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Aerosol bolus dispersion in healthy subjects

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ABSTRACT: Aerosol bolus dispersion is a physiological test of lungs, which uses monodisperse submicron particles to measure intrapulmonary convective gas mixing. In this study, aerosol bolus dispersion was measured in healthy subjects in order to assess reference values for possible clinical applications, to assess the reproducibility of these values, and to identify physical and physiological factors influencing aerosol bolus dispersion.

Aerosol bolus dispersion was measured in 79 healthy subjects using 20 cm^3 aerosol boluses consisting of monodisperse di-2-ethylhexyl sebacate (DEHS) particles.

The reproducibility of parameters characterizing the width of the exhaled bolus was of the same order as that of parameters of the flow-volume curve (10%). Aerosol bolus dispersion was independent of the level of lung inflation, and the slope of the relationship between flow rate and dispersion was on average not significantly different from zero (range 100–700 $cm^3 \cdot s^{-1}$). Multiple linear regression showed that aerosol bolus dispersion increased with increasing total lung capacity of the subject.

We conclude that differences in total lung capacity between individuals should be taken into account when using measures of aerosol bolus dispersion for possible clinical applications.

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Changes in lung ventilation distribution are presumed to be an early indication of lung disease. Such changes have been observed in patients with various lung diseases [1, 2], and in smokers [3]. A simple and noninvasive diagnostic test, which is sensitive to such ventilatory disturbances, could efficiently supplement conventional methods used in lung diagnosis, occupational and environmental medicine, and epidemiology. The aerosol bolus dispersion test is a technique with the potential to meet these requirements. This technique employs monodisperse submicron aerosol particles as tracers of the convective gas transport in the lungs. Its diagnostic capabilities have been shown in several studies: ventilatory disturbances in patients with cystic fibrosis [4]; papain-induced peripheral lung injury in excised animal lungs [5]; and changes in lung ventilation distribution due to ozone exposure [6]. Recently, it has been shown that this technique has higher sensitivity and specificity than conventional lung function tests in detecting early lung impairment due to cigarette smoking [7].

This study addresses one requirement for the possible clinical application of this technique, namely the reliable assessment of individual specific reference values for the healthy state. Respiratory experiments were conducted on a sample of 79 nonsmokers with normal, healthy lungs. The variability of the measurements over time was tested in two of these subjects over a period of 6 months. To characterize physical and physiological factors influencing aerosol bolus dispersion, the effect of lung inflation and flow rate was investigated in subgroups of these subjects.

Subjects

Seventy nine healthy nonsmokers (38 males and 41 females) were included in the study (table 1). They were selected in order to achieve an even age distribution and were then classified into four age groups: 20–29 yrs (20 subjects); 30–39 yrs (20 subjects); 40–49 yrs (20 subjects); and 50–60 yrs (19 subjects). Anamnestic data were collected using a questionnaire based on American Thoracic Society (ATS) recommendations [8]. Subjects

Table 1. – Anthropometric and lung function parameters of the study population

Parameter		Relative value
Age yrs	39±11	
Height m	1.7±0.1	
Weight kg	68±11	
TLC L	6.3±0.1	1.03
RV L	1.6±0.4	0.88
VC L	4.6±1.0	1.09
FEV_1 L	3.7±0.8	1.08
MEF_{25} $L \cdot s^{-1}$	1.7±0.6	0.89
MEF_{50} $L \cdot s^{-1}$	4.6±1.3	1.00
MEF_{75} $L \cdot s^{-1}$	7.7±1.8	1.10
PEF $L \cdot s^{-1}$	9.6±2.7	1.17
$_sR_{aw}$ KPA$\cdot s^{-1}$	0.59±0.14	

Values are presented as mean±SD. Relative values are normalized to the reference value. TLC: total lung capacity; RV: residual volume; VC: vital capacity; FEV_1: forced expiratory volume in one second; MEF_{25}, MEF_{50}, and MEF_{75}: maximal expiratory flow at 25, 50 and 75% VC, respectively; PEF: peak expiratory flow; $_sR_{aw}$: specific airway resistance.

were excluded from the study if they were active smokers, if they had ever smoked more than 4 pack-years, or if there was any hint of respiratory or cardiovascular disease or atopy. Informed written consent was obtained from each subject. The protocol was approved by the Ethics Committee of the Medical School of the Ludwig Maximilians University, Munich, Germany.

Methods

Gas transport in the lungs is due to diffusion and convection. Since monodisperse aerosol particles 0.5–1 μm in diameter behave like a "nondiffusive gas", they can be used as tracers for studying convective gas transport [9]. In the present experiments, a small volume (bolus) of the inspired air was labelled with these particles. During respiration, particles were convectively transported into air volumes which were initially particle-free. In the exhaled air, the aerosol bolus was, therefore, distributed over a larger air volume than in the inhaled air, *i.e.* the bolus was dispersed [10, 11]. This broadening of aerosol boluses in the respired air is increased in diseased lungs.

The width and shape of an inhaled and exhaled aerosol bolus can be quantified in different ways. The simplest way to specify the dimensions of an aerosol bolus is to calculate its volumetric half width (H_{50}), which is defined as the volumetric width of the bolus measured when the particle concentration is one half the maximum concentration (fig. 1). To account for the contribution of the width of the inhaled bolus ($H_{50,I}$) to the width of the exhaled bolus ($H_{50,E}$), a corrected half-width ($H_{50,C}$) was introduced, which is given by:

$$H_{50,C} = \sqrt{H^2_{50,E} - H^2_{50,I}} \quad (1)$$

In general, the width and shape of an arbitrary distribution can be quantified by normalized power moments. The k_{th} moment is given by:

$$\mu_k = \frac{\int (V-V_m)^k \, C(V)dV}{\int C(V)dV} \quad (2)$$

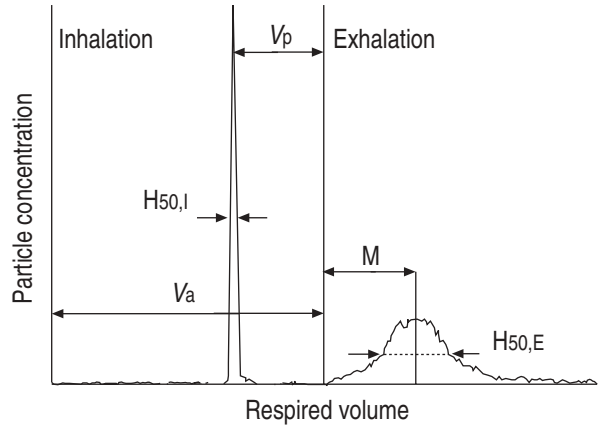

Fig. 1. – Particle number concentration as a function of the respired air volume during the measurement of aerosol bolus dispersion. $H_{50,I}$: width of the inhaled bolus; $H_{50,E}$: width of the exhaled bolus; V_p: volumetric lung depth; M: bolus mode; V_a: air volume.

where V is the respired volume, $C(V)$ the particle number concentration, and V_m is the volumetric centre of mass:

$$V_m = \frac{\int V \cdot C(V)dV}{\int C(V)dV} \quad (3)$$

The standard deviation (σ) of the bolus can be calculated using the second moment μ_2:

$$\sigma = \mu_2^{1/2} \quad (4)$$

The corrected standard deviation is defined similarly to the corrected half-width (Equation 1).

The skewness (ψ) of the bolus is given by:

$$\psi = \mu_3 / \sigma^3 \quad (5)$$

If $\psi = 0$, the bolus is symmetrical with respect to its mode. If $\psi \neq 0$, the bolus is asymmetrical: if $\psi > 0$, the distal portion of the bolus is prolonged compared to the proximal part. If $\psi < 0$, the distal part of the bolus is shortened.

To avoid integrating the noise signal at zero particle concentration, a threshold concentration level was defined: the volumetric limits of integration were chosen so that only concentration values larger than 15% of the expired maximum concentration (C_{max}) were considered. In this case, σ showed the least dependency on the C_{max} to noise ratio.

The volumetric position of the aerosol bolus within the exhaled air is characterized by the bolus mode (M), which is defined as that cumulative exhaled air volume at which the highest particle concentration is measured (fig. 1). The volumetric lung depth (V_p), the controlled experimental variable, is defined as the air volume between the volume at which the maximum particle concentration is measured and the end-inspiratory volume.

The difference between the V_p of the inhaled bolus and the M of the exhaled bolus is called mode shift (ΔM):

$$\Delta M = M - V_p \quad (6)$$

The position of M and V_p are estimated as follows: the raw data from the signal measuring the concentration levels are first smoothed by calculating a moving average of seven adjacent concentration values (≈6 mL). A normal distribution is numerically fitted to the upper values of the inhaled and exhaled boluses (90–100% of bolus height), and the calculated median of this fitted distribution is taken as an approximation of V_p and M, respectively.

The number of aerosol particles not recovered from the lungs during exhalation can be quantified by the particle deposition (D):

$$D = 1 - \frac{n_E}{n_I} = 1 - \frac{\int_{V_E} C(V)dV}{\int_{V_I} C(V)dV} \quad (7)$$

where n_E is the number of particles exhaled after inhalation of n_I particles.

Instrumentation

The assessment of aerosol bolus dispersion requires continuous monitoring of particle number concentration in the respired air as a function of the respired air volume. Data were collected using an on-line, open-flow apparatus, which combined aerosol photometry and pneumotachography [12]. To apply an aerosol bolus into the inhaled air, the inhalation channel of the apparatus was switched from clean air to aerosol supply using computer-controlled, pneumatic valves.

Inhalation protocols

Subjects were seated in front of the apparatus in an upright position. The mouthpiece was covered by a silicone dental compound, which filled part of the mouth cavity in order to reduce the extrathoracic dead space. After a few tidal breaths, the subjects inhaled from functional residual capacity (FRC), an air volume (V_a) with a constant flow rate. An aerosol bolus with a half-width of 20 cm^3 was applied to this air volume. The subject exhaled until the bolus was completely recovered from the lungs (fig. 2). The required flow rate was controlled by watching a visual flow signal.

V_a was chosen for each subject to ensure that the end-inspiratory lung volume of all subjects, FRC + V_a, was equal to the same fraction, F, of total lung capacity (TLC):

$$F \cdot \text{TLC} = \text{FRC} + V_a \quad (8)$$

All air volumes were corrected to body temperature, atmospheric pressure, and saturation with water vapour (BTPS).

Reference values. Boluses were applied at volumetric lung depths, V_p = 20, 50, 100, 200, 300, 400, 600 and 800 cm^3 in order to assess reference values for aerosol bolus dispersion as a function of lung depth. The end-inspiratory lung volume was 70% TLC (F=0.7). Measurements were performed three times on each subject using an airflow rate of 250 $cm^3 \cdot s^{-1}$.

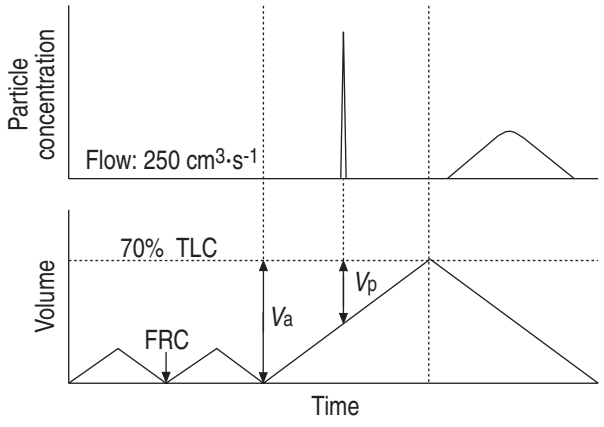

Fig. 2. – Schematics of the inhalation protocol. TLC: total lung capacity; FRC: functional residual capacity; V_a: air volume; V_p: volumetric lung depth.

Reproducibility. Intersubject variability of a bolus parameter was quantified by its relative standard deviation, defined as the standard deviation of the observations over all subjects in the sample divided by the mean of these observations (relative population standard deviation (σ_p)).

In order to assess the temporal variability of the aerosol bolus dispersion parameters, bolus dispersion measurements on two subjects were repeated three times a month over a period of 6 months. The relative standard deviations of these intrasubject observations was then calculated (intrasubject variability (σ_s)).

Effect of lung inflation. To investigate the influence of lung inflation on aerosol bolus dispersion, data were collected from a subset of the study population at a single volumetric lung depth of 800 cm^3 for two end-inspiratory lung volumes of 50% TLC (F=0.5) and 85% TLC (F=0.85). Measurements were performed twice for each subject and for each level of lung inflation.

Effect of airflow rate. To study the influence of airflow rate on aerosol bolus dispersion, data were collected from a subset of the study population. Boluses were inhaled to 600 cm^3 lung depth, with V_a = 1,000 cm^3. For each subject, 20 measurements were performed with airflow rates ranging 100–700 $cm^3 \cdot s^{-1}$.

Particle generation and classification

Monodisperse di-2-ethylhexyl sebacate (DEHS) particles were produced in a nitrogen atmosphere by heterogeneous nucleation of DEHS vapour on NaCl nuclei, and were then diluted with air. The terminal settling velocity (v_s) of the particles was measured in a convection-free sedimentation cell. The average settling velocity throughout the study was 23±2 $\mu m \cdot s^{-1}$, corresponding to 0.84 μm average geometrical particle diameter.

Lung function test

Each subject underwent conventional lung function tests before the aerosol bolus dispersion measurements. Lung function was assessed in a constant volume body-plethysmograph with integrated spirometer (Masterlab; Jäger, Würzburg, FRG) [13]. Three maximal forced expirations were recorded, and the flow-volume curve which yielded the highest sum of the two values, forced expiratory volume in one second and vital capacity, was selected for analysis.

The following parameters were included in the data analysis: specific airway resistance ($_sR_{aw}$), TLC, residual volume (RV), intrathoracic gas volume (ITGV), vital capacity (VC), expiratory reserve volume (ERV), peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1), and the maximal expiratory flows at 25, 50 and 75% vital capacity (MEF_{25}, MEF_{50}, MEF_{75}). Predicted values for conventional lung function parameters were calculated by normalizing the data to the reference values proposed by the European Community for Steel and Coal [13].

Data analysis

Data analysis was performed using the Statistical Analysis System (SAS) software package on an IBM 4381 computer (operating system CMS). Student's t-test was used to test group differences for statistical significance (SAS procedure TTEST). Correlation analysis was performed by applying the Pearson product-moment correlation test (SAS procedure CORR). Analysis of variance was performed by fitting a linear regression model to the data under consideration of conditional correlations (SAS procedure GLM). Results were judged to be significant when the error level p was less than 0.01.

Table 2. – Aerosol bolus parameters as a function of volumetric lung depth measured in 79 healthy subjects

Lung depth cm^3	Median	5th %	95th %
Half width cm^3			
800	529	439	697
600	434	340	572
400	332	268	446
300	284	222	389
200	235	185	323
100	180	130	239
50	112	80	148
20	66	38	112
Standard deviation cm^3			
800	221	178	291
600	183	147	240
400	149	118	198
300	133	102	173
200	107	85	129
100	72	55	88
50	49	37	65
20	33	20	51
Skewness			
800	0.200	0.077	0.327
600	0.241	0.064	0.373
400	0.219	-0.223	0.385
300	0.168	-0.200	0.387
200	0.243	0.006	0.405
100	0.382	0.223	0.515
50	0.480	0.377	0.590
20	0.415	0.257	0.562
Mode shift cm^3			
800	-64	-123	-18
600	-35	-79	-8.8
400	-22	-53	9.0
300	-10	-44	17
200	-3.9	-26	31
100	5.0	-15	30
50	5.2	-22	29
20	11	-1.2	26
Deposition %			
800	40.7	26.7	49.7
600	29.2	21.3	38.5
400	20.4	15.0	28.4
300	16.5	11.4	24.0
200	13.6	8.5	21.6
100	9.3	4.0	16.8
50	6.9	0.4	15.0
20	7.4	-1.9	13.6

5th % and 95th %: 5th and 95th percentile.

Results

Reference values

The median values as well as the 5th and 95th percentiles of all measured parameters are listed in table 2. Figure 3a shows the half-width $H_{50,c}$ (mean±SD) of expired aerosol boluses as a function of the volumetric lung depth obtained for the 79 healthy subjects. It increased with increasing lung depth and can be approximated by a power function:

$$H_{50,c} = 12\ V_p^{0.57} \quad (9)$$

The relative population standard deviation (σ_p) was 13% for lung depth 800 cm^3, 17% for lung depths 800 $cm^3 > V_p \geq 50\ cm^3$, and 30% for $V_p = 20\ cm^3$. The intra-subject variability (σ_s) of $H_{50,c}$ for all lung depths was below 10% (table 3).

The standard deviation of the exhaled boluses showed similar behaviour with respect to lung depth (fig. 3a). It can be approximated by:

$$\sigma - 6.2\ V_p^{0.54} \quad (10)$$

Figure 3b shows the skewness (ψ) as a function of the volumetric lung depth. In peripheral lung regions, ψ was about 0.2, indicating that the exhaled aerosol

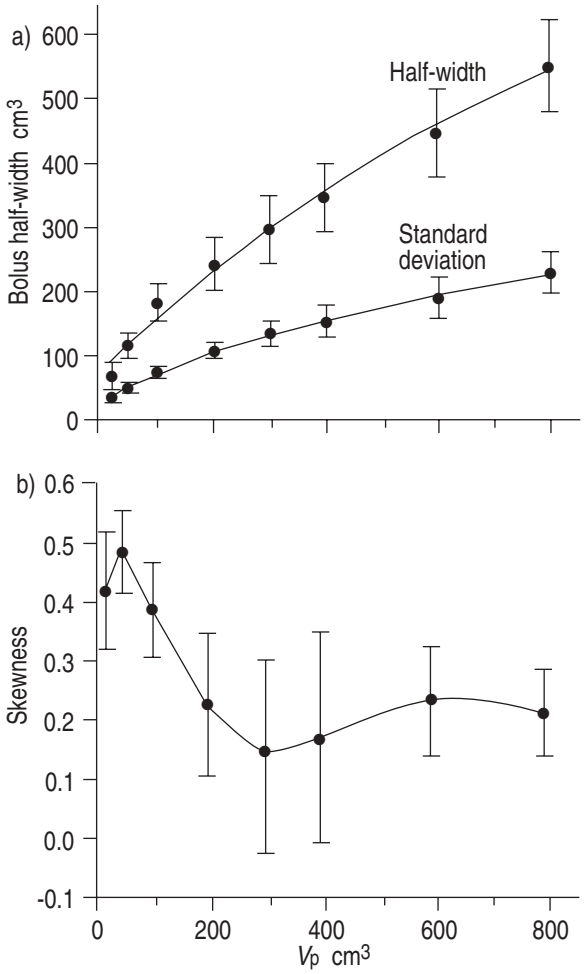

Fig. 3. – a) Volumetric half-width (mean±SD) and standard deviation; and b) skewness of exhaled aerosol boluses as a function of volumetric lung depth (V_p) measured in 79 healthy subjects.

Table 3. – Relative population standard deviation (σ_p) and intrasubject variability (σ_s) of aerosol bolus parameters measured in two different subjects as a function of volumetric lung depth (V_p)

V_p	σ_p %	σ_s %	
cm^3	Population	Subject 1	Subject 2
Half-width			
800	13	7	5
600	15	9	6
400	15	4	5
200	17	9	5
Standard deviation			
800	14	6	4
600	15	8	6
400	16	9	5
200	12	7	5
Skewness			
800	33	28	12
600	40	46	21
400	106	50	19
200	54	9	19
Mode shift			
800	52	82	242
600	71	96	160
400	126	150	120
200	600	48	186
Deposition			
800	17	12	12
600	17	18	17
400	20	26	25
200	28	41	64

bolus was slightly asymmetrical. In proximal lung regions, ψ increased to values of about 0.5, indicating a pronounced asymmetrical shape of the exhaled boluses. Inter- and intrasubject variabilities of ψ were much higher (10%–100%) compared to variability of parameters measuring the bolus width (table 3).

Figure 4 shows the measured mode shift (ΔM) as a function of the volumetric lung depth. For shallow lung depth, ΔM was practically zero. With increasing lung penetration, ΔM became increasingly negative reaching -70 cm^3 for V_p = 800 cm^3: the bolus was shifted proximally. Over the range of V_p, the variability parameters σ_s and σ_p were relatively high.

Particle deposition (D) increased linearly, from about D = 0.06 for V_p = 20 cm^3 to about D = 0.4 for V_p = 800 cm^3 (fig. 4b). Inter- and intrasubject variabilities for lung depths beyond 200 cm^3 were in the order of 20% (table 3).

Effect of lung inflation

$H_{50,c}$ measured at 85% TLC lung inflation was slightly larger than at 50% TLC (544±33 *vs* 511±67 cm^3). However, this difference was not statistically significant.

Effect of flow rate

Figure 5 shows $H_{50,c}$ at 600 cm^3 volumetric lung depth as a function of flow rate for 10 healthy subjects. The pooled data showed no significant correlation between the two parameters. Fitting linear regression curves to the individual data, an average slope of -(47±113) $cm^3 \cdot s \cdot L^{-1}$ was obtained for the relationship between $H_{50,c}$ and flow rate. This was also not significantly different from 0. Only 2 of 10 subjects showed a significant negative correlation between $H_{50,c}$ and flow. Aerosol deposition, on the other hand, was strongly dependent on airflow rate (fig. 5b). The longer the particles remained in the lungs, *i.e.* the lower the flow rate, the higher was their deposition. The relationship between deposition and flow rate can be approximated by a hyperbolic function, which implies a linear relationship between deposition and the mean residence time of the aerosol bolus within the lungs.

Correlations with anthropometric and lung function parameters

In order to identify parameters of conventional lung function tests and anthropometric data that might influence aerosol bolus dispersion, a linear regression was calculated for the following model assumptions: Y = f (sex, age, height, weight, TLC, RV, VC, ERV, FEV_1, MEF_{25}, MEF_{50}, MEF_{75}, PEF, sR_{aw}). For $H_{50,c}$ the model

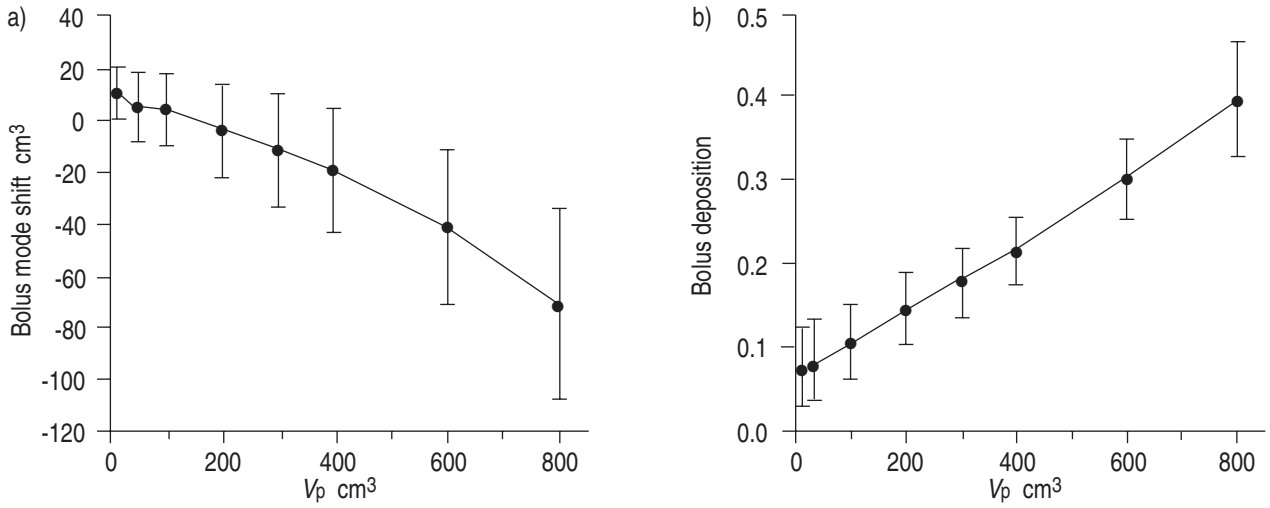

Fig. 4. – a) Mode shift (mean±SD); and b) deposition of exhaled aerosol boluses as a function of volumetric lung depth (V_p) measured in 79 healthy subjects.

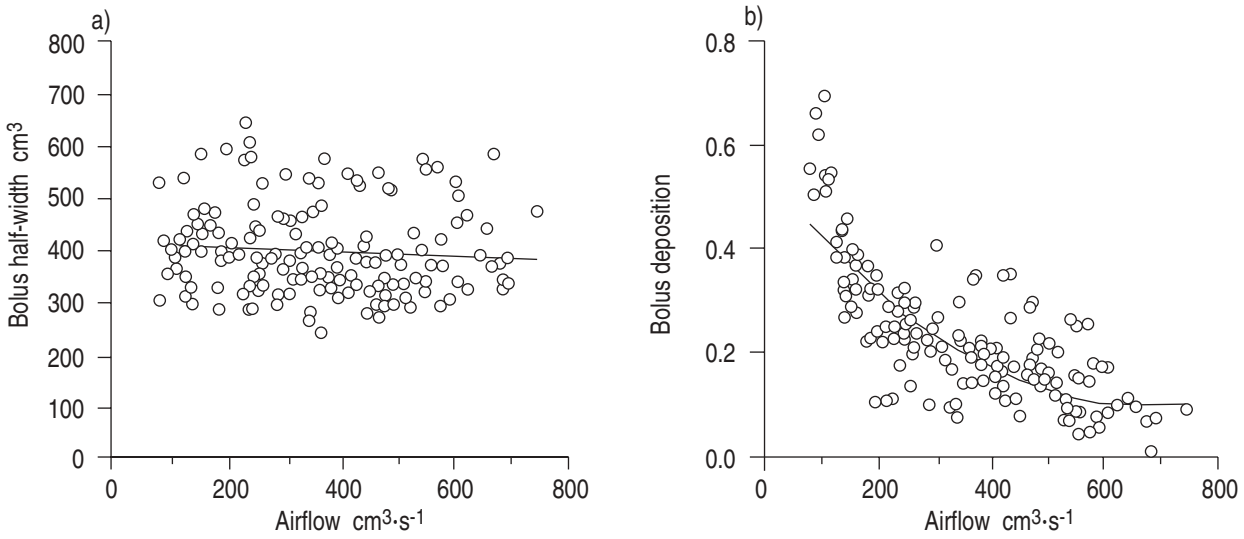

Fig. 5. – a) Volumetric half-width; and b) deposition of aerosol boluses inhaled and exhaled with various flow rates into a volumetric lung depth (V_p) of 600 cm^3, measured in 10 healthy subjects.

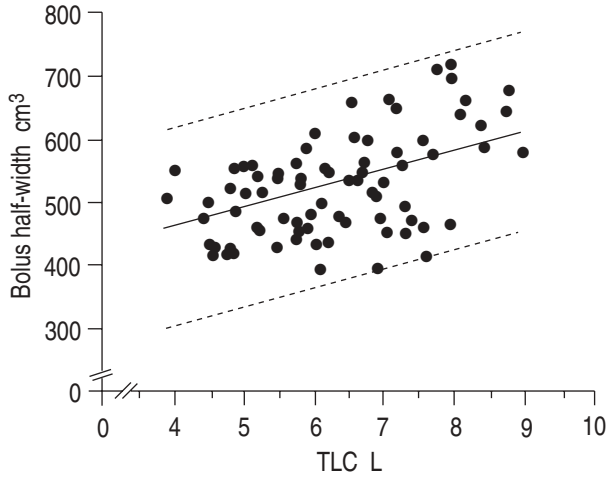

Fig. 6. – Correlation between volumetric half-width of exhaled aerosol boluses penetrating into a volumetric lung depth (V_p) of 800 cm^3 and total lung capacity (TLC) measured in 79 healthy subjects (correlation coefficient of the model r=0.62; p=0.01). The dotted lines represent the 95% prediction interval of the half-width as a function of TLC.

delivered correlation coefficients (r) ranging 0.55–0.68. $H_{50,c}$ increased significantly with TLC (p=0.0003–0.01) (fig. 6) at all volumetric lung depths. In volumetric lung depths between 400 and 200 cm^3, a negative dependency on VC was observed. For the bolus standard deviation, a positive dependency on TLC was found for V_p <800 cm^3 (r=0.61–0.62; p=0.006–0.01). Skewness of exhaled aerosol boluses was not dependent on anthropometric or lung function parameters. Deposition at shallow lung depth (V_p <200 cm^3) was positively dependent on TLC (r=0.41–0.56; p=0.01–0.001) and at V_p = 800 cm^3 negatively dependent on the age of the subject.

Discussion

In this study, aerosol bolus dispersion was studied in 79 healthy nonsmokers in order to establish reference values for bolus parameters and to assess their inter- and intrasubject variability. Bolus half-width and standard deviation showed, in general, lower variability than skewness, mode shift, and deposition. Intrasubject variability of half-width and standard deviation was below 10% and is, therefore, comparable to most parameters of the flow-volume curve [14, 15]. In the diameter range 0.5–2 μm, aerosol bolus dispersion was independent of particle size [16]. Therefore, the study was performed solely with 0.84 μm particles. These particles allow not only the assessment of aerosol bolus dispersion but also assessment of "aerosol derived airway morphometry" [17].

So far, experimental and theoretical studies on intrapulmonary gas transport have relied on the behaviour of inert test gases in the lungs. Since gases underlie both diffusive and convective transport, the assessment of pure convective gas transport by these tracers is limited to the conducting airways [18]. How far convection contributes to gas transport in the transitional or in the respiratory zone of the lungs cannot be determined by these techniques. Since diffusion of aerosol particles with diameters ~1 μm is negligible, aerosol boluses are suitable to measure convective gas transport even in peripheral lung regions. Therefore, the data presented in this paper may help research groups working on the theoretical modelling of convective gas transport in the lungs [19–21] to verify and calibrate their models.

Additionally, aerosol bolus dispersion measurements have shown their potential for pathophysiological research as well as for diagnosis. Observations from humans or animal models have shown lung disease to be associated with increased bolus width, mode shift and deposition [4], as well as enhanced skewness of exhaled boluses [5, 22]. However, the underlying pathophysiological mechanisms resulting in these changes are still under discussion [23]. Since aerosol particles 0.5–1 μm in diameter are considered as markers for convective gas flow, the width of exhaled boluses is indicative of the extent of convective mixing of air between different air volume elements. Both half-width and standard deviation of boluses increase with approximately the square root of volumetric lung depth. This indicates that mixing takes place in all volumetric lung depths, even in the lung periphery, to about the same extent in each

volume element [24]. The observed mode shift of boluses was relatively small (less than 10% of the volumetric lung depth on average) and may, at least partially, be attributed to particle deposition, which is more pronounced in the peripheral portion of the bolus. Therefore, it can be assumed that filling and emptying of the healthy lung as a whole is approximately symmetrical (serial first-in/last-out principle). However, small deviations from this principle may occur among adjacent volume elements and are supposed to result in increased bolus width and skewness.

Nevertheless, details about the mechanisms of bolus dispersion remain unknown. Phenomena of flow dynamics, as well as effects of parallel lung ventilation, must be taken into consideration. In this study, flow rate and lung distension were changed during aerosol bolus dispersion measurements in order to investigate the effect of flow dynamics on bolus dispersion.

Effect of lung inflation and flow rate

Dispersion tended to increase with increasing lung inflation but this result failed to reach statistical significance. Changing lung volume from 50 to 85% TLC is presumed to change airspace calibre by about 20% [25]. Therefore, changes in airway calibre of this order of magnitude do not alter intrapulmonary flow pattern sufficiently to result in distinct changes in aerosol bolus dispersion. Although, 2 out of 10 subjects showed a significant negative relationship between flow rate and aerosol bolus dispersion, the average slope of all measured relationships was not significantly different from zero. Variations of the flow rate in the range 100–700 $cm^3 \cdot s^{-1}$ seem not to change flow pattern enough to produce a significant change in bolus dispersion.

Correlation analysis

The analysis of dependencies between aerosol bolus dispersion and anthropometric and lung function parameters revealed a strong positive relationship between dispersion ($H_{50,c}$) and TLC of the subject: as TLC increased, bolus dispersion increased also. This is in agreement with observations in children [26]. The prediction interval of H_{50} as a function of TLC given in figure 6 may help to estimate the normal range for subjects with different TLCs. The actual volume of the lung increased with increasing lung inflation. Since a slight increase in dispersion with increasing lung inflation was additionally observed in this study, it may be concluded that dispersion in healthy subjects is dependent on the amount of air available for mixing.

Since airflow rate and airspace dimensions do not play a major role in determining aerosol bolus dispersion in healthy subjects, inhomogeneities in parallel lung ventilation may be associated with intrapulmonary aerosol dispersion. During inhalation, a bolus is divided into a large number of sub-boluses, which are reassembled during exhalation. In the case where the synchronization of this reassemblage is not perfect, a dispersed bolus would be exhaled, even if there was no other convective mixing mechanism operating in the lungs. This synchronization of ventilation is disturbed when the mechanical properties of the lungs are not homogeneously distributed. Differences in the elastic properties of different lung units can induce ventilation inhomogeneities, which may considerably influence bolus dispersion. Addi-tionally, differences in flow pattern between inhalation and exhalation induce differences in airway resistance during inhalation and exhalation, which may affect the reassembly of an exhaled aerosol bolus [27]. ROSENTHAL [28] has shown, in a simple modelling study, that, even in a two compartment lung model, differences in time constants within these compartments leads to increased bolus dispersion as well as skewness.

Summary

The aim of this study was to establish reference values for aerosol bolus dispersion in healthy subjects, to quantify their reproducibility, and to characterize physical and physiological factors influencing aerosol bolus dispersion. The results have shown that aerosol bolus dispersion is dependent on total lung capacity and is on average independent of flow rate and the level of lung inflation. Therefore, differences in total lung capacity between subjects should be taken into consideration in possible clinical applications of aerosol bolus dispersion tests.

References

1. Hughes JMB, Amis TC. Regional ventilation distribution. *In*: Engel LA, Paiva M, ed. Lung Biology in Health and Disease. Gas Mixing and Distribution in the Lung. Vol. 25. New York, Dekker, 1995; pp. 177–220.
2. Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. *J Clin Invest* 1969; 48: 1097–1106.
3. Banerjee M, Evans JN, Jaeger MJ. Uneven ventilation in smokers. *Respir Physiol* 1976; 27: 277–291.
4. Anderson PJ, Blanchard JD, Brain JD, Feldman HA, McNamara JJ, Heyder J. Effect of cystic fibrosis on inhaled aerosol boluses. *Am Rev Respir Dis* 1989; 140: 1317–1324.
5. Rosenthal FS. Aerosol deposition and dispersion characterize lung injury in a canine model of emphysema. *J Appl Physiol* 1995; 78: 1585–1595.
6. Keefe MJ, Bennett WD, Dewitt P, Seal E, Strong A, Gerrity T. The effect of ozone exposure on the dispersion of inhaled aerosol boluses in healthy human subjects. *Am Rev Respir Dis* 1991; 144: 23–30.
7. Brand P, Tuch T, Manuwald O, *et al*. Detection of early lung impairment with aerosol bolus dispersion. *Eur Respir J* 1994; 7: 1830–1836.
8. Ferris BG. Recommended respiratory disease questionaires for use with adults and children in epidemiological research. *Am Rev Resir Dis* 1978; 118: 7–55.
9. Altshuler B, Palmes ED, Yarmus L, Nelson N. Intrapulmonary mixing of gases studied with aerosols. *J Appl Physiol* 1959; 14: 321–327.
10. Heyder J, Davies CN. The breathing of half-micron aerosols. III. Dispersion of particles in the respiratory tract. *J Aerosol Sci* 1971; 2: 437–452.
11. Heyder J, Blanchard JD, Feldman HA, Brain JD. Convective mixing in the human respiratory tract: estimates with aerosol boli. *J Appl Physiol* 1988; 64: 1273–1278.

12. Gebhart J, Heigwer G, Heyder J, Roth C, Stahlhofen W. The use of light-scattering photometry in aerosol medicine. *J Aerosol Med* 1988; 1: 89–112.
13. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993; 6 (Suppl. 16): 5–40.
14. McCarthy DS, Craig DB, Cherniack RM. Intraindividual variability in maximal expiratory flow-volume and closing volume in asymptomatic subjects. *Am Rev Respir Dis* 1975; 112: 407–411.
15. Stanescu D, Veriter C, Van Leemputten R, Brasseur L. Constancy of effort and variability of maximal expiratory flow rates. *Chest* 1979; 76: 59–63.
16. Schulz H, Schulz A, Heyder J. Influence of intrinsic particle properties on the assessment of convective gas transport by aerosol bolus technique. *Exp Lung Res* 1995; 21: 853–876.
17. Brand P, Rieger C, Beinert T, Heyder J. Aerosol-derived airway morphometry in healthy subjects. *Eur Respir J* 1995; 8: 1634–1646.
18. Ultman JS, Doll BE, Spiegel R, Thoman MW. Longitudinal mixing in pulmonary airways: normal subjects respiring at a constant flow. *J Appl Physiol: Respirat Enivron Exercise Physiol* 1978; 44: 297–303.
19. Chang DB, Lewis SL, Young AC. A theoretical discussion of diffusion and convection in the lung. *Math Biosci* 1976; 29: 331–349.
20. Darquenne C, Paiva M. Two- and three-dimensional simulations of aerosol transport and deposition in alveolar zone of human lung. *J Appl Physiol* 1996; 80: 1401–1414.
21. Edwards DA. A general theory of the macrotransport of nondepositing particles in the lung by convective dispersion. *J Aerosol Sci* 1994; 25: 543–565.
22. Schulz H, Schulz A, Brand P, *et al*. Aerosol bolus dispersion and effective airway diameters in mildly asthmatic children. *Eur Respir J* 1995; 8: 566–573.
23. Blanchard JD. Aerosol bolus dispersion and aerosol-derived airway morphometry: assessment of lung pathology and response to therapy. Part 1. *J Aerosol Med* 1996; 9: 183–205.
24. Bishoff KB. Notes on the diffusion-type model for longitudinal mixing in flow. *Chem Eng Sci* 1960; 12: 69–70.
25. Hughes JMB, Hoppin FG, Mead J. Effect of lung inflation on bronchial length and diameter in excised lungs. *J Appl Physiol* 1972; 32: 25–35.
26. Schulz A, Tuch T, Brand P, *et al*. Aerosol bolus dispersion in the respiratory tract of children. *Exp Lung Res* 1994; 20: 119–130.
27. Briant JK, Cohen BS. Flow distribution through human and canine airways during inhalation and exhalation. *J Appl Physiol* 1989; 67: 1649–1654.
28. Rosenthal FS. The effect of nonuniform ventilation on the dispersion of inspired aerosol boluses: a modeling study. *J Aerosol Med* 1993, 6: 177–197.