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Aerosol bolus dispersion and effective airway diameters in mildly asthmatic children

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Aerosol bolus dispersion and effective airway diameters in mildly asthmatic children. H. Schulz, A. Schulz, P. Brand, T. Tuch, E. von Mutius, R. Erdl, D. Reinhardt, J. Heyder. ©ERS Journals Ltd 1995.

ABSTRACT: The contribution of aerosol techniques, the estimation of aerosol bolus dispersion and effective airway dimensions, to the clinical diagnosis of paediatric asthma was studied.

In 47 children, aged 11±2 yrs, with mild asthma (forced expiratory volume in one second (FEV_1) 83±9% of forced vital capacity (FVC)) effective airway diameters were derived from the recovery of inhaled 1 µm sebacate droplets. Intrapulmonary dispersion of inhaled boluses of 0.4 µm droplets was studied, by characterizing the concentration distributions of droplets in the exhaled air by their standard deviation and skewness.

Effective airway diameters increased in asthmatic subjects with increasing body size, and did not differ from those obtained in 16 healthy children of similar age and height. Standard deviation and skewness of particle boluses exhaled from shallow lung depths were higher in the asthmatic children than the healthy children (*e.g.* standard deviation 91±17 ml *vs* 79±15 ml, skewness 0.38±0.16 *vs* 0.23±0.16, respectively, for boluses in 140 ml lung depth). The sensitivity and specificity of bolus dispersion to detect alterations in lung function was comparable to that of FEV_1/FVC, the most sensitive conventional lung function parameter in the present study. There was no correlation between body height or lung function and bolus parameters.

We conclude that aerosol measurements do not provide an obvious benefit for the clinical diagnosis of mild paediatric asthma, but bolus dispersion supplies additional information on alterations in convective gas transport in the diseased lung.

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The fate of inhaled aerosol particles is determined largely by the geometrical and mechanical characteristics of an individual's lungs. Inert test aerosols have, therefore, been introduced both into the investigation of basic mechanisms of lung function and into the diagnosis of changes in lung function in the presence of lung disease. In basic research, submicron aerosol particles are applied as tracers of intrapulmonary convective transport and mixing phenomena [1–4]. A small portion of the inspired air is labelled with test particles which are inhaled as a particle "bolus" into the lungs. During the inspiratory and expiratory passage through the airways, particles are dispersed by convective mixing into previously particle-free air volumes, such that the exhaled bolus is spread over a considerably larger volume than the inspired bolus. The mechanisms leading to the dispersion of a particle bolus in the lungs are still under discussion. However, it has been found that bolus dispersion is higher in the presence of various pathological lung conditions. Bolus dispersion is increased in patients with manifest lung diseases, such as cystic fibrosis [5], or chronic obstructive lung disease [6], as well as in smokers [7], or after ozone exposure in healthy subjects [8].

Another application of inert aerosols in lung function studies is the determination of particle recovery after a single inhalation of a test aerosol. The narrower the airways, the more particles are deposited onto airway walls during breathing and, consequently, are not recovered in the expirate. Based on a model of randomly oriented tubes, this principle can be utilized to estimate an effective diameter of the airways [9].

The present study was conducted to evaluate the usefulness of aerosol techniques in the clinical diagnosis of paediatric asthma. Two aspects had to be considered, firstly to determine whether children could perform the tests and secondly to assess the sensitivity of the methods to detect lung function changes associated with reversible airway obstruction. Particle bolus dispersion was measured and effective airway diameters were estimated in children with mild asthma, and were compared to the

results obtained in a group of healthy children of similar age and height. Results of the aerosol techniques were compared to parameters of conventional lung function tests.

Methods

Particle bolus dispersion measurements

Small airborne particles, approximately 0.4 µm in diameter, are used as tracers for convective mixing processes in the lungs, since intrinsic particle motion due to gravitation, inertia, or diffusion is negligible for all practical purposes. Convective mixing causes particles which are inhaled as a small "bolus" to be dispersed in the lungs during breathing, so that the expired bolus always contains a lower concentration of particles in a larger volume than the inspired bolus. The deeper an inspired bolus penetrates into the lungs the more it is subject to mixing processes; and, therefore, the dispersion of a particle bolus increases with increasing penetration. The extent of convective mixing given by the bolus dispersion is quantified by calculating the standard deviation of the concentration distribution of particles in the expired air. The asymmetry of the exhaled bolus as compared to a Gaussian distribution is characterized by the parameter skewness. A negative or a positive skewness value indicates whether mixing processes lead to preferential transport of particles either into more proximal or into more distal lung compartments. Standard deviation and skewness were calculated according to standard mathematical techniques [10] (see Appendix).

Measurements of effective airway diameters

A single breath of monodisperse aerosol particles approximately 1 µm in diameter is inhaled. During a postinspiratory breathhold, particles settle slowly in the airways with a constant velocity. The smaller the airways and the longer the duration of the breathhold period, the larger is the probability that particles settle onto airway walls, deposit there, and are not recovered upon expiration (fig. 1a). The expirate can be conceived as being composed of many small volume elements δV expired successively from different volumetric depths within the lungs. Estimates of "local" airway size can be obtained for any volumetric lung depth of interest, by determining particle recovery in the respective expiratory volume element δV [9] (see Appendix).

Subjects

Measurements were performed in a group of 47 children (24 boys and 23 girls), aged 6–16 yrs, with mild asthmatic disease. The patients had a known history of asthma for 3.6±2.7 yrs. The diagnosis of asthma was based on a history of recurrent episodes of shortness of breath and wheeze, altered lung function, and airway hyperresponsiveness to cold air or exercise. Forty four children (94%) had symptoms related to allergic reactions, and a positive skin test response or specific immunoglobulin E against one or more common allergens. Treatment of the asthmatic children was according to the recommendations of the International Paediatric Asthma Consensus Group [11]. Thirty nine percent of the patients were treated only with $beta_2$-adrenergic agonists on demand, but 15% of the children were additionally receiving regular anti-inflammatory medication. Forty seven percent of the patients were receiving regular anti-inflammatory and bronchodilator therapy.

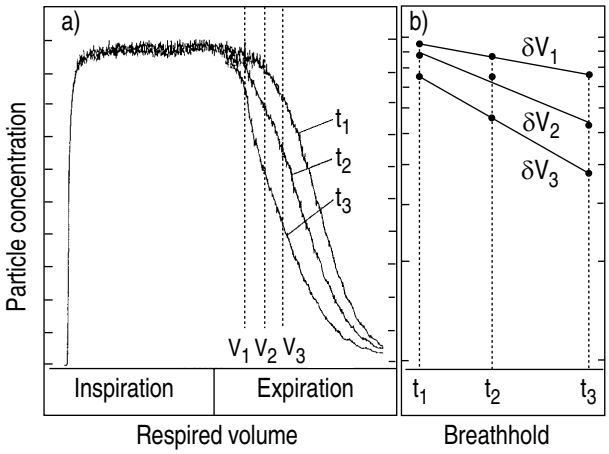

Fig. 1. – Schematic representation of the method for determining effective airway diameters from particle recovery. a) Particle concentration over respired volume on a normalized scale for three different breathholds, $t_1<t_2<t_3$. The vertical dotted lines indicate three lung depths, for which the decline in particle recovery with breathholding time is plotted on a log-linear scale in panel (b).

On the day of the study, the subjects were free of asthmatic symptoms and signs of acute respiratory infection. The frequency of episodes of shortness of breath, wheeze, or cough was evaluated by questionnaire. Symptoms occurring less than once a month were reported by 42% of the asthmatic children, 37% of the children had symptoms at least once a month, and 16% at least once a week. Five percent of the asthmatic children had had no symptoms during the past 6 months. Thirty six percent of the patients reported asthmatic symptoms related to allergen exposure. In 51% of the asthmatic children symptoms were related to exercise, in 42% to cold and/or foggy air. The asthmatic subjects had normal or mildly altered lung functions at the time of the study, according to the standards given by ZAPLETAL *et al.* [12]. Forced expiratory volume in one second as percentage of forced vital capacity (FEV_1/VC) was 83±9% (mean±SD) and maximal expiratory flow rate at 50% of FVC (MEF50) was 79±27% of predicted values (table 1). According to their lung function, the asthmatic children were divided into two subgroups, *i.e.* asthmatic children with normal FEV_1/FVC and MEF50 values (Group A), and those with altered FEV_1/FVC and/or MEF50 values according to the references of ZAPLETAL *et al.* [12] (Group B). Group A asthmatic patients had a known history of asthma for 2.8±2.4 yrs, whilst those of Group

Table 1. – Parameters of body size and lung function in study subjects

	Control group (n=16)	Matched asthmatics (n=16)	All asthmatics (n=47)	Group A asthmatics (n=20)	Group B asthmatics (n=27)
Height cm	137±10 (116–153)	137±9 (121–154)	143±14 (121–173)	142±14 (122–166)	143±14 (121–173)
Weight kg	32±7 (21–45)	33±8 (20–52)	36±10 (20–63)	36±11 (22–54)	36±10 (20–63)
Age yrs	10±1 (7–11)	10±2 (8–14)	11±2 (7–17)	11±3 (7–17)	11±2 (8–15)
TLC *l*	3.37±0.85 (2.29–5.13)	3.19±0.47 (2.14–3.83)	3.61±1.08 (2.14–8.18)	3.60±1.02 (2.27–5.88)	3.63±1.14 (2.14–8.18)
FEV_1 *l*	1.97±0.31 (1.24–2.39)	1.80±0.31 (1.32–2.40)	2.08±0.10 (1.28–5.04)	2.28±0.85 (1.36–5.04)	1.93±0.49 (1.28–3.28)
FEV_1/FVC %	89±7 (81–99)	82±8 (65–95)	83±9 (63–98)	85±5 (80–98)	78±8 (63–95)
MEF_{50} % pred	97±26 (79–146)	70±19 (39–105)	79±27 (26–175)	96±13 (78–175)	63±19 (26–112)

Data are presented as mean±SD and range in parenthesis. TLC: total lung capacity; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MEF_{50}: maximal expiratory flow at 50% of FVC; % pred: percentage of predicted value.

B had asthma for 4.1±2.8 yrs. Anthropometric parameters and results of lung function tests in the asthmatic children, in the control group, and in a subset of 16 asthmatic children matched to the control group by sex and height are summarized in table 1. The control group consisted of 16 healthy children (6 boys and 10 girls) with normal lung function [12]. They were free from chronic respiratory disease and free from acute respiratory symptoms at the time of the study. Informed written consent was obtained from all children and from their parents. The study protocol was approved by the Ethics Committee of Ludwig-Maximilians University Munich.

Apparatus

Lung volumes, maximal expiratory flows, and respiratory resistance were measured in a constant volume body plethysmograph. Functional residual capacity (FRC), expiratory reserve volume (ERV), and total lung capacity (TLC) were used for the standardization of breathing manoeuvres for the aerosol techniques.

The inhalation apparatus for the aerosol techniques consisted of a pneumotachograph for measurement of respiratory flows and a valve system providing an expiratory path and two alternative inspiratory paths for inhalation of either aerosol or filtered air. The number concentration of respired aerosol particles was monitored by aerosol photometry. The principle and design of the inhalation apparatus, as well as aerosol production and particle classification, have been reported in detail previously [13, 14]. The aerosol consists of hydrophobic droplets of di-(2-ethylhexyl) sebacate in air. Particle concentration between study days ranged 4.5–5.5× 10^4 particles·cm^{-3}. Mean particle size for the measurement of effective airway diameters was 0.96±0.04 µm (range 0.88–1.06 µm). Particle size for the determination of particle bolus dispersion was 0.4±0.1 µm (range 0.3–0.5 µm).

Experimental protocol

$Beta_2$-agonists were withheld for at least 6 h prior to lung function tests. Lung volumes (FRC, ERV, TLC) were measured by body plethysmography. Three to five maximal forced expirations were recorded, and the flow-volume curve which yielded the highest sum of FEV_1 and FVC was selected for analysis. After body plethysmography and measurements of forced expiratory flows, the children were given time to adapt to the mouthpiece and the inhalation apparatus for the aerosol techniques. They practiced deep inhalations and exhalations at 300 ml·s^{-1}, guided by an arrangement of coloured light-emitting diodes indicating flow to be at the required value or more than 50 or 75 ml·s^{-1} off the required flow. They were then asked to breathe quietly in order to find a relaxed end-expiratory level, which, when reproducible, was assumed to be FRC.

For the measurement of particle bolus dispersion, the child was asked to inhale at 300 ml·s^{-1} and exhale again, whilst the valves were switched automatically such as to allow an inspiration from FRC to 80% TLC and a consecutive deep exhalation. At a preset volume during inspiration, the inspiratory path was switched from filtered air to aerosol and then back to filtered air, yielding a 50 ml aerosol bolus to be inhaled by the subject. A sequence of these breathing manoeuvres was performed to introduce aerosol boluses 95, 140, 240, ... up to 540 ml before the end of inspiration. The quality of inspired and expired particle concentration profiles was checked by the investigator immediately after the measurement. The measurement was repeated in the case of artefacts due, for instance, to swallowing during the breathing manoeuvre, or a leakage at the mouthpiece or noseclip. In the case of persistent artefacts, the recording was judged to be unacceptable for data analysis.

The breathing manoeuvre for the determination of effective airway diameters started with an exhalation by half the ERV followed by an inhalation of test aerosol

up to 80% of TLC. After a breathhold of varying duration, the aerosol was exhaled, and normal breathing of clean air was resumed. The breathing manoeuvre was subsequently performed with breathholds of 0, 1, 2, 3, 4, 6 and 10 s duration. Inspiratory and expiratory flows were again assigned to 300 ml·s^{-1}.

The children usually completed the aerosol measurements within 20–30 min. Since they had to perform conventional lung function tests prior to the aerosol measurements, some of the children did not complete all of the subsequent aerosol measurements, because the experimental protocol became too long for their span of attention. No attempt was made to perform a test if the child definitely refused to continue or if he or she was obviously exhausted from prior measurements. After 30 min, the measurements were stopped regardless of whether aerosol measurements were completely finished.

Statistical analysis

The relationship between anthropometric parameters and bolus dispersion or effective airway diameters was tested within the group of healthy children by linear regression analysis. The relationship between parameters of conventional lung function tests and bolus dispersion or effective airway diameters was then investigated by simple linear, as well as multiple linear regression analyses, including the data of asthmatics and healthy children. Since standard deviation and skewness of exhaled boluses were found to be independent of body height or lung size, pooled data of normal children were compared to pooled data of asthmatic children by the nonparametric Mann-Whitney U-test. Effective airway diameters were found to increase with body size, and therefore a matched-pairs analysis was performed by comparing a subset of 16 asthmatic children with height-matched controls of the same sex. To evaluate the diagnostic usefulness of aerosol techniques the sensitivity and specificity were quantified by their Receiver Operating Characteristics (ROC) [15] and compared to that of the most sensitive conventional lung function parameter in the present study (FEV_1/FVC). The diagnostic value of a test can be inferred from the area under the ROC-curve (fig. 2), which represents the probability that a randomly selected pair of asthmatic and healthy children is correctly ranked [16].

Results

Parameters of body size and conventional lung function of the study groups are given in table 1. Anthropometric parameters were similar in all groups. The only conventional lung function parameter which was significantly different between healthy children and all asthmatics was FEV_1/FVC (p=0.02). Beside FEV_1/FVC, MEF50 was significantly reduced in the matched subset of asthmatics and in the Group B asthmatics as compared to normal children (p=0.001).

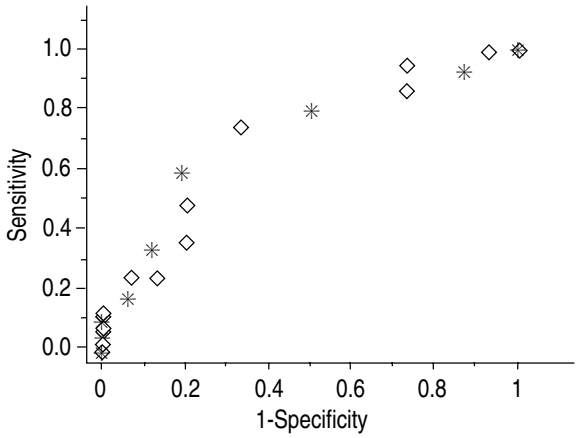

Fig. 2. – Diagnostic value of aerosol bolus measurements and FEV_1. ROC-curves are given for FEV_1/FVC% and bolus dispersion in 140 ml lung depth (SD-bolus 140 ml) as determined for the study population. ✳ : FEV_1/FVC%; ◇ : SD-bolus 140 ml. FEV_1/FVC: forced expiratory volume in one second as percentage of forced vital capacity; ROC: Receiver Operating Characteristics.

Fifty one out of 63 children successfully completed all measurements. The youngest among these 51 children were four 6 and 7 year olds. Bolus dispersion measurements could not be obtained in five children (8%), and effective airway diameters could not be determined in 10 (16%). The 12 children who could not complete the measurements were somewhat younger (8.5±1.8 yrs) compared to the group as a whole (p=0.02). In 8 of the 12 children, a complete set of data could not be obtained, because the experimental protocol became too long for their span of attention. This was the case for one child on the bolus dispersion measurements and for seven children on the measurements of airway diameters. In two 8 year old children, no attempt was made to perform aerosol measurements, because the children were too jittery after conventional lung function testing and not able to concentrate on the aerosol measurements. One 8 year old child was not able to keep the mouthpiece tight. On one occasion the measurements could not be completed for technical reasons.

Of the 58 children who performed aerosol bolus measurements, 54 children (93%) could complete the protocol successfully. Because of artefacts, recordings had to be partially rejected, *i.e.* for at least two lung depths in four children (7%). Of the 53 children, for whom effective airway diameters were measured, 47 children (89%) completed the test. The data of 11% of the children had at least partially to be rejected, because of an unacceptable correlation between particle recovery and the duration of breathholding time.

Standard deviation and skewness of exhaled aerosol boluses were larger in asthmatic than in normal children (figs. 3 and 4). Regarding individual lung depths, the differences were significant only for shallow boluses. In Group A patients, dispersion and skewness normalized with increasing lung depth. Dispersion of boluses inhaled to 500 ml lung depth was 134±32 ml in Group A asthmatic patients as compared to 129±31 ml in normal children (NS). On the contrary, in Group B asthmatic patients bolus dispersion was significantly elevated for

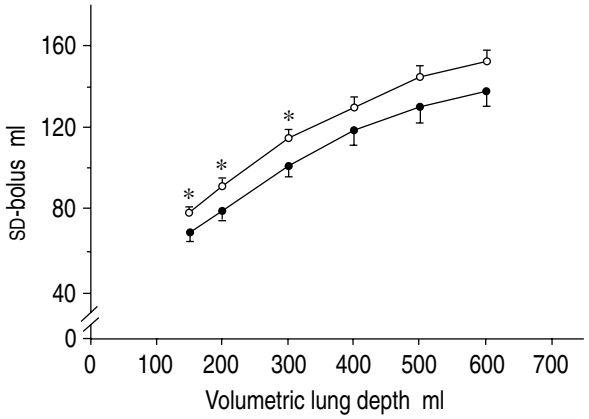

Fig. 3. – Standard deviation of exhaled particle boluses (SD-bolus) as a function of the volumetric penetration of the inhaled bolus in 16 normal subjects and 42 children with asthma. Values are presented as mean±SEM. *: indicates significant differences between groups ($p<0.05$). —●— : Normal children; —○— : asthmatic children.

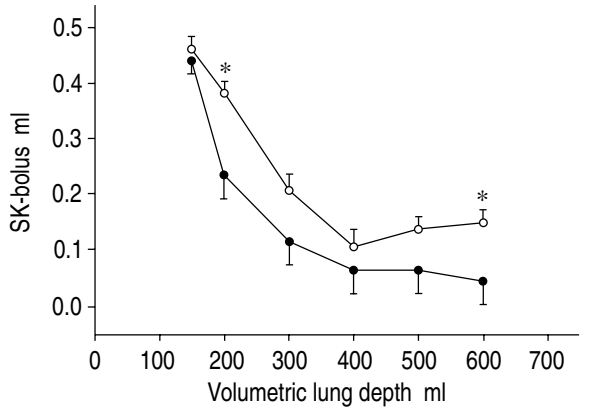

Fig. 4. – Skewness of exhaled particle boluses (SK-bolus) as a function of the volumetric penetration of the inhaled bolus in 16 normal subjects and 42 children with asthma. Values are presented as mean±SEM. *: indicates significant differences between groups ($p<0.05$). —●— : normal children; —○— : asthmatic children.

shallow and for deeper boluses. In the 500 ml lung depth, bolus dispersion was 152±30 ml ($p=0.04$). Similarly, the skewness of boluses exhaled from deep lung regions tended to be higher in Group B patients, but the difference was not statistically significant ($p<0.1$). The single best parameter to discriminate between healthy children and asthmatics was FEV_1/FVC for the conventional lung function tests, and bolus standard deviation in 140 ml lung depth for the diagnostic aerosol tests. Although the number of healthy children was limited in the present study, ROC-curves for FEV_1/FVC and bolus standard deviation in 140 ml lung depth revealed that sensitivity and specificity were similar for both parameters (fig. 2).

There was no consistent correlation between anthropometric parameters, bolus dispersion, skewness, and conventional parameters of lung and airway function, except that standard deviation of boluses introduced into 140–340 ml lung depth was weakly and negatively related to FEV_1/FVC (correlation coefficients -0.26 to -0.34; $p<0.05$).

Effective airway diameters (EAD) did not differ significantly between normal and asthmatic children, regardless

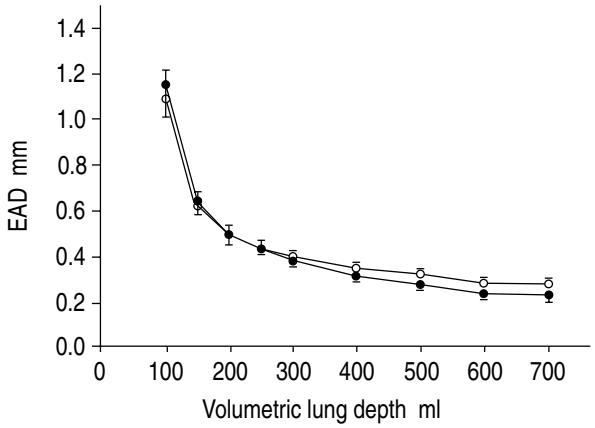

Fig. 5. – Effective airway diameters (EAD) as a function of volumetric lung depth in 16 normal subjects and 16 asthmatics matched for height. Values are presented as mean±SEM. —●—: normal children; —○— : asthmatic children.

Table 2. – Correlations between effective airway diameters (EAD) and parameters of body size and lung function

	TLC	MEF_{50}	MEF_{25}	FEV_1
EAD_{100}	0.28*	-	-	0.37**
a/b	0.69/0.16			0.52/0.36
EAD_{150}	0.39**	0.35**	0.33*	0.53***
a/b	0.41/0.08	0.52/0.07	0.57/0.11	0.32/0.18
EAD_{200}	0.37**	0.40**	0.41**	0.52**
a/b	0.36/0.04	0.40/0.05	0.43/0.08	0.30/0.11
EAD_{250}	0.44***	0.40**	0.38**	0.57***
a/b	0.28/0.04	0.35/0.04	0.37/0.07	0.24/0.09
EAD_{300}	0.39**	0.38**	0.38**	0.53***
a/b	0.27/0.04	0.31/0.03	0.33/0.06	0.22/0.08
EAD_{400}	0.50***	0.31*	0.29*	0.54***
a/b	0.15/0.05	0.26/0.03	0.28/0.05	0.14/0.10
EAD_{500}	0.49***	0.29*	0.27	0.53***
a/b	0.12/0.05	0.23/0.03	0.25/0.05	0.12/0.09
EAD_{600}	0.50***	-	-	0.50***
a/b	0.09/0.05			0.10/0.08
EAD700	0.47**	-	-	0.44**
a/b	0.11/0.04			0.12/0.06

The correlation coefficients are presented as well as intercept (a) and slope (b) values of the linear regression. A significant slope is indicated according to, *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$. MEF_{25}: maximal expiratory flow at 25% of FVC.

of whether they were measured at absolute volumetric lung depths or at lung depths normalized to end-inspiratory lung volume. However, there was a consistent trend for peripheral EAD to be larger in asthmatics than in normal children ($p<0.1$) (fig. 5). Effective airway diameters at absolute lung depths were correlated with body height, TLC, FEV_1, and maximal expiratory flows (table 2). Overall, FEV_1 was the best predictor of effective airway dimensions, and a multiple regression analysis showed that beyond FEV_1, other parameters did not contribute significantly to the prediction of EAD at most lung depths. Normalizing lung depth to lung size caused all individual correlations to become clearly weaker, so that most of them lost their statistical significance (p-levels 0.07–0.09).

Discussion

Clinical aspects of the aerosol techniques

This study was performed to evaluate the application of inert test aerosols in the diagnosis of mild asthmatic disease in children. Two techniques were evaluated: the measurement of particle bolus dispersion and the measurement of effective airway dimensions.

Most of the children could complete the measurements successfully within 20–30 min, a time span comparable to that required for conventional lung function testing. Failure was observed mainly in the younger children, and was mostly due to a progressive loss of attention in the course of the measurements. As the children had to perform body plethysmography and forced expiratory flow-volume curves at the beginning of the protocol, several of them had insufficient concentration to go through the entire aerosol measurements.

Of those children who undertook the aerosol tests, 93% were able to successfully complete aerosol bolus measurements, whilst effective airway diameters could be determined in 89% of the children. Taking into account that the children studied were familiar with the conventional lung function testing, but had their first encounter with the aerosol techniques, it appears that the age range and the percentage of children from which successful measurements can be obtained are similar for bolus measurements and for conventional lung function tests [17, 18]. The determination of effective airway diameters proved to be more difficult and yielded less satisfactory results than the measurement of bolus dispersion. A possible cause for this is that it was difficult for the children to maintain a constant respiratory flow during the subsequent measurements, an assumption implicit to the theory of effective airway diameter [9] (*cf.* Appendix). Therefore, to some extent the performance of airway diameter measurements seems to be reserved to older children and adults.

Effective airway diameters at all lung depths were not significantly different between normal children and asthmatics, but there was a consistent trend for measured peripheral airway diameters to be larger in asthmatic than in healthy children. This apparent airway enlargement is most likely to be due to phenomena associated with altered ventilation distribution in asthma. In the presence of airway obstruction, there is a certain amount of ventilation inhomogeneity [19–21] as has also been shown by the enhanced bolus dispersion. Only those lung compartments which are sufficiently ventilated to be reached by the inhaled aerosol are characterized by the measurements of effective airway diameter [22], *i.e.* the better ventilated lung regions with less obstructed airways, which may be inflated to a higher degree. Therefore, airway narrowing, if inhomogeneously present, may be missed by the measurement of effective airway diameter.

The dispersion of inert particle boluses was altered in asthmatic subjects, as shown by the increase in standard deviation and skewness of exhaled boluses. This indicates the presence of altered convective gas transport in the diseased lung (see "Pathophysiological aspects"). In the present study, the most sensitive conventional lung function parameters to distinguish between healthy and asthmatic children were FEV_1/FVC and MEF50, which is in agreement with data from the literature [18, 23, 24]. A comparable sensitivity was found for the standard deviation of boluses exhaled from shallow lung depths (*cf.* fig. 2). Hence, our data suggest that aerosol measurements do not provide an obvious benefit for the clinical diagnosis of mild paediatric asthma. However, bolus standard deviation and skewness could not be consistently related to any of the conventional parameters of lung and airway function. This was taken as an indication that the measurement of particle bolus dispersion captures features of airway (dys)function which are basically different from those described by body plethysmography and spirometry, and which may give insight into mechanisms of impaired gas transport in the diseased lung.

Pathophysiological aspects

Particle bolus dispersion in the lungs is a measure of convective mixing processes during breathing [4, 25]. These processes, which in the healthy lung provide for adequate mixing between inspired and residual air, may be altered in the diseased lung through the action of several mechanisms. In the conducting airways, the nonreversibility between inspiratory and expiratory flow profiles, caused by the occurrence of secondary motions at airway bifurcations [26], is considered to contribute to the dispersion of particle boluses. Changes in the geometric configuration of airways and, particularly, of airway bifurcations due to mild airway constriction, enhanced airway secretions, or local increases in mucosal thickness may significantly influence particle bolus dispersion in asthmatic subjects, even if they are too mild to cause respiratory symptoms or decrease in respiratory flows. Bolus dispersion is also considered to be dependent on the distribution of regional time constants between different compartments of the alveolar space [27]. These time constants reflect both the compliance of peripheral lung units and the resistance of the subtending airways [28]. The presence of unequal inspiratory and expiratory time constants can cause bolus dispersion to be increased and the exhaled bolus to be asymmetrical or skewed, if lung units empty very slowly and contribute a "tail" of particles during the last part of expiration.

In Group A asthmatic patients, changes in bolus dispersion and skewness were found only for superficially inhaled particle boluses. This suggests that in Group A gas transport is primarily impaired in the conducting airways and hence, in particular, the reversibility between inspiratory and expiratory flow profiles is altered. As in Group B asthmatic patients, bolus dispersion was increased throughout all lung depths and also skewness tended to be higher, gas transport was not only affected in the conducting airways but also in peripheral lung

units. These findings suggest that in addition to changes of flow profiles in the conducting airways in Group B patients, time constants of peripheral lung units are altered due to modifications in regional compliance. Since these patients had a history of asthmatic disease for about 4 yrs, and some of them for almost 10 yrs, the enhanced bolus dispersion may be interpreted as a first sign of mild structural alterations in the lung periphery. Our present data do not allow the clinical significance of these findings to be assessed, but follow-up studies in patients with mild asthmatic disease may be able to evaluate this question.

In summary, the measurement of effective airway diameters was difficult for children to perform and yielded no significant differences between patients with mild asthmatic disease and healthy children. Hence, it appears, that the test has no clinical significance in the diagnosis of mild paediatric asthma. Measurements of the dispersion of inhaled aerosol particles were found to be enhanced in asthmatic patients, but the sensitivity and specificity of bolus dispersion to detect alterations in lung function was comparable to that of FEV_1/FVC, the most sensitive conventional lung function parameter in the present study. Therefore, bolus dispersion appears to provide no obvious benefit for the clinical diagnosis of mild paediatric asthma. However, bolus dispersion gives additional information on alterations in convective gas transport in paediatric asthma. The clinical significance, *i.e.* in monitoring the course or therapeutic management of asthmatic disease, cannot be inferred from the present data, but should be an issue in future studies.

Appendix

Characterization of the concentration distribution of particles in the respired air

The mean volume of the inspired or expired concentration distributions was set to zero, and standard deviation, with the dimension of a volume, was calculated separately for the inspired and for the expired particle concentration distribution [10]:

$$SD_{in/ex} = \frac{\int V^2 \cdot C(V)\, dV}{\int C(V)\, dV} \quad (1)$$

where V is the inspired or expired volume with respect to the mean volume of the inspired or expired concentration distribution, and C(V) is the particle concentration at volume V. Standard deviation of the expired bolus (SD_{ex}) was corrected for the standard deviation of the inspired bolus (SD_{in}) to yield the net dispersion, SD, introduced by the passage through the lungs [29]:

$$SD = (SD_{ex}^2 - SD_{in}^2)^{0.5} \quad (2)$$

Skewness (SK) was calculated for the expired particle concentration distribution [10]:

$$SK = \frac{\int V^3 \cdot C(V)\, dV}{SD_{ex}^3 \cdot \int C(V)\, dV} \quad (3)$$

Standard deviation and skewness of a bolus may be influenced by a noisy baseline signal at the tails of the distribution, in that this causes the integrals in Equations (2) and (3) to become an unstable measure. To surmount this problem we analysed only that part of the bolus where aerosol concentration exceeded 15% of the bolus peak level.

Determination of effective airway diameters

For the determination of an effective airway diameter, the airway at any lung depth, V, is modelled as an assembly of randomly oriented cylinders of identical diameter, d(V). Particle recovery from lung depth V as a function of time, R(V,t), is approximated by an exponential equation [9]:

$$R(V,t) = \exp(-4\, v \cdot t/\pi \cdot d(V)) \quad (4)$$

Particle recovery was defined as the ratio of particle number concentration in an expired volume element δV of 10 ml over the mean inspired particle number concentration. Figure 1a illustrates the exponential decline in particle recovery on a log-linear scale. Inspiration and expiration are assumed to be constant between successive breaths, so that the decrease in particle recovery with time is due only to the events during breathholding. For absolute lung depths, V, of 100, 150, ... up to 700 ml, and relative lung depths of 4, 6, 8, ... up to 30% of the end-inspiratory lung volume, a linear regression was fitted to the relation of the logarithm of particle recovery, ln R(V,t), and the duration of the breathhold, t. Only those measurements where the correlation coefficient of the linear regression exceeded 0.9 were considered valid for further data analysis. Effective airway diameters (EAD) were calculated according to Equation (5) from the slopes of the regression lines and the measured settling velocities, v, of the aerosol particles:

$$EAD(V) = -4\, v/\pi \cdot d(\ln R(V,t))/dt \quad (5)$$

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