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The excretion of highly soluble gases by the lung in man

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Abstract. The excretion (E) of inert gases by the lung depends on, among other things, their blood-gas partition coefficients (λ). According to conventional gas exchange models, E should increase with increasing λ. However, recent models that take into account the tidal character of breathing and the buffering capacity of lung tissue predict that E will show a minimum in the range of large λ values ($\lambda > 10$). Further, this local minimum should shift to larger λ values in exercise conditions as compared to rest conditions. The aim of this study is to verify this predicted behaviour of E. The experiments were carried out with seven healthy subjects at rest and at three work loads (50 W, 100 W and 150 W) on a bicycle ergometer. The behaviour of E was determined from the results of a simultaneous washin of four tracer gases: ethyl acetate ($\lambda \approx 75$), acetone ($\lambda \approx 330$), ethanol ($\lambda \approx 2000$) and acetic acid ($\lambda \approx 20000$). The washin lasted 4 min, and E was calculated from $E = 1 - P_{\bar{E}}/P_I$, where P_I and $P_{\bar{E}}$ are the partial pressures of the tracer gas in inspired and mixed expired gas determined from the recordings obtained during the last minute of washin. P_I and $P_{\bar{E}}$ were measured with a mass spectrometer. Comparison of the E values of the four gases shows that at rest a minimum value for E is found for acetone. In exercise conditions, however, the smallest E value is found for the more soluble ethanol or acetic acid. Further, under exercise conditions the E values for ethyl acetate and acetone are larger than their respective values at rest. In general, the experimental findings are consistent with the predicted behaviour of E. This means that gas exchange in the airways between gaseous and dissolved tracer gas in the airway lumen and in the airway tissue, respectively, cannot be ignored for highly soluble tracer gases. In addition, the observed differences between the E values of the four highly soluble tracer gases imply that the dead space ventilation ($\dot{V}_D$) depends on λ, i.e. the value of $\dot{V}_D$ is not unique. Therefore, the result for $\dot{V}_D$ obtained from a highly soluble tracer gas will, in general, not apply to other tracer gases.

Key words: Blood-gas partition coefficient – Excretion – Lung model – Tracer gases – Buffering of lung- and airway tissue

Introduction

In steady state conditions, gas transfer across the lung can be characterized by the excretion (E) and retention (R) data of inert tracer gases (Wagner et al. 1974; Zwart and Luijendijk 1981, 1982). E and R depend on, among other things, the blood-gas partition coefficient (λ) of the tracer gas. According to conventional gas exchange models, E should increase with increasing λ (Wagner et al. 1974). However, recent models that take into account both the tidal character of breathing and the buffering capacity of superficial lung tissue predict that E will decrease as a function of λ in the range of large λ values ($\lambda > 10$) and will increase again in the range of very large λ values, e.g. $\lambda > 1000$. Thus, a local minimum of E is predicted in the range of λ values larger than 10. Further, in exercise conditions, this minimum should shift to larger λ values in comparison with rest conditions (Zwart et al. 1986, Fig. 4). In a previous investigation, using short lasting washin experiments, we observed that, in general, E for acetone ($\lambda \approx 330$) was smaller than E for ether ($\lambda \approx 13$) (Schrikker et al. 1985). Similar results were obtained by other investigators using the multiple inert gas elimination technique (MIGET) (Dueck et al. 1980). Observations where E for acetone is smaller than E for ether are in qualitative agreement with the recent model predictions, but as yet a local minimum in E was not observed. This may be due to the selection of tracer gases used so far and the correspondingly low upper limit of the λ range (≈ 330). We have, therefore, extended the λ range of the tracer gases up to $\lambda \approx 20000$. In this paper we will verify the predicted behaviour of E by applying tracer gases with $75 < \lambda < 20000$ and short lasting washin experiments in human subjects at rest and at different work loads on a bicycle ergometer.

Material and methods

Selection of tracer gases. We have applied four tracer gases: ethyl acetate, acetone, ethanol and acetic acid. These organic compounds are highly soluble in aqueous media, such as blood and lung tissue, and they cover a wide range of λ values (Table 1). The large effective λ value of acetic acid is due to the dissociation of the acid into its ions.

Method for the determination of E. The general definition for the excretion of gases by the lung is given by:

$$E = (P_{\bar{E}} - P_I)/(P_{\bar{v}} - P_I) \quad (1)$$

where P_I, $P_{\bar{E}}$ and $P_{\bar{v}}$ are the partial pressures of the tracer gas in inspired gas, mixed expired gas and mixed venous blood, respectively (Zwart and Luijendijk 1981, 1982). Usually, E is determined with MIGET (Wagner et al. 1974). This technique involves administering the tracer gases by

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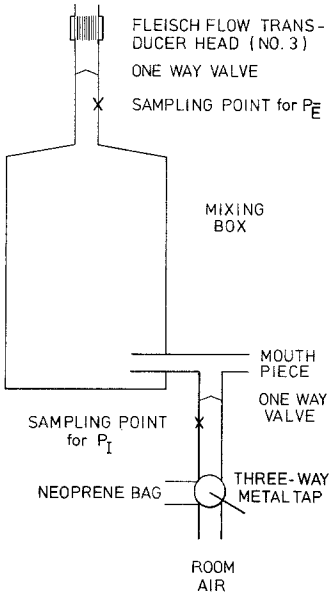

Fig. 1. Schematic illustration of the breathing circuit

intravenous infusion. In this case $P_I = 0$ and E can then be calculated from $E = P_{\bar{E}}/P_{\bar{v}}$ [Eq. (1)]. In a previous study we applied an alternative method for the determination of E where the E values of ethyl acetate and acetone were determined from the results of short lasting washin experiments of the tracer gases from inspired gas (Schrikker et al. 1985). The short duration of the washin in combination with the high solubilities of the tracer gases in tissue involved $P_{\bar{v}}$ remaining virtually equal to zero, i.e., $P_{\bar{v}} \ll P_I$. Further, for highly soluble gases stationary levels of $P_{\bar{E}}$ were attained within about 30 s after the beginning of the washin (Schrikker et al. 1985). For the present investigation, we applied this washin method again. As $P_{\bar{v}}$ in Eq. (1) can then be neglected, the excretion of the tracer gases follows from:

$$E = 1 - P_{\bar{E}}/P_I. \quad (2)$$

As a consequence, mixed venous blood samples for the determination of $P_{\bar{v}}$ are not needed. A further advantage of the applied method is the short duration of the measurements which makes it possible to investigate the behaviour of E under heavy exercise conditions as well. In the Appendix, a more detailed discussion of the theoretical basis of this non-invasive method is given.

The experimental set-up. The breathing circuit is shown in Fig. 1. The subjects breathed through a mouthpiece and inspired gas was separated from expired gas by one-way valves. The dead space of the mouthpiece was 10 ml. The inspiratory line of the circuit could be connected either to room air or to a neoprene bag (300 l) containing a mixture of room air and tracer gases at low concentrations (Table 1). A small amount of water (100 ml) was added to this bag to stabilize the concentrations of the tracer gases in the gas mixture. The outlet of the mouthpiece was connected to a mixing box with a volume of 2.5 l, and the outlet of this mixing box was connected to a Fleisch pneumotachograph (no. 3, Gould Godart). Further, two side-ports were provided for, one near the beginning of the inspiratory line and one near the outlet of the mixing box. They were used for

Table 1. Concentrations in inspired air, λ values and the mass-to-charge ratios (m/e) at which the four tracer gases were measured

	Concentration in inspired air	λ	m/e
Ethyl acetate	0.025 vol%	75[a]	70
Acetone	0.1 vol%	330[b]	58
Ethanol	0.5 vol%	2000[c]	31
Acetic acid	0.025 vol%	$\approx$ 20000[d]	60

[a] Schrikker et al. (1985); [b] Wagner et al. (1974); [c] Jones (1983); [d] measured in this laboratory

sampling of inspiratory and mixed expiratory gas, respectively. All tubes were made of metal and the mixing box was made of glass. These materials should minimize the adsorption of tracer gases on the inner walls of the equipment. The flow transducer was kept at 37° C, and the further parts of the inspiratory and expiratory line were heated to about 50° C. As expired tracer gases might be lost by dissolution in condensed water vapour, the increased temperature of the equipment served to prevent condensation of water vapour from expired gas. The increased temperature was also useful to reduce adsorption of tracer gases on the inner walls of the equipment. In view of this adsorption, the one-way valve in the expiratory line was placed downstream of the sampling point (Fig. 1). Tidal volume (V_T) was obtained from the output of the pneumotachograph. The partial pressures of the tracer gases in inspired gas (P_I) and in mixed expired gas ($P_{\bar{E}}$) were measured with a mass spectrometer (Balzers, QMG 511). To that end, the inlet of the heated sampling capillary of the mass spectrometer was inserted via the one side-port into the inspiratory line for the measurement of P_I or via the other side-port into the expiratory line for the measurement of $P_{\bar{E}}$. The side-port that was not in use was closed with a small rubber stop cork.

The output signal of the pneumotachograph for V_T and the multiplexed output signal of the mass spectrometer were recorded with a four channel *x-t* recorder (Elema-Schönander), and in addition, the output signal of the mass spectrometer was recorded with a wide range, single channel *x-t* recorder (Servogor) for accurate readings of the amplitudes of P_I and $P_{\bar{E}}$.

Measurements of P_I and $P_{\bar{E}}$. The applied tracer gases have different peaks of their mass spectra in common. In this connection we selected the following settings of the mass-to-charge ratio (m/e) for the different gases: m/e = 31, 58, 60 and 70 for ethanol, acetone, acetic acid and ethyl acetate, respectively. At m/e = 31, there was a small overlap with the main peak of O_2 at m/e = 32. For P_I, this overlap was larger than for $P_{\bar{E}}$, because the O_2 content in inspired gas ($\approx$ 21 vol%) was larger than that in mixed expired gas ($\approx$ 15 vol%). This had consequences for the experimental protocol and the data handling, see below.

In previous experiments with ether, ethyl acetate and acetone, the P_I values could be measured within the mouthpiece on each inspiration from the neoprene bag (Schrikker et al. 1985). Unfortunately, this was not possible for acetic acid due to the large time constant of the mass spectrometer for this gas. The shortest time constant we could achieve

was about 45 s by heating of the sampling capillary and the analyzer to about 100° C and by adding a liquid nitrogen trap to the high vacuum pumping unit of the mass spectrometer. The large time constant for acetic acid is probably due to adsorption to the ceramic parts of the analyzer which serve as electrical insulators. The time constants for the remaining three gases were less than 100 ms. The time constant of 45 s for acetic acid implies that the measurements of P_I and $P_{\bar{E}}$ should last at least 3 min, and, consequently, we had to adjust the experimental protocol to this technical limitation.

Subjects, experiments and protocol. Seven healthy male subjects aged from 28 to 47 years and with no history of lung disease participated in this investigation. Each subject performed two experiments under resting conditions and three experiments at different levels of exercise on a bicycle ergometer (50, 100 and 150 W). The protocols of the two experiments for rest conditions were different. In one of the two experiments, the subjects held their breath for about one second at the end of each inspiration. This post-inspiratory apnea was aimed at improving gas mixing between residual and tidal gas which might result in increased values of E. The two experiments under resting conditions were performed on the same day with an interval of several hours, whereas the experiments under exercise conditions were carried out on different days within a week.

Taking into account the technical limitations summarized in the preceding paragraph, we arrived at the following experimental protocol. Each experiment started with the determination of the zero levels at the selected m/e values. To that end, the subject breathed room air via the mouthpiece for some minutes at the same physical exercise condition and breathing manoeuvre as used during the experiment, while the sampling capillary was connected to the sampling point for P_I. After 1 min, the sampling capillary was transferred to the sampling point for $P_{\bar{E}}$ in order to determine the second zero level at m/e = 31, see previous paragraph. Next, the P_I values of the tracer gases were measured. For this purpose, a flow calibration set (Godart, type 18987) was used with which a constant flow of gas of about 5 l/min was maintained from the neoprene bag via the inspiratory line. This lasted about 3 min. Immediately thereafter, the washin experiment of the tracer gases was started. This lasted 4 – 5 min, and during that time the $P_{\bar{E}}$ values were measured. Under exercise conditions, the subjects resumed cycling at the intended work load 2 min before the beginning of the washin. At the end of the measurement of $P_{\bar{E}}$, the P_I values were measured again. The zero levels and the P_I and $P_{\bar{E}}$ values of the tracer gases were determined from the recordings obtained during the last minute of each measurement.

For acetic acid a minimal concentration of 0.025 vol% was necessary to be able to measure properly, but this level was not always easily tolerated by the subjects. It mainly irritated their throat initially, resulting sometimes in coughing or swallowing, which passed after a short time. With the applied protocol, the subject was exposed only 4 min to the acetic acid vapour and this caused no further problems.

Data handling and corrections. All P_I and $P_{\bar{E}}$ values were read from the recordings made with the wide range $x-t$ recorder. As mentioned above, two different zero levels for ethanol had to be used for the readings of P_I and $P_{\bar{E}}$. For each tracer gas two values for P_I were obtained, one from the measurement preceding the washin of the tracer gases and one from the measurement after the washin. In general, these two values were slightly different (< 5%), and the P_I value that should apply to the last minute of the washin was obtained by linear interpolation.

Table 2. Peak heights measured at the different m/e values for each of the four gases separately

	m/e			
	70	58	31	60
Ethyl acetate	100	0	1.25 (1.2–1.3)	25.6 (24.7–27.2)
Acetone	0	100	1.25 (1.2–1.3)	11.3 (11.0–11.6)
Ethanol	0	0	100	12.5 (10.7–14.2)
Acetic acid	0	0	0	100

Peak heights are expressed as a percentage of the peak height at the m/e value at which that particular gas was measured. The data are based on three determinations performed on different days. The range is given in parentheses

The data obtained from the recordings should be considered to be raw data as some of the mass-to-charge ratios are shared by two or more tracer gases. Table 2 shows for each tracer gas the amplitudes at the four applied m/e values in relative units. Different settings for sensitivity and resolution were used at the different m/e values. Therefore, the values shown in Table 2 have no particular physical meaning. The contributions of ethanol and acetone to the spectrum at m/e = 60 are remarkable as the molecular weights of these gases are less than 60. These contributions, however, must be due to oxidation of fragments of these molecules into acetic acid within the ion source of the mass spectrometer, since these contributions were nil when pure nitrogen was used as bulk gas instead of air. Table 2 shows that the raw data of ethyl acetate and acetone need no corrections. For ethanol (m/e = 31), the correction of P_I is equal to $(0.0125P_{I,\text{ethyl acetate}} + 0.0125P_{I,\text{acetone}})$, and, similarly, the correction for $P_{\bar{E}}$ is equal to $(0.0125P_{\bar{E},\text{ethyl acetate}} + 0.0125P_{\bar{E},\text{acetone}})$ (Table 2), where P now represents the output signal of the mass spectrometer. The magnitudes of the output signals of the mass spectrometer for the different tracer gases were roughly the same, therefore, these corrections for ethanol were small, and the differences between the E values (ΔE) computed with the corrected data and with the raw data ranged from 0.01 up to 0.04. Table 2 further shows that considerable corrections had to be applied to the raw data of acetic acid.

For statistical analysis of the relationships between the different data for E we have used a Wilcoxon matched-pairs signed-ranks test, 2-tailed (SPSS/PC+ V2.0, according to Siegel 1956).

Results

The individual results for E are shown in Fig. 2. The different panels refer to the different subjects (A through G) and the different experimental conditions. The four data points in

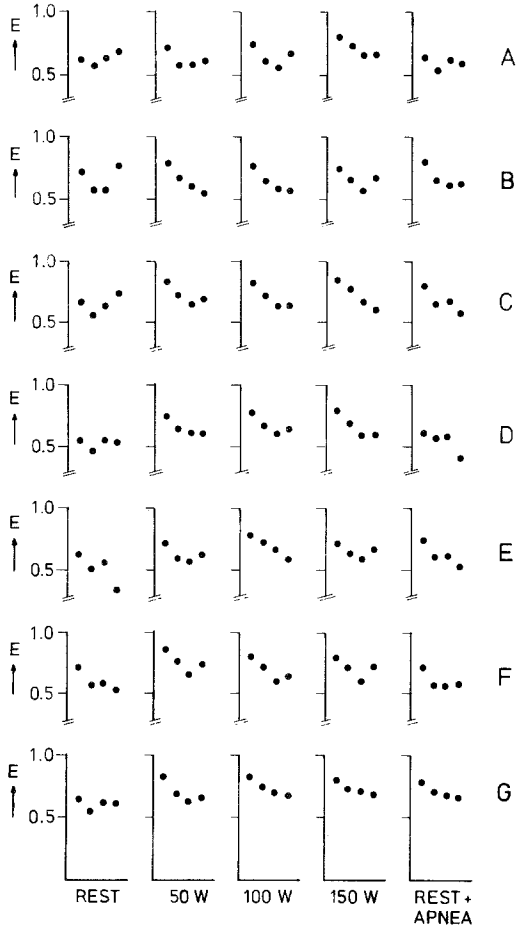

Fig. 2. Excretion values of the four tracer gases for the seven subjects ($A-G$) at the different conditions. In each *panel, from left to right,* the E values of ethyl acetate, acetone, ethanol and acetic acid, respectively

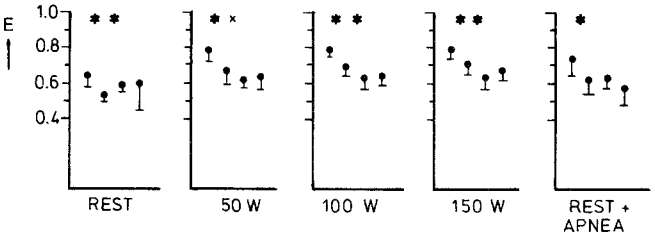

Fig. 3. Mean excretion values and standard deviations for the seven subjects. In *each panel, from left to right* the mean E values are depicted of ethyl acetate, acetone, ethanol and acetic acid, respectively. Significant differences between mean E values are indicated by the symbols * and × referring to $P = 0.018$ and $P = 0.028$, respectively. In *each panel,* the *symbol on the left refers* to the mean E values of ethyl acetate and acetone, and the *second symbol* refers to the mean E values of acetone and ethanol

each panel refer to the four tracer gases and they are plotted in such a way that λ increases from left to right. Three patterns can be distinguished in Fig. 2. In 19 panels out of 35 the data points constitute a U-shaped pattern, and in 8 panels a decrementing pattern is shown with increasing λ. The decrementing pattern is obtained especially under exercise conditions, and this pattern suggests that minimum E is still outside the λ range covered by the selected tracer gases. Thus, in 27 out of the 35 experiments ($\approx$ 77%) the pattern of the data points in Fig. 2 is consistent with the predicted behaviour of E in the range of large λ values. In the remaining 8 panels, the data points for ethyl acetate, acetone and ethanol are compatible with a U-shaped pattern. However, the behaviour of the data points for acetic acid is in conflict with this shape as the E values for acetic acid are smaller than those for ethanol. As a consequence, the pattern of the data points in these 8 panels is incompatible with the predicted behaviour of E as a function of λ. These panels refer to rest conditions both with and without apnea.

In Fig. 3 the mean values of the excretion data for the seven subjects are shown. The data points in each panel correspond to the mean E values of the four tracer gases and they are plotted in the same way as in Fig. 2. For all conditions these data points constitute a U-shaped pattern with the exception of the data points that refer to rest with a post-inspiratory apnea. The dominant, U-shaped pattern shown in Fig. 3, however, is not seen in all individual panels of Fig. 2. Therefore, the differences between the successive data points in Fig. 3 were tested for statistical significance. Both at rest (with and without apnea) and at the three levels of exercise we found significant differences between $E_{\text{ethyl acetate}}$ and E_{acetone} ($P = 0.018$), where $E_{\text{ethyl acetate}} > E_{\text{acetone}}$. Further, it was found that $E_{\text{acetone}} < E_{\text{ethanol}}$ ($P = 0.018$) at rest, whereas at exercise $E_{\text{acetone}} > E_{\text{ethanol}}$ ($P = 0.028$ for 50 W and $P = 0.018$ for 100 and 150 W). In Fig. 3 these statistically significant differences between the E values of these three gases are indicated by symbols. For all conditions $E_{\text{acetic acid}}$ was not statistically different from E_{ethanol}. Thus, minimum E found for acetone at rest, and the shift of this minimum to ethanol or acetic acid at exercise do have statistical significance.

At the three levels of exercise and at rest with a post-inspiratory apnea the E values for ethyl acetate and acetone are significantly larger than their respective E values at rest ($P = 0.018$, but for acetone at rest with apnea $P = 0.043$). On the contrary, for ethanol and acetic acid no significant differences were found when the E values at exercise and those at rest with apnea were compared with their respective E values at rest.

Discussion

We determined the E values of four tracer gases which are highly soluble in blood and tissue. E was calculated from $1\text{-}P_{\bar{E}}/P_I$ [Eq. (2)]. Equation (2) is based on the assumption that $P_{\bar{v}} \ll P_I$ (see Material and methods). In order to verify this assumption, we studied in two subjects the washout of the applied tracer gases after a similar washin period of 4 min as used for the experiments described in this paper. After 1 min of washout, ethyl acetate, acetone and ethanol could no longer be detected in expired gas. This absence of tracer gases in expired gas implies that $P_{\bar{v}}$ should be virtually zero. Body tissues show large time constants for their washout of highly soluble gases (Kety 1951). By extrapolation, we may conclude, therefore, that throughout the washin period of our experiments $P_{\bar{v}} \ll P_I$. On the basis of the results described above for ethyl acetate, acetone and ethanol, we assume that this holds true for acetic acid as well. However, because of the large time constant of the

mass spectrometer for this gas, it was not possible to verify this in the same way.

During washin a part of the inspired tracer gas is dissolved in superficial airway tissue, and with each expiration a fraction of this dissolved tracer gas is released again from this tissue. This released gas augments $P_{\bar{E}}$ and, therefore, also $P_{\bar{E}}/P_I$, which results in a decrease in E. It is clear that this negative effect on E will be negligible for gases that are poorly soluble in tissue but may be of importance for gases which are easily soluble in tissue. For gases with very large λ values the situation may again be different from the behaviour described above because once dissolved in tissue these gases may not be released again, and this contributes to an augmentation of E. Accordingly, recent models for transpulmonary gas exchange predict that E as a function of λ will show a local minimum with a U-shaped pattern in the range of λ values larger than about 10 (Zwart et al. 1986). In our experimental study, evidence was obtained for the existence of a local minimum in E at rest in the range between $\lambda = \lambda_{\text{ethyl acetate}}$ and $\lambda = \lambda_{\text{ethanol}}$. Further, evidence was obtained for a shift of minimum E to larger λ values in exercise conditions as compared to rest. However, the U-shaped pattern of the data points shown in most of the panels in Fig. 2 was not fully supported by the statistical analysis: i.e., the tendency shown in Fig. 3 for $E_{\text{acetic acid}}$ to be larger than E_{ethanol} appeared not to be significant. Clearly, this is due to the irregular behaviour of the data points for acetic acid with regard to the data points for the remaining three tracer gases (Fig. 2). This irregular behaviour may be related to the technical problems involved in the measurement of $P_{\bar{E}}$ and P_I for acetic acid (Material and methods).

Two different experiments were performed under rest conditions. The results show that significantly larger E values are obtained for ethyl acetate ($P = 0.018$) and acetone ($P = 0.043$) when breathing with a short post-inspiratory apnea as compared to breathing spontaneously. This can be explained as follows: during such an apnea the uptake of tracer gases by superficial airway tissue is continued as well as mixing of tidal gas with residual gas by diffusion. As a consequence, a larger fraction of inspired tracer gas is removed from tidal gas with the result that $P_{\bar{E}}$ is decreased and E increased. However, this effect is not significant for ethanol and acetic acid. The observed effect of a post-inspiratory apnea on E for ethyl acetate and acetone also demonstrates that the breathing pattern is an important determinant of E.

From a theoretical point of view, E for highly soluble gases is largely determined by the fraction of expired gas (V_D/V_T) that originates from the anatomical dead space and lung regions with very large ventilation-perfusion ratios (Wagner et al. 1974; Zwart and Luijendijk 1981, 1982). For highly soluble gases $V_D/V_T \approx 1 - E$ (Zwart and Luijendijk 1981, 1982). As $E = 1 - P_{\bar{E}}/P_I$ in our experiments, this means that $P_{\bar{E}}/P_I \approx V_D/V_T$.

In Fig. 3 only minimal increases in E for ethyl acetate and acetone are observed with a further increase in work load from 50 W to 150 W. This can be ascribed to the fact that the mean tidal volumes at the three levels of exercise do not differ by more than 21% (Table 3). As a consequence, also V_D/V_T will not differ much for the three exercise conditions and, therefore, no clear differences in E may be expected. The difference between the mean values of V_T at rest and during exercise, however, is quite large. The concomitant large difference in V_D/V_T will account for the considerably larger E values for ethyl acetate and acetone under exercise conditions as compared to their E values under resting conditions. For ethanol and acetic acid, however, no evident increase in E is observed under exercise conditions when compared with rest conditions, i.e. the E values of these two gases are hardly affected by both a change in V_T and a post-inspiratory apnea (see above). Evidently, the gas exchange properties of ethanol and acetic acid are completely different from those of gases with considerably smaller λ values. This discrepancy may indicate that the gas exchange of very highly soluble gases is mainly limited to the conducting airways.

Table 3. Tidal volumes (in litres) of the seven subjects (A – G) for the different experimental conditions

	Rest	50 W	100 W	150 W	Rest + apnea
A	0.55	1.35	1.83	2.46	0.73
B	1.57	2.34	2.96	3.31	1.14
C	0.91	3.02	2.91	3.86	0.88
D	0.57	2.01	2.70	3.06	0.73
E	0.58	1.73	2.68	1.95	0.98
F	1.28	3.70	3.16	3.44	0.94
G	0.52	2.75	2.46	2.35	0.87
Mean	0.85	2.41	2.67	2.92	0.89
SD	0.42	0.81	0.43	0.68	0.15

The observed decrease in E in the range of large λ values is in conflict with the results of classical gas exchange models which predict E to increase with increasing λ. In these classical models the different lung compartments are assumed to be ventilated with a continuous flow of air, and, as a result, the partial pressures of the tracer gases in such a model are constant. At constant partial pressures, constant amounts of tracer gases will also be dissolved in lung tissue, and this is of no consequence for transpulmonary gas exchange. The observed behaviour of E as a function of λ is in qualitative agreement with the model predictions of Zwart et al. (1986). These model predictions were obtained with a model that, in contrast with classical models, accounts for the varying amounts of tracer gases dissolved in superficial lung and airway tissue as a result of the within-breath oscillations in the partial pressures of the tracer gases in the airway lumen. Evidently, gas exchange in the airways between the gas phase in the lumen and the dissolved gas in the airway tissue cannot be ignored for highly soluble tracer gases.

The observed decrease in E with increasing λ was the result of the measured increase in $P_{\bar{E}}/P_I$ [Eq. (2)], i.e. the fraction of inspired tracer gas ($P_{\bar{E}}/P_I$) that is expired without having participated in the circulating blood is increased for very large λ values in comparison with $P_{\bar{E}}/P_I$ for ethyl acetate (see Appendix). This means that the aforementioned gas exchange in the airways contributes to protect the body against the uptake of, for example, highly soluble, toxic gases and vapours from inspired air.

MIGET was developed for the determination of the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) distribution of the lung. In the application of MIGET, the recovered dead space ventilation ($\dot{V}_D$) is strongly related to the excretion of the most soluble tracer gas. Our results show that $\dot{V}_D$ ($\approx (1\text{-}E) \cdot \dot{V}_E$) for acetone will be larger than $\dot{V}_D$ for ethyl acetate. Thus, the recovered $\dot{V}_D$ from MIGET appears to

depend on the choice of the most soluble tracer gas, and it is unlikely that the value of $\dot{V}_D$ obtained with acetone as the most soluble tracer gas will apply to the remaining, poorly and moderately soluble tracer gases used in MIGET. Further, it should be noted that the result for $\dot{V}_D$ also has consequences for the rest of the recovered $\dot{V}_A/\dot{Q}$ distribution. It may be better, therefore, not to use highly soluble tracer gases in MIGET.

Conclusions

A local minimum for E is found at rest in the range of large λ values near $\lambda = 330$.

Under exercise conditions this local minimum shifts to λ values larger than 2000.

These experimental findings are in qualitative agreement with recent model predictions where the tidal character of breathing and the buffering capacity of superficial lung tissue are taken into account.

The observed differences between the E values of highly soluble gases imply that $\dot{V}_D$ depends on λ.

Acknowledgement. The authors express their gratitude to Dr. H.J.M. Beijer for performing the statistical analyses.

Appendix

Excretion measured by a non-invasive method

In this study we determined the excretion of highly soluble tracer gases in an alternative way be adding the tracer gases to inspired air and by measuring their partial pressures in inspired and mixed expired gas during short-lasting experiments. This non-invasive method is based on the following considerations. Due to gas exchange in the lung, part of the inspired tracer gas is dissolved in the blood and subsequently carried away from the lung by the circulation. Evidently, the rest of the tracer gas is expired at any moment without having participated in the circulating blood. The partial pressure of this tracer gas in mixed expired gas will be denoted by $P_{\bar{E},1}$. In full equilibrium

$$P_I = P_{\bar{v}} = P_{\bar{E}}. \tag{3}$$

In that condition, expired tracer gas further consists of tracer gas that has been released from the circulating blood and subsequently expired. The contribution of this tracer gas to $P_{\bar{E}}$ will be denoted by $P_{\bar{E},2}$. Hence,

$$P_E = P_{E,1} + P_{E,2}. \tag{4}$$

According to the original definition of Wagner et al. (1974),

$$E = P_{\bar{E},2}/P_{\bar{v}} \tag{5}$$

Substitution of Eqs. (3) and (4) into Eq. (5) results in:

$$E = (P_{\bar{E}} - P_{\bar{E},1})/P_{\bar{v}} = (P_I - P_{\bar{E},1})/P_I = 1 - P_{\bar{E},1}/P_I. \tag{6}$$

This equation shows that E can be calculated from the fraction $P_{\bar{E},1}/P_I$ of inspired tracer gas that is expired without having participated in the circulating blood. In our short-lasting experiments with highly soluble gases $P_{\bar{v}}$ and, therefore, also $P_{\bar{E},2}$ remain virtually equal to zero. Hence, under our experimental conditions,

$$P_{\bar{E}} = P_{\bar{E},1}. \tag{7}$$

Substitution of Eq. (7) into Eq. (6) results in Eq. (2) which was used in our investigation.

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