12	0.497 (0.049)	0.090 (0.019)	0.780 (0.241)
Enflurane	0.525 (0.034)	0.095 (0.011)	0.438 (0.111)
Ether	0.536 (0.019)	0.097 (0.010)	0.332 (0.103)
Acetone	0.554 (0.012)	0.089 (0.007)	0.398 (0.081)
$V_{D,MIGET}$	0.513 (0.020)	0.093 (0.009)	0.405 (0.092)
$V_{D,washout}$			
He	0.518 (0.014)	0.058 (0.007)	0.664 (0.153)
SF_6	0.576 (0.013)	0.048 (0.009)	0.775 (0.129)

Table 3 Mean values for the differences between the different dead space fractions for the four breathing patterns. Values were determined for $n = 8$ dogs, except for $t_a = 0.5$ s for which $n = 5$ (t_a period of post-inspiratory apnoea, V_T tidal volume)

t_a (s)	0	0.5	1.0	2.0
$(V_{D,phys}/V_T - V_{D,Fowler}/V_T)$				
SF_6	+ 0.306***	+ 0.372***	+ 0.379***	+ 0.401***
Krypton	+ 0.047	−0.051	−0.029	−0.006
Freon 12	−0.039	−0.028	−0.066	−0.085*
Enflurane	−0.020	−0.060 *	−0.032	−0.053 **
Ether	+ 0.009	−0.019	+ 0.005	+ 0.004
Acetone	+ 0.185***	+ 0.178***	+ 0.177***	+ 0.177***
$(V_{D,washout,SF6}/V_T - V_{D,Fowler,SF6}/V_T)$	+ 0.037***	+ 0.050*	+ 0.084***	+ 0.066***
$(V_{D,washout,SF6}/V_T - V_{D,washout,He}/V_T)$	+ 0.058***	+ 0.064***	+ 0.072***	+ 0.066***

*$0.05 < P < 0.1$, **$0.01 < P < 0.05$, ***$P < 0.01$ for the differences between the various dead space fractions determined using Student's t-test for paired observations. Two-tailed probabilities are given for $V_{D,phys}/V_T - V_{D,Fowler}/V_T$ and one-tailed probabilities for the remaining differences

tracer gases by diffusion from the alveolar space to the conducting airways during a post-inspiratory apnoea of less than 2 s will, therefore, hardly affect their concentrations in the alveolar space. In early models of pulmonary gas exchange the alveolar space was represented by a single compartment connected to a tube representing the conducting airways. Assuming a tracer gas in the alveolar compartment of this simple, physical model with a constant concentration for time $t > 0$ and zero concentration in the tube at $t = 0$, the transition zone of this tracer gas will advance into the tube and its distance to its original location at $t = 0$ will increase directly proportional to $t^{0.5}$ [3]. The volume of the tube promixal to the transition zone can then be described by Eq. 3, where A corresponds to the total volume of the tube, $\beta = 0.5$ and B depends, among other things, on the diffusion coefficient of the tracer gas. This example explains why we have chosen the empirical Eq. 3 to describe V_D/V_T as a function of t_a.

Although $V_{D,washout,SF6}$ is greater than $V_{D,Fowler,SF6}$, the difference is modest and, on average, less than 10% of V_T for all t_a (Table 3). Similarly, $V_{D,phys}$ and $V_{D,Fowler}$ do not differ much except for SF_6 and acetone (Table 3). Evidently, $V_{D,Fowler}$ is the major determinant of $V_{D,washout}$ and $V_{D,phys}$ in our experiments. $V_{D,Fowler}$ decreases with increasing t_a as a result of the ongoing mixing of residual gas with tidal air in the airways during the post-inspiratory apnoea. This mixing process has been frequently studied in the past with mathematical models, but, to the best of our knowledge, data concerning the relationship between $V_{D,Fowler}$ and t_a have never been published. We have considered the following to explain the order of magnitude of the β values found for $V_{D,Fowler}$ which range from about 0.3 to 0.4 (Table 2). The cumulative cross-section of the airways (per generation) decreases towards the airway opening. As a consequence, the effect of the displacement of the transition zone during a post-inspiratory apnoea on $V_{D,Fowler}$ will decrease the further the transition zone proceeds towards the airway opening, which implies that β will be smaller than 0.5. This range is consistent with most of the β-values shown in Table 2.

The shunt fraction ($\dot{Q}_s/\dot{Q}$, where $\dot{Q}$ is the cardiac output and $\dot{Q}_s$ the blood flow through shunt pathways) varied between the experiments with different t_a. Although these variations in $\dot{Q}_s/\dot{Q}$ were small, they had a considerable impact on the results for $V_{D,phys}$ for SF_6, as discussed below. As a consequence, the values obtained for B and β for SF_6 for $V_{D,phys}/V_T$ do not reflect the effect of t_a on intrapulmonary gas mixing alone. We have included the results for B and β for SF_6 for the sake of completeness, but in our opinion they are without meaning. This interpretation is supported by the large values for SEM (Table 2). Apparently, the aforementioned variations in $\dot{Q}_s/\dot{Q}$ also affected the results for B and β for $V_{D,phys}/V_T$ for Krypton and Freon12, however, to a lesser extent (Table 2). The effect of small variations in $\dot{Q}_s/\dot{Q}$ on the results of well-soluble gases should be negligible and, accordingly, the results for B and β for $V_{D,phys}/V_T$ for enflurane, ether and acetone agree well with the corresponding values for $V_{D,Fowler}/V_T$.

The values for B and β for $V_{D,washout,SF6}$ are different from the corresponding values for $V_{D,Fowler,SF6}$. The $V_{D,Fowler}$ is included in $V_{D,washout}$ so that these differences can be attributed only to additional effects of the post-inspiratory apnoea on intrapulmonary gas mixing. We suppose that the origin of the differences in B and β between $V_{D,washout}$ and $V_{D,Fowler}$ is related to diffusive gas exchange between units of different size within the acini during the apnoea, as has been demonstrated by the model calculations of de Vries et al. (see Fig. 2 in [19]). Other mechanisms, however, may be involved as well. Further investigations are therefore needed to ascertain the origin of the differences in B and β between $V_{D,washout}$ and $V_{D,Fowler}$.

Physiological and Fowler dead space fraction

$V_{D,phys}/V_T$ and $V_{D,Fowler}/V_T$ for Kr, Freon12, enflurane and ether are very similar in magnitude (Figs. 2 and 3,

and Table 3). $V_{D,phys}/V_T$ for SF_6, however, is much larger than $V_{D,phys}/V_T$ for the other gases (Figs. 2 and 3). This can be attributed to the occurrence of a small shunt fraction ($\dot{Q}_s/\dot{Q}$) in most experiments. $\dot{Q}_s/\dot{Q}$ was determined with MIGET and ranged from 0.000 to 0.018 (mean 0.004). Even a small shunt fraction results already in a relatively large P_a for SF_6 and, therefore, in a large $V_{D,phys}/V_T$ ($= 1 - P_{\bar{E}}/P_a$). Further, $V_{D,Fowler}$ V_T for acetone is considerably smaller than that for the other tracer gases (Figs. 2 and 3). The following observations may contribute to explain this. A rebreathing manoeuvre of 20 inspirations and expirations with the aid of the 190-ml syringe showed that the well-soluble gas ether reached a constant level in expired air after about ten breaths which corresponded to approximatively 1.25 times the value of $P_{E'}$ prior to the rebreathing manoeuvre (Fig. 4). For acetone and enflurane a constant level, corresponding to about 1.4 times $P_{E'}$ was observed after about 15 breaths. For the less soluble gases no constant level was obtained within 20 breaths (Fig. 4). The constant levels that are obtained for acetone, ether and enflurane mean that an equilibrium has been reached between the partial pressures of these tracer gases in the residual gas and in mixed venous blood. As a consequence, the constant levels reached for these tracer gases correspond to their $P_{\bar{v}}$. For acetone, and to a lesser extent also for ether, the relatively high level for $P_{\bar{v}}$ compared with $P_{E'}$ points to the fact that $P_{E'}$ measured during normal breathing is not representative for the partial pressure in the alveolar gas (P_A). P_A can be approximated by $P_{\bar{v}} \cdot \lambda/(\lambda + \dot{V}_A/\dot{Q})$ [20]. Hence, for acetone P_A is virtually equal to $P_{\bar{v}}$ due to its high solubility in blood. Evidently, there is a considerable difference of about 40% between $P_{E'}$ and P_A for acetone during steady state washout from mixed venous blood. This indicates that an important exchange between gaseous and dissolved acetone in the airways takes place during the breathing cycle. The phase I that can be observed in the expirograms of acetone is very short lasting compared with phase I for other gases (Fig. 5) and the correspondingly small values for $V_{D,Fowler}/V_T$ for acetone compared with those of the other tracer gases can then be explained by a substantial release of acetone from the airway walls into the airway lumina during inspiration. This phenomenon has been observed and described before [16].

The large $V_{D,phys}/V_T$ obtained for SF_6 and the small $V_{D,Fowler}/V_T$ obtained for acetone result in significant differences between $V_{D,phys}/V_T$ and $V_{D,Fowler}/V_T$ for these two gases (Table 3). In general, $V_{D,phys}/V_T$ can be expected to be larger than $V_{D,Fowler}/V_T$ since $V_{D,phys}/V_T$ includes $V_{D,Fowler}/V_T$ and the fraction of tidal air that is directed to non-perfused alveolar space, so called alveolar dead space [2]. Further, as mentioned above, $V_{D,phys}/V_T$ is also enhanced by shunt perfusion. The very small shunt fractions and the monomodal and narrow $\dot{V}_A/\dot{Q}$ distributions, with a SD for $\dot{V}_A$ of 0.155–0.483 (mean 0.241), recovered with MIGET in 28 of the 29 experiments are, therefore, consistent with the small differences between $V_{D,phys}/V_T$ and $V_{D,Fowler}/V_T$ for Kr, Freon12, enflurane and ether (Table 3). It is remarkable, however, that in many cases, the mean $V_{D,phys}/V_T$ was less than the mean $V_{D,Fowler}/V_T$ for these gases (Table 3), and this relationship could be shown to be significant for enflurane with $t_a = 2.0$ s (Table 3). $V_{D,phys}/V_T$ being less then $V_{D,Fowler}/V_T$ is in conflict with general consensus (see above), but can be explained as follows. In man during a normal inspiration the

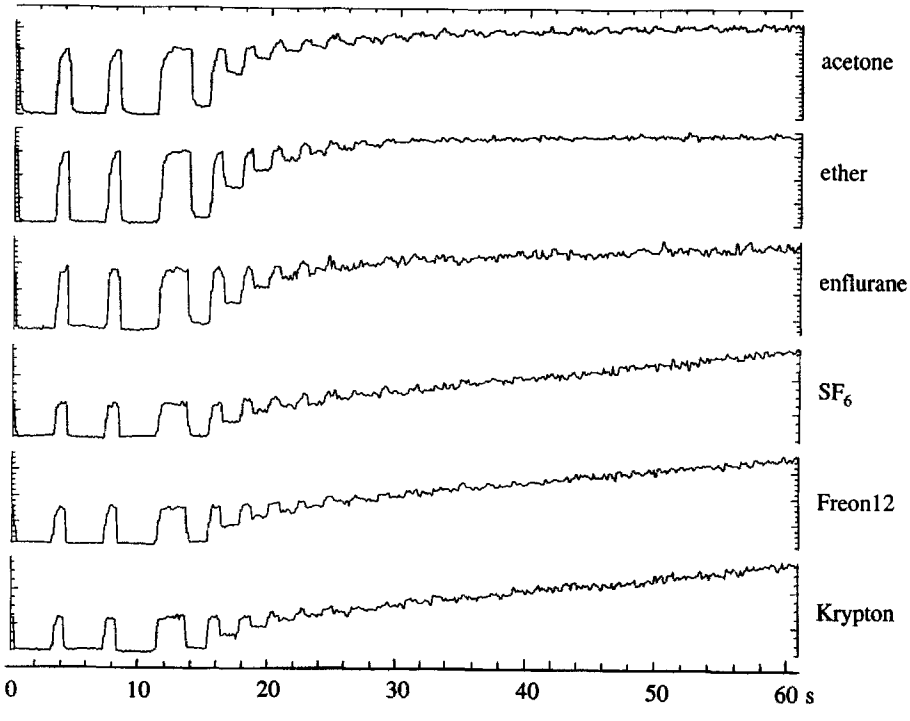


Fig. 4 Recordings of the partial pressures (in arbitrary units) of six tracer gases in inspired and expired gas during the rebreathing manoeuvre preceded by three breathing cycles during artificial ventilation with room air. The gases were sampled simultaneously over a 60-s period with a frequency of 10 Hz

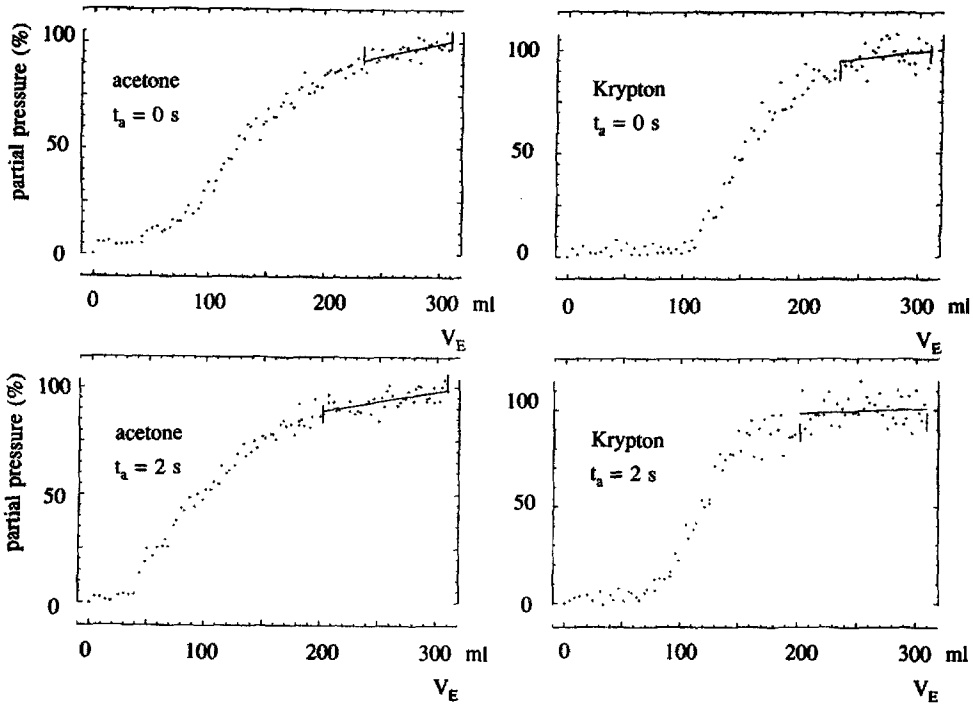


Fig. 5 Expirograms for acetone (*left panels*) and krypton (*right panels*). The two *upper* expirograms were recorded during breathing without post-inspiratory apnoea, while the two *lower* expirograms were recorded during breathing with a post-inspiratory apnoea of 2.0 s. The partial pressures of the tracer gases are expressed as a percentage of their end-expiratory partial pressures (V_E expired volume)

transition zone between tidal air and residual gas establishes itself between airway generations 17 and 20 [7, 13, 14]. For the alveoli located proximally to this zone, gas exchange conditions are optimal during the larger part of the inspiration; the partial pressure differences for the tracer gases between capillary blood and luminal gas are maximal in this area, and the total ventilatory flux passes along a small portion of the total perfusion in a "cross-current" fashion [24]. To a certain extent this also applies to the area of the transition zone where the partial pressures of the tracer gases are still considerably smaller than in the distal acinar airways, i.e., in the residual gas. The enhanced gas exchange in the proximal parts of the acini during inspiration adds to $P_{\bar{E}}$ and diminishes P_a, and, therefore, also diminishes $V_{D,phys}/V_T$ ($= 1 - P_{\bar{E}}/P_a$), which may result in $V_{D,phys}/V_T$ being smaller than $V_{D,Fowler}/V_T$.

As discussed above, $V_{D,phys}$ being smaller than $V_{D,Fowler}$ is not likely to occur for SF_6 and acetone due to the enhancing effect of shunt perfusion on $V_{D,phys}$ for SF_6 and due to the reducing effect of exchange of acetone in the airway lumen and acetone dissolved in airway tissue on $V_{D,Fowler}$ for this tracer gas. In other words, $V_{D,phys}$ being smaller than $V_{D,Fowler}$ is most likely to occur only for gases with intermediate λ values for which the just mentioned effects are small. This may explain the behaviour of $(V_{D,phys}/V_T - V_{D,Fowler}/V_T)$ as shown in Table 3.

Washout dead space fraction

Helium and SF_6 are both poorly soluble in blood and lung tissue. Their diffusivities in alveolar gas, however, differ considerably. For these reasons, these gases are often used together to study the properties of intrapulmonary gas mixing, as in the present study.

In all experiments $V_{D,washout,SF6}$ was larger than $V_{D,washout,He}$. Our results further show that $V_{D,washout}$ decreases with increasing t_a (Figs. 2 and 3) while the difference between $V_{D,washout,SF6}/V_T$ and $V_{D,washout,He}/V_T$ remains virtually the same (Table 3), i.e., these two parameters do not converge with increasing t_a. These findings thus demonstrate unequivocally that $V_{D,washout}$ and, therefore, $\dot{V}_A$ depend on the diffusivity of the test gas, irrespective of the time available for diffusive mixing of the test gas with tidal air. $V_{D,washout}/V_T$ includes $V_{D,Fowler}/V_T$, and is further affected by unequal ventilation. The less well ventilated parts of the lung delay the washout, which eventually results in smaller values for P_O/P_N and $\dot{V}_A/V_{L,E'}$ (Eq. 2). The value obtained for $\dot{V}_A/V_{L,E'}$ thus reflects the overall efficacy of the ventilation of the alveolar space, where smaller values for $\dot{V}_A/V_{L,E'}$ correspond with larger values for $V_{D,washout}$ (see Materials and methods). $V_{D,washout}$ may, therefore, be expected to be larger than $V_{D,Fowler}$, which is confirmed by our experimental findings for $(V_{D,washout}/V_T - V_{D,Fowler}/V_T)$ for SF6 (Table 3).

Comparison with data published so far

The decrease of V_D with increasing t_a is a well-known experimental finding, however, the evidence for this relationship between V_D and t_a is mainly based on observations of $V_{D,Fowler}$ [4, 10, 11, 15]. In the present study we have shown that the decrease of V_D with

increasing t_a is also found for other types of dead space (Figs. 2 and 3), although in some cases this relationship could not be shown, e.g. for $V_{D,phys}$ for SF_6. In addition, we have assessed the mathematical relationship between V_D/V_T and t_a (Table 2) and the differences between the different dead space fractions as functions of t_a (Table 3). To the best of our knowledge, data similar to those presented in these tables have not been published so far. As a consequence, the further comparison with data from the literature concerns a limited fraction of our results mainly related to SF_6.

Studying the effects of breath holding on intrapulmonary gas mixing Engel et al. have found in six open-chested dogs that $V_{D,Fowler}$ for N_2 decreased on average by about 39% for t_a = 2.5 s [4]. In our experiments the decrease of $V_{D,Fowler}$ for t_a = 2 s was close to 20% for all gases except acetone, for which this decrease was 29%. The larger relative change in $V_{D,Fowler}$ found by Engel et al. may be attributed, at least in part, to the larger value of t_a and to the sampling site used. They sampled gas directly from the lumen of the trachea. This more peripheral location of the sampling site, compared with that in our experiments, resulted in smaller values for $V_{D,Fowler}$, 113 ml [4] versus about 148 ml for all gases except acetone in our study, and the smaller $V_{D,Fowler}$ is for $t_a = 0$ the larger the relative effect of breath holding on $V_{D,Fowler}$ will be.

The experimental set-up used by Meyer et al. [11] was very similar to ours, and these authors report an overall mean value of 151 ± 25 (mean ± SD) for $V_{D,Fowler}$ for SF_6 and $t_a = 0$ in ten dogs with venous loading. This result is nearly equal to our value of 150 ± 24 ml for $V_{D,Fowler,SF6}$. Further, these authors report that $V_{D,Fowler,SF6}$ decreased by 24, 29 and 31% with post-inspiratory apnoea periods of 4,8 and 12 s respectively. Using our data for A, B and β for $V_{D,Fowler,SF6}$ (Table 2) and Eq. 3 the corresponding computed percentages are 26, 33 and 38% respectively. Given the considerable degree of extrapolation involved in the computation of these percentages, they correspond fairly well with those found by Meyer et al. (see above) and, accordingly, the best agreement is found for $t_a = 4$ which is closest to the range of t_a values used in our study (0 – 2 s). In a further experiment performed by the same group $V_{D,Fowler}$ with venous loading of C_2H_2 and Freon22 decreased by about 34% for $t_a = 5$ s [10] which, in contrast with the results discussed above for SF_6, is more than predicted (25%). This predicted percentage was computed with the help of the mean values for A, B and β for Freon12 and enflurane (Table 2: $V_{D,Fowler}$). Meyer et al. [10] found the same decrease for $V_{D,Fowler,CO_2}$, i.e. 34%, for $t_a = 5$ s, which is somewhat larger than predicted (30%) from our results for CO_2.

Thus far we have compared our results with those obtained by other investigators in the same species, the dog. This is preferable, as the behaviour of V_D as a function of t_a may be species dependent. Similar observations in human subjects, however, have already been performed in the fifties. Roos et al. [15] have reported that $V_{D,Fowler}$ for N_2 washed out from the alveolar space decreased from 165 ml for $t_a = 0$ to 60 ml for $t_a = 75$ s. This decrease corresponds to 64% which is compatible with the predicted percentage (71%) obtained from our data for $V_{D,Fowler,SF6}$ (Table 2). This may mean that respiratory dead spaces of any type in humans and dogs behave fairly similarly as functions of breath-holding time as $V_{D,Fowler}$ is the main determinant of the different types of dead space in healthy subjects.

In conclusion, we have demonstrated that the respiratory dead space fractions decrease considerably with increasing duration of the post-inspiratory apnoea. Using He and SF_6 we have shown that the washout dead space depends on the diffusivity of the test gas, irrespective of the time available for diffusive mixing of gases in the lung. Accordingly, the decrease of the dead space fractions with increasing duration of the post-inspiratory apnoea can be attributed to continued, diffusive mixing of gases in the lung during the apnoea. The washout dead space is larger than the Fowler dead space, while the physiological dead space is larger than the Fowler dead space for poorly and for highly soluble test gases only. For gases that are intermediately soluble in blood, the physiological dead space tends to be smaller than the Fowler dead space. This peculiar behaviour of the physiological dead space versus the Fowler dead space indicates the importance of the particular properties of pulmonary gas exchange for gases with different solubilities in blood.

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