

Intrapulmonary gas mixing and the sloping alveolar plateau in COPD patients with macroscopic emphysema

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ABSTRACT: Chronic obstructive pulmonary disease patients, especially those with emphysema, show steep slopes of the alveolar plateau (S). This study tested the hypothesis that continued gas exchange between poorly and well-ventilated lung units by means of collateral ventilation would contribute to S in these patients.

Nine young volunteers, nine older volunteers and 11 patients with macroscopic emphysema performed wash-out tests with helium (He) and sulphur hexafluoride (SF₆). S was determined for breaths 1–5 (range 1), and for breaths between 95% and 98% of complete wash-out (range 2). An unequal ventilation index (UVI) was defined as the ratio between the estimated mean alveolar pressure and the end tidal pressure (P_{ET}) of each tracer gas, calculated over range 2. Over the same range, a phase III ratio was calculated by dividing P_{ET} by the estimated pressure at Fowler dead space.

In all groups of subjects, the S for He and SF₆ were greater for range 2 than for range 1 ($p \leq 0.012$). In the emphysema patients, the correlations between S and UVI were 0.72 for He ($p=0.012$) and 0.81 for SF₆ ($p=0.002$), while the mean phase III ratios were 1.7 for He and 2.4 for SF₆, much less than their theoretical maxima.

It was concluded that in patients collateral ventilation may account for only a small part of the increase in the alveolar plateau slope between ranges 1 and 2, and that this increase was mainly caused by unequal ventilation in combination with sequential emptying of lung units. The degree of sequential emptying, however, was modest compared with its full potential.

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During multiple breath wash-outs of inert tracer gases such as helium and sulphur hexafluoride, unequal ventilation of lung units causes differences in tracer gas concentrations across the lung. These differences, in combination with sequential emptying of lung units, may explain the steep slopes of the alveolar plateaus (S) that are found for these gases in patients with chronic obstructive pulmonary disease (COPD). This is a well-known hypothesis [1] that dates from 1956, which assumes that the contribution to the expirate of lung units that are poorly ventilated and, therefore, contain relatively high tracer gas concentrations, increases in the course of each expiration. In later studies, however, it was shown that convective/diffusive interdependence of gas mixing at the acinar level and continued gas exchange across the alveolocapillary membrane for gases that are washed out from mixed venous blood are major determinants of the S in healthy subjects [2–6]. In patients with emphysema, the contribution of convective/diffusive interdependence of gas mixing to S may be enhanced due to the enlarged peripheral airways and airspaces that are characteristic of this disease. Further, there is the possible contribution to S from continued gas exchange between (very) poorly and well-ventilated lung units by means of collateral ventilation. The effect of this special type of continued gas exchange on S will be

similar to that of continued gas exchange across the alveolocapillary membrane, mentioned above. For these reasons, this study evaluated the contributions of continued gas exchange and diffusion-limited gas mixing in the lung to the steep S which are found in patients with COPD. In addition, the relationship between S and the degree of unequal ventilation, and the role of sequential emptying of lung units were evaluated. For this purpose, a new index for unequal ventilation (UVI) was developed. The experiments were performed on patients with emphysema and on healthy subjects for comparison.

Continued gas exchange by means of collateral ventilation between poorly and well-ventilated lung units is most likely to occur in patients with severe emphysema [7, 8]. For the present study, a group of patients with macroscopic emphysema, as determined by high-resolution computed tomography (HRCT), was selected.

Materials and methods

The study was performed on nine young and nine older healthy male subjects and 11 male patients with macroscopic emphysema. The patients (mean age 67 yrs) were selected from the outpatient clinic. All patients had a history of heavy smoking. The young subjects (two smokers, two exsmokers, five nonsmokers) had a mean age of

33 yrs; the older subjects (six smokers and three non-smokers) had a mean age of 64 yrs. None of the healthy subjects had pulmonary complaints.

For all subjects, the inspiratory vital capacity (IVC), forced expiratory volume in one second (FEV₁) and diffusion capacity for carbon monoxide ($D_{L,CO}$) were determined. Spirometry and $D_{L,CO}$ determination were carried out using MasterLab equipment, (Jaeger, Würzburg, Germany).

The HRCT scores of the patients were determined from HRCT scans of five thin sections of lung tissue (Somatom Plus; Siemens, Erlangen, Germany) obtained at full inspiration with the patient in the supine position: two sections of the upper zones at 3 and 6 cm above the carina, two sections of the lower zones at 3 and 6 cm below the carina and one at the level of the carina. Scanning parameters were 1.0-mm collimation, 137 kVp, 220 mA, 1.0 s scanning time and a high-resolution reconstruction algorithm. Hard copy images were photographed using a window setting appropriate for viewing lung parenchyma (level -800 HU; width 1,600 HU).

Using the direct observational method developed by SAKAI *et al.* [9], a visual score was determined for each section by two experienced radiologists who were unaware of clinical findings and of each others' scores. The method of SAKAI *et al.* [9] is based on two aspects of emphysema: severity and extent. Severity was graded on a 4-point scale: 0=no emphysema, 1=low attenuation areas <5 mm in diameter, 2=circumscribed low attenuation areas >5 mm in addition to those <5 mm, and 3=diffuse low attenuation areas without normal intervening lung tissue. The extent of emphysema was also determined using a 4-point scale: 1=<25% of parenchyma involved, 2=25–50% involved, 3=50–75% involved, and 4=75–100% involved. For each hemisection, the score for severity was multiplied by that for extent. The 10 scores (two for each of the five sections) were summed to yield the patient's HRCT score. The scores of the two observers were averaged. The lowest possible HRCT score is 0 (no emphysema) and the highest 120. Patients were considered to have no emphysema if their HRCT score was <30, and to have severe emphysema if the score was ≥60.

Experimental procedure

During the experiments the subjects breathed spontaneously and were seated on a chair. Using a T-piece, they breathed from a bias flow containing a mixture of ~1% He and 0.5% SF₆ in warm (25–28°C) humidified air for 12 min. This combination of tracer gases was chosen for their large difference in diffusivity in residual gas. A Fleisch No. 2 pneumotachograph (Godart, Bilthoven, the Netherlands) situated between the subject and the T-piece was used to assess ventilatory flow as a function of time ($V'(t)$). He, SF₆ and CO₂ concentrations were measured using a mass spectrometer (QMG 511; Balzers, Liechtenstein). The sampling point of the mass spectrometer was located between the Fleisch head and the mouthpiece. The sample flow was 30 mL·min⁻¹ and the equipment dead space 65 mL. He, SF₆ and CO₂ were measured consecutively, each for 10 ms, yielding an effective sample frequency of 33.3 Hz. The time constants of the mass spectrometer were 5.5, 5.5 and 9.5 ms for He, CO₂ and SF₆, respectively. The time delay of the mass spectrometer was ~100 ms. This represents the

time needed for the gas sample to pass through the inlet capillary of the mass spectrometer. The data were corrected for these time constants and this delay. The wash-out was recorded for 15 min, but was not stopped until the expired concentrations of He and SF₆ were <1% of their initial values. Data were stored on hard disk for off-line analysis using a sample frequency of 100 Hz.

S (in %·s⁻¹) were determined for breaths 1–5 (range 1) and for the breaths between 95% and 98% of complete wash-out (range 2). Breathes with small or large tidal volumes (V_T) were excluded, *i.e.* $V_T < 2.5$ Fowler dead space volume (V_{FDS}) or $V_T > 5.0$ V_{FDS} . Slopes are defined as:

$$S = \frac{dP_E/dt}{P_E} \times 100\% \quad (1)$$

where dP_E/dt represents change in P_E per unit time and P_E and $P_{\bar{E}}$ are the partial pressures of the tracer gas in expired gas and mixed expired gas, respectively. $P_{\bar{E}}$ represents volume averaged P_E and was calculated from the measured data through integration of the product of expiratory flow ($V'(t)$) and P_E as a function of time (t) divided by (expiratory) V_T :

$$P_{\bar{E}} = \frac{1}{V_T} \int_{t=0}^{t=tE} V'(t) \times P_E(t) dt \quad (2)$$

and

$$V_T = \int_{t=0}^{t=tE} V'(t) dt \quad (3)$$

where tE is the duration of expiration.

The derivative dP_E/dt was computed from the last part of each expirogram, *i.e.* between 75 and 100% of expired V_T . For theoretical reasons (see *Appendix*), it was necessary to calculate the increase per second in the partial pressure of the tracer gas in the alveolar space (dP_A/dt). During expiration, P_A at time t is reflected by P_E at time $t+t_{delay}$, where t_{delay} corresponds to the time needed for alveolar gas to pass the dead space ($=V_{FDS}$). In general, t_{delay} is not constant due to varying expiratory flow and, therefore, dP_E/dt and dP_A/dt may deviate substantially from one another. Thus, S was calculated from P_E in such a way that it reflected dP_A/dt . The consequences of this correction for the values of S are explained in the *Discussion* section.

The UVI was defined as the ratio between the estimated mean alveolar partial pressure ($P_{\bar{A}}$) and the end tidal partial pressure (P_{ET}), calculated from the breaths between 95 and 98% of complete wash-out. This index was determined separately for each tracer gas. Using the mass balance, the $P_{\bar{A}}$ after the n th breath ($P_{\bar{A},n}$) was calculated from

$$P_{\bar{A},n} = P_0 - \frac{\sum_{i=1}^n P_{\bar{E},i} \times V_{E,i}}{FRC} \quad (4)$$

where i is the summation index, $P_{\bar{E},i}$ is the partial pressure of the tracer gas of the i th breath in mixed expired gas, $V_{E,i}$ is total expired volume of the i th breath, P_0 is the pressure of the tracer gas at the beginning of wash-out and FRC is the functional residual capacity. At complete wash-out, $P_{\bar{A},n}=0$. FRC can then be calculated as follows: $FRC = \sum P_{\bar{E},i} \times V_{E,i} / P_0$.

For the same range (95–98% of complete wash-out), a phase III ratio (r) was calculated by dividing P_{ET} by the estimated pressure at Fowler dead space (P_{FDS}) [10]. P_{FDS} was obtained by linear extrapolation of phase III.

The wash-out behaviour of He and SF₆ can be characterized by the decay of $P\bar{A}$. With regard to the patient data, the decay of $P\bar{A}$ was described by a serial two-compartment model of the lung, *i.e.* the values of the FRCs of the two compartments (FRC₁ and FRC₂), the value of the alveolar ventilation of compartment "1" (V'_{A1}) and the value of the serial ventilation of compartment "2" (V'_{serial}), which provided the best fit between experimental and model data for $P\bar{A}$, were computed using the Levenberg-Marquardt algorithm. This computation was carried out separately for each tracer gas. The results for FRC in healthy subjects and FRC₁ in patients were used to compute the ratios for minute ventilation (V'_E)/FRC and V'_E /FRC₁, respectively. These ratios should correspond to the contribution of continued gas exchange in the lung during expiration to the S for breaths of range 2 (see Appendix). In healthy subjects, this continued gas exchange is related to gas released by capillary blood. In addition, in patients, continued gas exchange also takes place between very poorly and well-ventilated lung units by means of collateral gas transport.

Prior to the computations of UVI, $P\bar{A}$ and FRC, the measured values for P_{ET} and $P\bar{E}$ were corrected for the small amounts of tracer gas released by capillary blood in the lung which originates from wash-out of the body compartments, using the equations:

$$P_{ET} = (P_{ET,measured} - \frac{\lambda \times Q'}{V'_A} \times e^{-t/\tau} \times P_0) / (1 - \frac{\lambda \times Q'}{V'_A}) \quad (5)$$

$$P\bar{E} = (P\bar{E}_{,measured} - \frac{\lambda \times Q'}{V'_E} \times e^{-t/\tau} \times P_0) / (1 - \frac{\lambda \times Q'}{V'_A}) \quad (6)$$

The applied time constant (τ) was 715 and 685 s for He and SF₆, respectively, and their partition coefficients (λ) were 0.01 and 0.0073, while effective cardiac output (Q') was 1.9 L·min⁻¹ for both gases. These data were determined from the very last part of the wash-out curves of young healthy subjects, the behaviour of which is com-

pletely determined by the release of tracer gas from capillary blood. Alveolar ventilation (in L·min⁻¹) for each tracer gas was estimated from:

$$V'_A = V'_E - f_R \times V_{FDS} \quad (7)$$

where f_R is the respiratory frequency. The effect of the above corrections on the results for FRC for He (FRC_{He}) and SF₆ (FRC_{SF6}) amounts maximally to 226 mL and 158 mL, respectively.

Statistical analysis was performed using the Mann-Whitney U-test for differences between groups and the paired Wilcoxon test for differences within groups. A p-value <0.05 was considered significant, unless multiple comparisons were made, in which case a Bonferroni correction was made (p<0.05/n, where n is the number of tests). Pearson correlations were calculated after visual control of the linearity of the relationship between the two variables.

Results

General data, lung function characteristics and HRCT scores are listed in table 1. In the emphysema group, the HRCT score ranged 36–115, mean 62.9, suggesting moderate-to-severe disease. According to the criteria of the European Community for Steel and Coal [11], the lung volumes of all healthy subjects were within normal limits.

The age of the patients (mean 67.3 yrs) did not differ significantly from that of the older healthy subjects (mean 63.7 yrs), whereas FEV₁, FEV₁/IVC and DL_{CO} did (44.1% versus 106.9%, p<0.001; 33.1% versus 75.3%, p<0.001; and 51.2% versus 115.7%, p<0.001, respectively). Except for age, the young subjects did not differ from the older ones for the measures presented.

Figure 1 shows the S for all three gases and both ranges. In the emphysema group, all the S were considerably steeper than the corresponding S for the older healthy subjects (p≤0.007). In the healthy groups, the older subjects showed somewhat steeper S than the young subjects (not significant). The S for He (S_{He}) and SF₆ (S_{SF6}) increased significantly from range 1 to range 2 for the emphysema group (p=0.003), whereas for the older healthy subjects the increase was only significant for SF₆ (p=0.008). As expected, the S of CO₂ remained unchanged between the two ranges in all groups. In all three

Table 1. – General data, lung function characteristics and high-resolution computed tomography (HRCT) scores

	Healthy subjects				Patients with emphysema (n=11)	
	Young (n=9)		Older (n=9)		Mean±SD	Range
	Mean±SD	Range	Mean±SD	Range		
Age yrs	33.1±4.3	27–39	63.7±4.1*	58–70	67.3±5.6	58–77
Height m	1.81±0.10	1.73–2.05	1.74±0.03	1.70–1.79	1.67±0.07	1.52–1.81
FEV ₁ L	4.56±0.66	3.85–5.75	3.39±0.54	2.89–4.72	1.26±0.58	0.58–2.48
FEV ₁ % pred	106.6±10.2	93–126	106.9±13.0	89–134	44.1±17.0 ⁺	30–80
IVC % pred	108.2±12.6	95–132	105.2±12.3	91–129	100.4±23.8	60–149
FEV ₁ /IVC %	79.9±11.1	59.2–93.1	75.3±6.1	67.4–84.7	33.1±8.0 ⁺	20.0–50.0
DL _{CO} % pred	108.5±10.4	92–121	115.7±19.7	93–143	51.2±24.6 ⁺	16–85
HRCT score [#]					62.9±23.9	36–115

[#]: score range 0–120 (see text). FEV₁: forced expiratory volume in one second; IVC: inspiratory vital capacity; DL_{CO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography. *: significantly different from values for young subjects; ⁺: significantly different from values for older subjects (p<0.001).

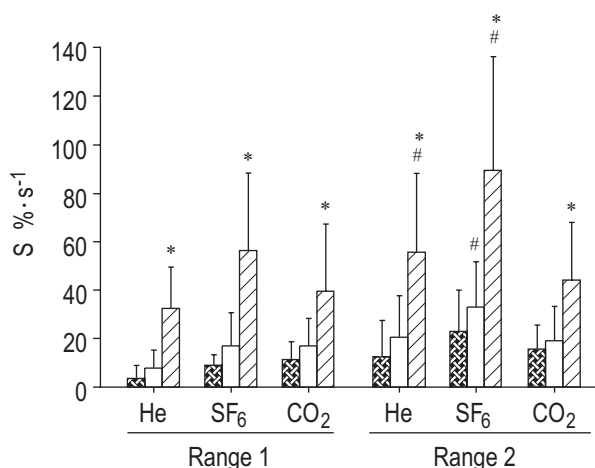


Fig. 1. – Slopes of the alveolar plateaus (S) for He, SF₆ and CO₂ in young (▣) and older healthy subjects (□) and in patients with macroscopic emphysema (⊘), obtained from the early and late parts of wash-out (range 1 and 2, respectively). *: significantly different from older healthy group. #: significantly different from corresponding value for range 1. p<0.02.

groups and for both ranges, the mean SSF₆ were significantly greater than the mean SHe (table 2).

Figure 2 shows that the UVI and r were higher in patients with emphysema than in the older healthy subjects (p<0.01). Further, both UVI values appeared to be larger in the older healthy subjects compared with the young healthy subjects (p≤0.002). Consistent with SSF₆ being >SHe, the UVI for SF₆ (UVISF₆) was found to be > the UVI for He (UVIHe) for young healthy subjects (p=0.012) and emphysema patients (p=0.006). For patients, the correlation coefficient between S and UVI was 0.72 for He (p=0.012) and 0.81 for SF₆ (p=0.002).

Values for specific ventilation ($V'E/FRC$ in %·s⁻¹) are listed in table 3. No significant differences between the three groups were found.

Discussion

The S found in the present study for the group of young healthy subjects are ~2–3 times steeper than the S reported by SCHRIKKER *et al.* [6] for a comparable group of subjects at rest. This large difference may be attributed, at least in part, to a difference in the methods applied to compute S

Table 2. – Slopes of the alveolar plateaus (S) for helium and sulphur hexafluoride

Subjects	Range	S %·s ⁻¹		p-value
		He	SF ₆	
Young	1	3±6	9±4	0.008
	2	12±15	23±17	0.012
Older	1	8±7	17±13	0.011
	2	21±17	33±18	0.008
Emphysema	1	33±17***	56±32***	0.003
	2	56±33**	90±46***	0.003

Data are presented as mean±SD. Range 1 encompasses breaths 1–5, and range 2 includes those breaths that correspond to 95–98% of complete wash-out. The p-values refer to the differences between the slopes for He and SF₆. **, ***: p<0.01, p<0.001 compared to older subjects.

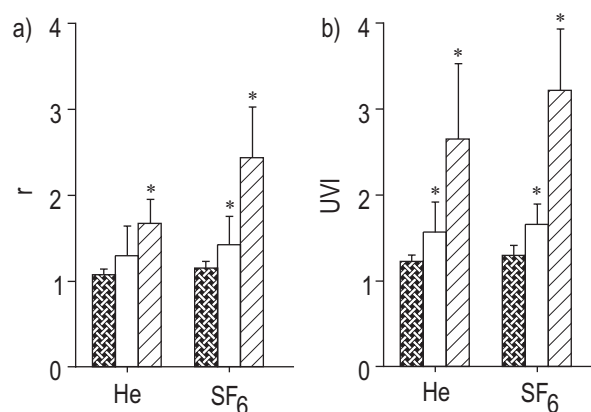


Fig. 2. – a) Phase III ratio (r) and b) unequal ventilation index (UVI) for He and SF₆ in young (▣) and older healthy subjects (□) and in patients with macroscopic emphysema (⊘), calculated from the late parts of wash-out (range 2). *: significantly different from previous group. p<0.02.

from the recordings. SCHRIKKER *et al.* [6] normalized S using mid-tidal PE, whereas the present study used P_E (see *Materials and methods*). In healthy subjects, mid-tidal PE is considerably higher than P_E. As a consequence, lower values for S are obtained when they are normalized using mid-tidal PE instead of P_E.

In order to be able to estimate the contribution of continued gas exchange to the S of range 2, dPE/dt should represent dPA/dt (*Materials and methods*). The relationship between these quantities, however, is affected by differences in transit time of successive gas samples between the alveolar space and the sampling site of the mass spectrometer due to the varying expiratory flow. For this reason, this difference in transit time of successive gas samples was corrected for through a transformation of the time axis for PE (*Materials and methods*). This correction was not performed by SCHRIKKER *et al.* [6]. In general, the flow reaches a maximum in early expiration and then declines until the end of expiration. Thus, the S was computed from the part of expiration (between 75 and 100% of total expired volume) in which the flow declined. As a consequence, during this part of expiration, the separation in time of the two gas samples increases during the passage of the dead space, and, as a result, dPA/dt is reflected in a smaller dPE/dt. Hence, the applied correction for the difference in transit time of successive gas samples in the dead space enhanced the results for S, and this too contributed to the higher values for S found in the present study compared to those reported by SCHRIKKER *et al.* [6].

Table 3. – Specific ventilation ($V'E/FRC$) of helium and sulphur hexafluoride in young and older healthy subjects and in patients with emphysema

Subjects	$V'E/FRC$ %·s ⁻¹	
	He	SF ₆
Young	5.1±1.8	4.9±1.5
Older	6.3±3.1	6.4±3.1
Emphysema	5.5±1.6	4.9±1.5

Data are presented as mean±SD. V'E: minute ventilation; FRC: functional residual capacity.

Continued gas exchange and the sloping alveolar plateau

The contribution of continued gas exchange to S may be estimated from $V'E/FRC$ (Appendix). The mean results for $V'E/FRC$ are $\sim 5.5\% \cdot s^{-1}$ for all groups of subjects (table 3). This can account for approximately a half of the increase in S between early (range 1) and late (range 2) wash-out in healthy subjects (table 2). In patients, the mean increase in S between early and late wash-out amounts to $22\% \cdot s^{-1}$ and $34\% \cdot s^{-1}$ for He and SF₆, respectively (table 2). These results are considerably higher than $V'E/FRC_1$ (table 3), which suggests that, in this group of subjects, the contribution of the continued gas exchange to S is of minor importance. CRAWFORD *et al.* [12] attributed the increase in S found in healthy human subjects to inhomogeneities of tracer gas concentrations that develop during wash-out as a result of unequal ventilation. This assumption, however, has not been verified experimentally. In a later study, SCHRIKKER *et al.* [6] concluded that continued gas exchange across the alveolocapillary membrane alone can account for the increase in S between early and late wash-out. These authors, however, did not correct for the differences between dP_E/dt and dP_A/dt . The present data show that continued gas exchange can account for only a smaller fraction of the increase in S between range 1 and range 2.

The results from the present study for $V'E/FRC$ and $V'E/FRC_1$ (table 3) mean that the absolute contribution of continued gas exchange across the alveolocapillary membrane and collateral ventilation to S in late wash-out are virtually equal for the three test groups. Since these groups (healthy subjects and patients with macroscopic emphysema) constitute the extremes of the whole spectrum of subjects with unequal ventilation, it is expected that other patients with obstructive lung disease, *e.g.* asthma or chronic bronchitis, will show similar results for $V'E/FRC$ and $V'E/FRC_1$. This means that the relative contribution of continued gas transport to S in late wash-out is inversely related to S. As a consequence, it is expected that, for other categories of patients with obstructive lung disease, this relative contribution to S will be inbetween those found in this study for healthy subjects and patients with emphysema. Other possible mechanisms causing an increase in S will be discussed below.

Unequal ventilation, gas mixing and the sloping alveolar plateau

The UVI is equal to $P\bar{A}/P_{ET}$ in late wash-out (see *Materials and methods*). In an ideal lung, P_{ET} is equal to $P\bar{A}$, and, as a consequence, the $UVI=1$. In both healthy and diseased lungs, however, unequal ventilation in combination with sequential emptying of lung units may cause $P\bar{A}$ to be higher or lower than P_{ET} .

At the onset of wash-out, *i.e.* after complete wash-in of the tracer gases, $P_{ET}=P\bar{A}$. During wash-out, $P\bar{A}/P_{ET}$ for He increased on average from 1 to 1.23 in young healthy subjects, from 1 to 1.57 in older healthy subjects, and from 1 to 2.65 in the emphysema group (fig. 2). This difference in increase in $P\bar{A}/P_{ET}$ may be attributed to a much more

severe degree of unequal ventilation in the patient group, which resulted in larger relative differences in gas concentration in their lungs in late wash-out, *i.e.* a much more pronounced inhomogeneity of tracer gas concentrations. In all groups, $UVI > 1$, which means that $P\bar{A}$ is $>P_{ET}$. This suggests that end-tidal gas originated mainly from the better-ventilated parts of their lungs, otherwise UVI would have been < 1 .

In patients and young healthy subjects, UVI_{He} was $< UVI_{SF_6}$, which means that the degree of unequal ventilation is inversely related to the diffusivity of the tracer gas in alveolar gas. The large, relative differences between the slopes for SF₆ and He (SS_{SF_6} being $>S_{He}$, table 2) show that, at least for SF₆, limited gas mixing by diffusion is a major determinant of the sloping alveolar plateau. Gas mixing by diffusion takes place mainly in the small airways and air spaces of the acini. For healthy subjects, the contribution of limited gas mixing to S has been ascribed to convective/diffusive interdependence of intra-acinar gas mixing, in which S increases with increasing flow [4, 5]. In COPD, the flow to diseased parts of the lung is diminished. Therefore, it is unlikely that the high values of S found in the present patients are due to convective/diffusive interdependence of intra-acinar gas mixing. The correlation coefficient between S and UVI for patients with emphysema was 0.72 for He and 0.81 for SF₆. These high values suggest that the sloping alveolar plateau in patients with emphysema is mainly due to unequal ventilation in combination with sequential emptying of lung units.

A further consequence of the difference in diffusivity between He and SF₆ is that the alveolar ventilation of lung units for He is larger than that for SF₆. This difference will be enhanced for diseased parts of the lung with enlarged airways and airspaces in which mixing by diffusion is less efficient. This may explain why the differences between the SS_{SF_6} and S_{He} are largest in the patient group (table 2).

Sequential emptying and the sloping alveolar plateau

The maximum value of r that can be reached by sequential emptying is equal to P_{max}/P_{min} , where P_{max} and P_{min} are the partial pressures of the tracer gas in the poorest and best ventilated lung units, respectively. For maximum r, the best ventilated units should determine the expirate in early phase III and the poorest ventilated lung units the expirate in late phase III. P_{max}/P_{min} can be written as:

$$\frac{P_{max}}{P_{min}} = \frac{P_{max}}{P\bar{A}} \times \frac{P\bar{A}}{P_{ET}} \times \frac{P_{ET}}{P_{FDS}} \times \frac{P_{FDS}}{P_{min}} \quad (8)$$

where P_{FDS} is the extrapolated value of phase III at $V_E = V_{FDS}$. Substitution of UVI and r in this expression results in

$$\frac{P_{max}}{P_{min}} = \frac{P_{max}}{P\bar{A}} \times UVI \times r \times \frac{P_{FDS}}{P_{min}} \quad (9)$$

The two unknown terms, $P_{max}/P\bar{A}$ and P_{FDS}/P_{min} , are both > 1 . Therefore, P_{max}/P_{min} is $> UVI \times r$. In the emphysema group, UVI_{He} was 2.65. This implies that the measured r is only a smaller fraction of the maximum r ($= P_{max}/$

P_{\min}). Thus, the degree of sequential emptying of lung units in patients with emphysema constitutes only a modest part of its full potential.

In conclusion, in patients with macroscopic emphysema, continued gas exchange by means of collateral ventilation and transport across the alveolo-capillary membrane does not play an important role in the genesis of the sloping alveolar plateau during tidal breathing. This slope is caused mainly by unequal ventilation in combination with sequential emptying, where the degree of unequal ventilation is inversely related to the diffusivity of the tracer gas in the residual gas. The degree of sequential emptying of lung units in patients with emphysema constitutes only a modest part of its full potential.

Appendix

During wash-in, small fractions of the tracer gases cross the alveolocapillary membrane and are subsequently dissolved in capillary blood. From there, the tracer gases are transported to the body compartments by the circulating blood. During wash-out, this process is reversed causing a continuous supply of tracer gases to the lung. The wash-out of He and SF₆ from the body compartments proceeds for a long time (see *Materials and methods*). As a consequence, in late wash-out, nearly all the tracer gas that is still present in the lung originates from the body compartments. For this situation, DE VRIES *et al.* [13] and SCHRIKKER *et al.* [6] have shown that the contribution of the continued gas exchange across the alveolocapillary membrane to the S can be estimated from the $V'A/FRC$ ratio. This result follows from the equation:

$$\frac{P'A}{\bar{P}A} = \frac{V'A}{FRC} \quad (10)$$

where $P'A$ represents the increase in the partial pressure of the tracer gas in the alveolar space per unit time resulting from the continued exchange of tracer gas across the alveolocapillary membrane during expiration, and $\bar{P}A$ represents the mean partial pressure of the tracer gas in expired alveolar gas.

For healthy subjects, $\bar{P}A$ and $V'A$ can be determined from experimental data. SCHRIKKER *et al.* [6] estimated $\bar{P}A$ from mid-tidal P_E while $V'A$ was computed from the first 20 breaths of wash-out. For this reason, these authors normalized S with regard to mid-tidal P_E . For patients, however, neither $V'A$ nor $\bar{P}A$ can be accurately estimated from the data. The current study replaced, therefore, $V'A$ with $V'E$ and $\bar{P}A$ with $\bar{P}E$, based on the following consideration. The amount of tracer gas that is expired per unit time is equal to both $V'A \times \bar{P}A / (R \times T)$ and $V'E \times \bar{P}E / (R \times T)$, where R is the gas constant and T is tem-

perature. Thus, $V'A \times \bar{P}A = V'E \times \bar{P}E$. Substitution into the above equation results in

$$\frac{P'A}{P_E} = \frac{V'E}{FRC} \quad (11)$$

$V'E$ and $\bar{P}E$ can be accurately determined for all categories of subjects without the need for making disputable assumptions. This also explains why, in the present study, the slopes of the alveolar plateau (in %·s⁻¹) were normalized with regard to $\bar{P}E$.

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