Review

Age-dependence and intersubject variability of tracheobronchial particle clearance

Robert Sturm, PhD MSc

Division of Physics and Biophysics
Department of Material Science and Physics
University of Salzburg
Hellbrunner Strasse 34
A-5020 Salzburg
Austria

Key words:
- intersubject variability
- deposition
- clearance
- tracheobronchial tree
- inhaled particles

Abbreviations

A_{i-1}: cross section area of airway i-1
A_i: cross section area of airway i
d_g: geometric diameter of a deposited particle
FRC: functional residual capacity
$FRC_{reference}$: functional residual capacity of a reference subject
$FRC_{subject}$: functional residual capacity of a subject of interest
f_s: fraction of slowly cleared particles
ICRP: International Commission on Radiological Protection
L_i: length of airway i
sf: scaling factor
t_d: mucus delay time
TLC: total lung capacity
$t_{r,i}$: total residence time of particle in airway i
VC: vital capacity
v_{i-1}: mucus velocity in airway i-1
v_i: mucus velocity in airway i

Correspondence to:
Dr. Robert Sturm
Brunnleitenweg 41
A-5061 Elsbethen
Salzburg/Austria
E-mail: robert.sturm@sbg.ac.at

SUMMARY.
BACKGROUND: The detailed study of tracheobronchial clearance of inhaled particles represents one of the basic research questions in lung medicine. The clearance efficiency varies in different age groups and between males and females.The differences can be partly clarified by the application of a well validated theoretical approach. This study applied a relevant model to children (1 year, 5 years, 10 years), juveniles (15 years), and adults of different ages (18, 21, 25, 34, 50, and 60 years) and to both sexes. **METHODS:** The mathematical model used for clearance simulation is based on the concept of a stochastic lung structure and considers both early fast mucociliary clearance and a later, slow clearance fraction, f_s, effected by particular uptake by tracheobronchial cells, e.g., macrophages and epithelial cells. According to this model, the calculated mucus velocities for each airway generation of the tracheobronchial compartment are normalized to a respective tracheal mucus velocity that is estimated for each of the age groups studied from an allometric function. **RESULTS:** In general, tracheobronchial clearance efficiency undergoes a significant increase from childhood to young adulthood, reaching a maximum at 25-30 years and decreasing again from about 30 years to 60 years. Conversely to the improvement of clearance, the continuous change of airway morphometry with increasing age causes a decrease of the filtering effect in the trachea and main bronchi, which is of marked importance in infants. The modelling results demonstrate differences in tracheobronchial clearance between males and females, generally in the range from 0 to 5%, which are exclusively determined by the individual lung geometry. **CONCLUSIONS:** Based on theoretical computations it can be concluded that tracheobronchial clearance is a phenomenon that depends on both age and sex. Biological studies are necessary to determine the cellular and molecular mechanisms underlying the age-dependent development of tracheobronchial clearance. ***Pneumon 2011, 24(1):77-85.***

INTRODUCTION

After their deposition in the lung airways, insoluble inhaled particles are subject to a variety of site-dependent types of clearance mechanisms. As outlined by numerous authors,[1-4] these mechanisms include a fast clearance phase, which can be observed in the tracheobronchial region and is mainly represented by the so-called mucociliary escalator, and a much slower phase, which takes place in the alveoli and consists of the mechanical removal of particles from the lung surface by alveolar macrophages or by simple transcytosis through the alveolar epithelium, and their subsequent accumulation in the adjacent lymph nodes. According to earlier studies[5,6] tracheobronchial clearance includes, apart from the fast transport of particles on the mucus layer soon after exposure, several slower processes such as particle uptake into epithelial cells or phagocytosis by airway macrophages, which had been considered to be of only minor importance, with tracheobronchial clearance in effect being limited to the first 24 hours after exposure. Recent experiments, however, using the aerosol bolus technique[7-11] have yielded evidence that significant particle fractions are retained in the tracheobronchial region well after 24 hours. In addition to the slow clearance mechanisms introduced above, the possibility of prior alveolar deposition, the variability of airway lengths and the uneven filling of the lung lobes have been discussed as explanations for the experimental results. Based on numerous experiments and the advanced theories of tracheobronchial clearance, the International Commission on Radiological Protection (ICRP)[12] introduced the concept of a slow bronchial clearance fraction, f_s, with a uniform half-time of 20 days and marked dependence on particle size. By simulating the aerosol bolus experiments performed by Stahlhofen[10] and Scheuch et al[11], Sturm et al[13] were able to demonstrate that within the size range 0.1 to 6.7 μm, f_s correlates with the particle diameter in a linear fashion.

Numerous morphometric models of the human lung have shown that the airway diameter and length display an inherent biological variability between adult humans, commonly known as 'intersubject variability'. In addition to the morphometric variations within one sex, significant differences between females and males can also be recognized, which are mainly expressed by respective differences in the total lung capacity (TLC), functional residual capacity (FRC) and vital capacity (VC).[12] The greatest variations in lung morphometry are observed between children at different ages (notably 3 months to 5 years), when the lungs are subject to a complex developmental process, and adults. In order to take into consideration the intersubject variability and age dependence of lung morphometry in the recently formulated mathematical models, various kinds of airway scaling have been developed. While Phalen[16] has shown that the dimensions of the trachea and bronchi are related to body height, the ICRP[12] has suggested a scaling of the respiratory airways by the one-third power of the FRC quotient between the subject of interest and a reference subject. For the bronchiolar airways a parabolic interpolation of diameters and lengths is commonly used, while scaling of the alveolar region is hardly possible at present because of lack of sufficient morphometric information. As deposition of particles is affected mainly by the age dependence and intersubject variability of the lung morphometry, these parameters have become the focus of scientific interest in the last few years,[17-20] but there is still a paucity of information about intersubject variablity of particle clearance from the tracheobronchial region and the differences between humans of different ages. The first insights into this topic are provided by the high variability of documented tracheal mucus velocities, ranging from 3.6 ± 1.5 mm min^{-1} to 21.5 ± 5.5 mm min^{-1}.[21,22] Goodmann et al[21] have shown that mucus velocity in the trachea reaches its maximum (10.1 ± 1.1 mm min^{-1}) in non-smokers in the age group 19-28 years and decreases thereafter with age, until in 56-70 year-old non-smokers it has fallen to 5.8 ± 0.98 mm min^{-1}. Mauderly & Hahn[23] have introduced an empirical equation for the calculation of age-dependent tracheal mucus velocity, using measurements in beagle dogs and applying a suitable age transformation (Figure 1). The studies of Wolff[24], Valberg et al[25], and Gross et al[26] yielded evidence that mucociliary clearance is significantly altered by exercise. As further explanations for the 'intrasubject variabilty' of clearance, sleep and various kinds of biological rhythms (e.g. the menstrual cycle) are proposed.[27,28] These preliminary findings confirm that particle clearance appears to be characterized by marked variability, both between different individuals and within a single individual at different phases, and thus a theoretical approach to the problem by the application of a stochastic clearance model is justified.

In the present study the mucociliary clearance is modelled for humans of different ages (specifically, 1 year, 5 years, juveniles, adults), to reflect the possible developmental aspects of clearance. In addition, intersubject variability in clearance due to variations in the lung morphmetry of adults aged from 18 to 60 years[29]

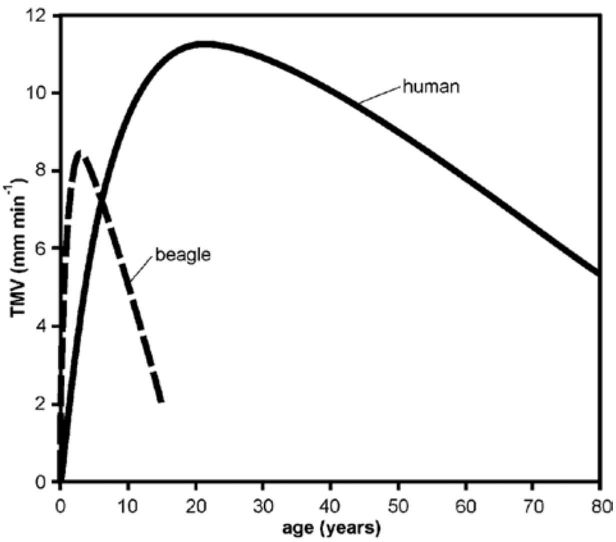

FIGURE 1. Relationship between tracheal mucus velocity (TMV) and age in beagle dogs and humans according to the allometric function provided by Mauderly & Hahn.[31]

is presented and discussed and the variations between females and males are explored. To check the validity of the stochastic clearance model used, experimental clearance data documented by Philipson et al[30] have also been simulated. These data are very suitable for use in the present study, because they supply clearance measurements of males and females of different ages and therefore provide a good opportunity for model calibration.

METHODS

The calculations presented here were executed using a combined deposition-clearance model for the bronchial airways of the human lung. Within the deposition model, asymmetric lungs are generated according to a specific Monte Carlo algorithm ('random-walk model') outlined by Koblinger & Hofmann.[31] This model allows the computation of particle deposition fractions per airway generation within a stochastic lung architecture and it has been used successfully in many recent studies.

The stochastic clearance model includes several assumptions and experimental findings that have been published in recent years.[10-12] As particle deposition is considered to take place in the first half of any airway, by means of diffusion, inertial impaction or sedimentation, clearance always starts from the midpoint of the initial bifurcation within the computed path. Particle deposition in the trachea is significantly affected by the vibration of the vocal chords and the resulting laryngeal jet, with the result that the deposition probability has been found to decrease along the trachea in a linear fashion. This phenomenon has been optionally implemented into the clearance model by dividing the trachea into three distinct parts, each with a slightly different mucus velocity, thus maintaining mass balance throughout the tracheobronchial tree. If the effect of the laryngeal jet is negligible (e.g. for medium-sized aerosols), mucus velocity in the trachea can be switched to a constant value. The calculation of the mucus velocity within a specific airway of the clearance path is made possible by including the airway geometry. Concerning a single bifurcation, the first step in this algorithm is the determination of a velocity factor derived from the respective cross-section function, i.e., the quotient of cross section areas between the daughter airway (A_i) and the related parental airway (A_{i-1}). The mucus velocity in a daughter airway, v_i, is then calculated by multiplying the velocity of the parent tube, v_{i-1}, by this factor:

$$v_i = v_{i-1} \cdot \frac{A_i}{A_{i-1}} \quad (1)$$

According to this concept, all the velocities needed for a simulation are calculated from the initial tracheal mucus velocity. Changes in this initial velocity or in the lung morphometry can significantly influence clearance rates within the whole tracheobronchial tree.[32,33]

As found by instillation of labelled material into the upper bronchial airways of rats[15], mucus transport is affected by a delay at the carinal ridges of single bifurcations. At these sites, mucus flow is split, on the one hand, and accumulated for some time, on the other hand. In the rat lung, the half-life of clearance from the carinal ridges has been shown to be about 1 hour, but similar information for the human lung is not yet available. In the stochastic clearance model, this phenomenon can be considered optionally by defining a mucus delay time, t_d, which is uniformly applied to all the bifurcations of the tracheobronchial tree. As a simplification, all mucus is affected by this delay, not only the mucus at the carinal ridges (about 10 %), so that delay time has to be diminished substantially (about 10 minutes). The total residence time, $t_{r,i}$, of a deposited particle in airway i with length L_i is given by the formula:

$$t_{r,i} = \frac{L_i}{v_i} + t_d \quad (2)$$

As shown above, tracheobronchial clearance can include a significant fraction, f_s, of particles slowly cleared by uptake into the epithelium, accumulation in the sol phase or phagocytosis by airway macrophages. As already demonstrated by shallow aerosol bolus experiments[10-12], f_s is strongly dependent on the size of the inhaled particles. In the clearance model used in this study, the slow clearance fraction is calculated from the following linear equation[34]:

$$f_s = 0.77 - 0.12 \cdot d_g \text{, (3)}$$

where d_g denotes the particle geometric diameter in μm. The final residence time of particulate matter of a given size is derived from equation (2) as follows:

$$t_{r,i} = f_s \cdot t_s + (1 - f_s) \cdot \left(\frac{L_i}{v_i} + t_d \right) \text{, (4)}$$

with t_s denoting the average half-time of the slow clearance process (5-20 days).[12,13] A detailed mechanistic model describing the main features of slow tracheobronchial clearance will be implemented into the existing model in the near future.

In the present study, the age dependence of tracheobronchial clearance was investigated by comparing the clearance behaviour of humans aged 1 year, 5 years, 10 years, and 15 years, both between each other and with that of adults. Intersubject variability was investigated by comparing adults of different ages, and females and males. The physiological and morphometric lung parameters for the children and adults were taken from the ICRP report (1994, pp. 23 f; Table 7).[12] Scaling factors, sf, for the diameters and lengths of the tracheobronchial airways were calculated according to the following formula:

$$sf = \left(\frac{FRC_{subject}}{FRC_{reference}} \right)^{1/3} \text{, (5)}$$

where $FRC_{subject}$ denotes the functional residual capacity of the subject of interest and $FRC_{reference}$ represents the functional residual capacity of a reference subject (i.e., 5,500 mL).[12] For investigation of intersubject variabilty of tracheobronchial clearance among adult males aged from 18 to 60 years, the morphometric investigations of Ménache[29] were used and these were stored in a specific input file of the stochastic program code. Between these individuals, the 8 'primary' airways[17] show only slight differences in dimension, while the stochastically calculated diameters and lengths of the remaining airways are more variable.

RESULTS

Mucociliary clearance

A widely used way of expressing the clearance efficiency in the tracheobronchial tree is the plot of retained particle fractions against time. The resulting retention curves were computed for all age groups and are shown in Figures 2 and 3. Preceding deposition calculations were carried out using standard breathing conditions.[12] In a first step, the respective curves for various particle sizes (0.1, 1.0, and 10 μm) were calculated without the assumption of a slow clearance fraction f_s, i.e., assuming that particles are exclusively cleared by the mucociliary escalator, and the shape of the curves is determined solely by the mucus velocities and the morphometric dimensions of the bronchial and bronchiolar airway generations. In this step, differences in the retention curves between males and females of the same age group are minor, and those between subjects aged10 years, 15 years and adults differ only very slightly. The major differences are recognizable between adults and young children (i.e., 1 year, 5 years). In 1 year-old subjects, 10-μm particles are cleared out of the lung much faster than in adults (full clearance: 10 vs. 25 hours), but 0.1-μm particles show significantly higher retention than inolder subjects (Figure 2). Since for all particle sizes the same transport velocities on the mucociliary escalator are assumed, the variations in the retention curves are the result of individual deposition patterns. Specifically, the 10-μm particles are deposited mainly in the upper lung, while the smaller particles reach more distal parts. In children the filtering of larger particles in the trachea and main bronchi is enhanced by the 50 % downscale of these airways.

For comparison between the various adult age groups, the retention curves of 1-μm particles have been used for the documentation of a possible age-dependent clearance efficiency. The single retention functions are marked by very similar shapes (Figure 3). In general, retained particles in the tracheobronchial region decrease from 18 to 25 years due to higher mucus velocities in the older subjects (Figure 1). From 34 to 60 years particle retention increases again, as an effect of decreasing mucus velocity.

Slow bronchial clearance

For more realistic characterization of particle clearance from the tracheobronchial tree, the slow clearance fraction, f_s, also needs to be taken into account. The half-life of particle capture in the sol layer has been determined to be 5 days, not dependent on the site of particle deposition. The 24-hour retention values for clearance calculations including f_s are summarized in Figure 4. In contrast to the first step computation, without f_s, differences in the 24-hour retention between males and females of

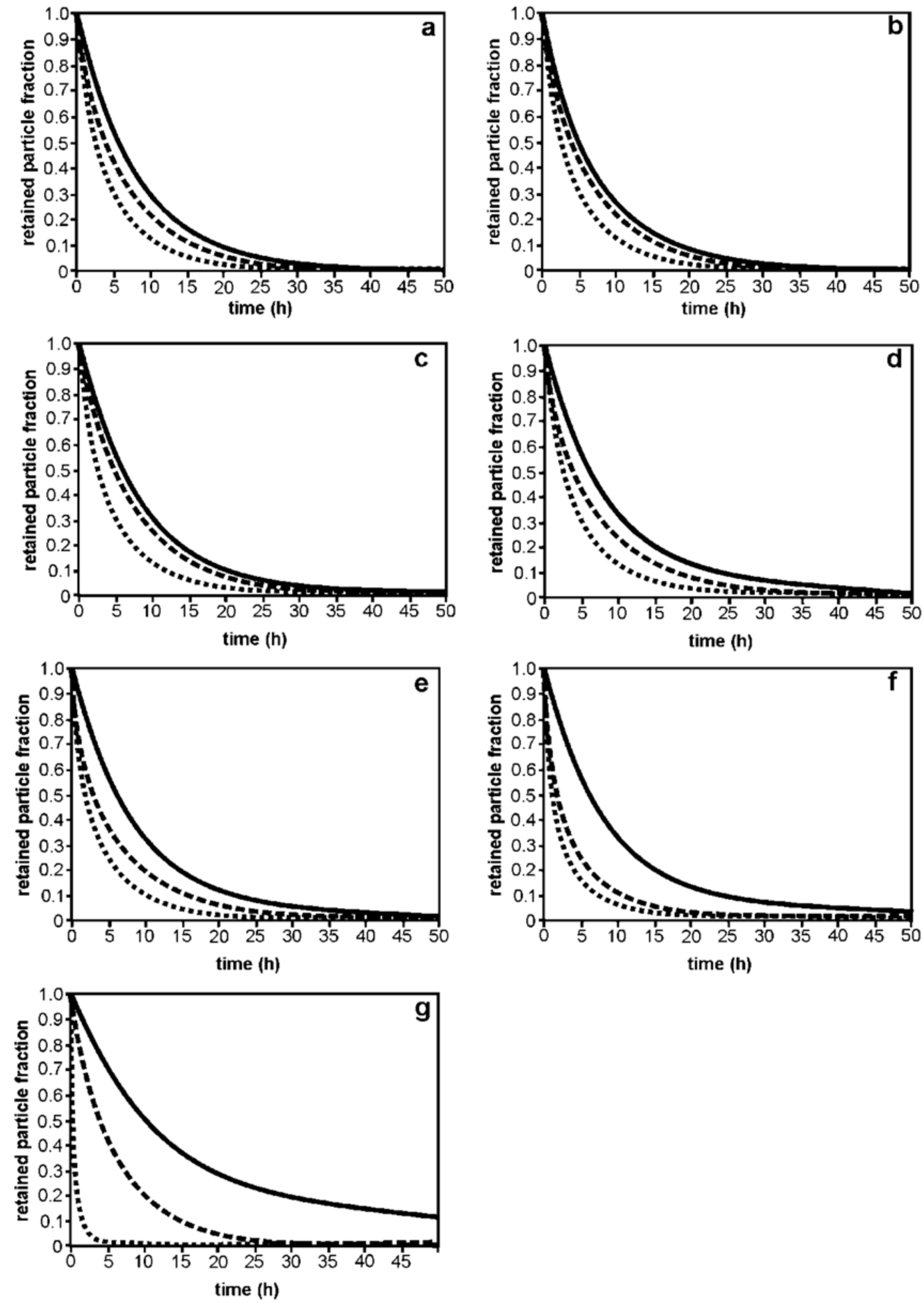

FIGURE 2. Time-dependent retention of three different particle sizes (0.1 μm = bold line, 1 μm = dashed line, and 10 μm = dotted line) in the lungs of subjects in various age groups: a) adult male, b) adult female, c) 15 year-old male, d) 15 year-old female, e) 10year-old child, f) 5 year-old child, g) 1 year-old infant.

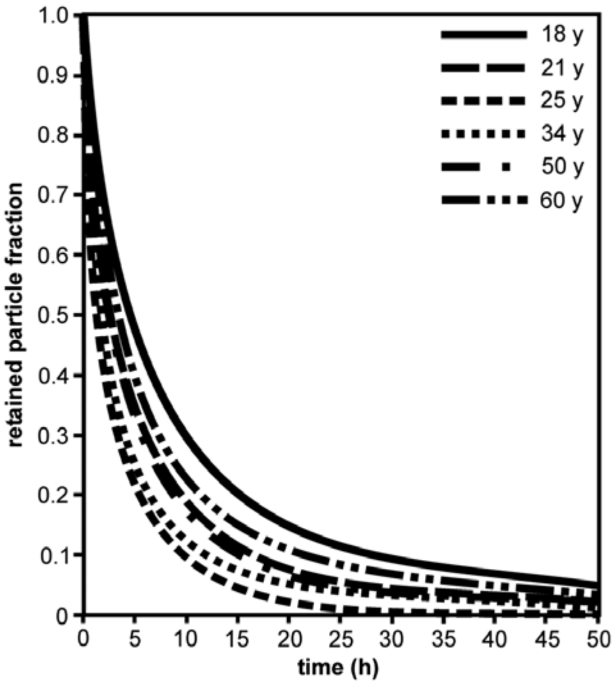

FIGURE 3. Retention curves of 1-μm particles for the adult age groups.

a specific age group have practically disappeared for smaller particles, due to the significant slowing down of their transport out of the lung. The dependence of f_s on particle size can be clearly recognized in the respective diagrams. In general, 24-h retention decreases from 0.7-0.8 for 0.1-μm particles to the original value computed without f_s for 10-μm particles (Figures 4a-c). Within the childhood age groups, also, differences between the 24-h retentions of smaller particles come down to a much lower level, reaching a maximum of about 10%.

The first step differences in clearance efficiency between the adult age groups decrease in a similar way (Figures 4d-e). With the incorporation of f_s into the clearance model, the respective 24-hour retention of smaller particles differs by 2 to 10 % between 18 and 60 years, while for the 10-μm particles the same differences as depicted in Figure 2 can be determined.

Simulation of clearance experiments

In order to check the validity of the clearance model presented in this study, the experimental data documented by Philipson et al[30] were simulated. The authors used two

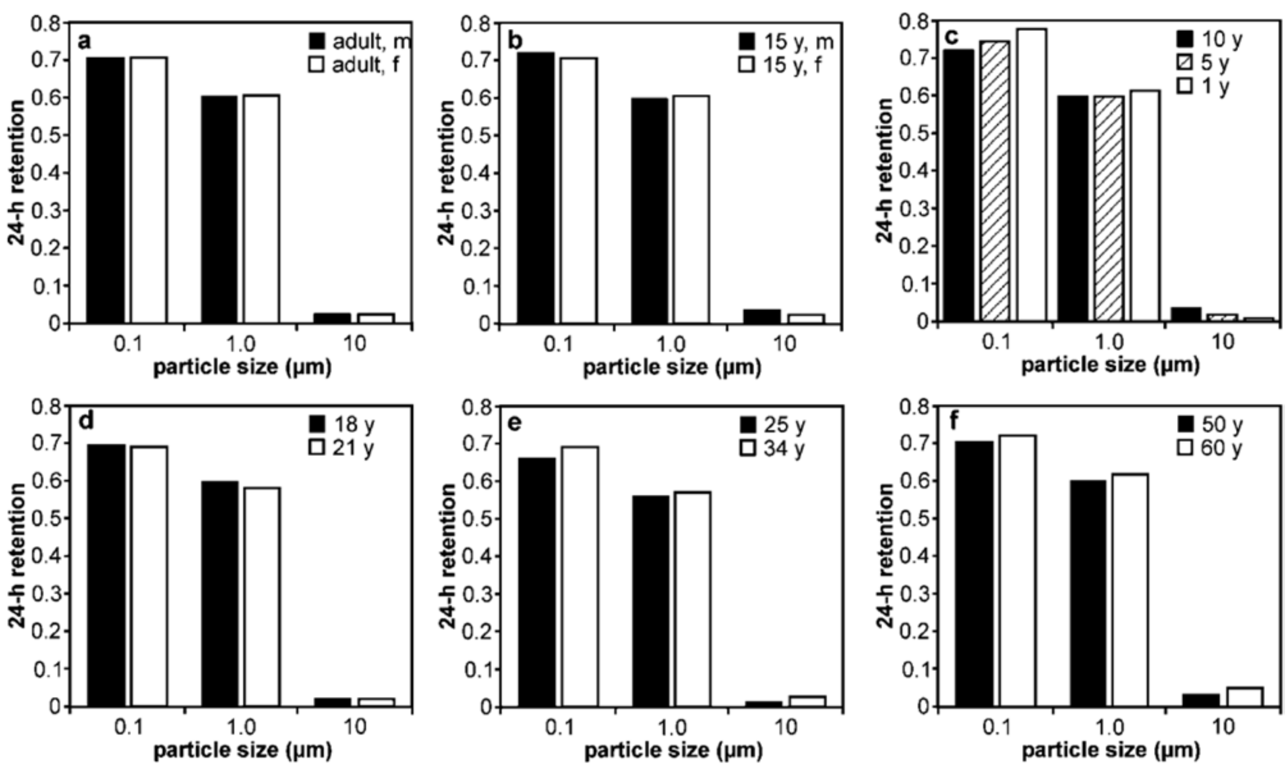

FIGURE 4. 24-hour retention values of tracheobronchial clearance (including f_s) of three particle sizes (0.1 μm, 1 μm, and 10 μm) for various age groups: a) adult males and females, b) 15 year-old males and females, c) 1 year-old infants and children aged 5 and 10 years, d) 18 and 21 year-old subjects, e) 25 and 34 year- old subjects, f) 50 and 60 year-old subjects.

kinds of [111]In-labelled particles (polystyrene: d_g = 6.05 μm, and teflon: d_g = 4.47 μm) which were deposited in the lungs of 9 test subjects (6 females/3 males) during extremely slow inhalation (flow rate: 0.045 L/s). Due to the slow air velocity, the particles were transported to more distal airways ('small ciliated airways'), where they finally settled down by sedimentation. For both kinds of particles, radioactivity in the body was measured after 0, 24, 48, and 72 hours and after 1 and 2 weeks. Experimentally derived 24-hour retention figures are displayed in Figure 5. According to the limited experimental data, 24-hour retention reaches a minimum at between 25 and 30 years of age and then increases again with age. Clearance is slightly faster for teflon than for polystyrene particles. Model data were generated by computing specific airway scaling factors for each test subject (equation [5]) and deriving the respective tracheal mucus velocity from the Figure 1 graph (note: for both sexes the same diagram was used). Results of the simulations are plotted in Figure 5 along with the experimental data. For the polystyrene particles, the differences between the

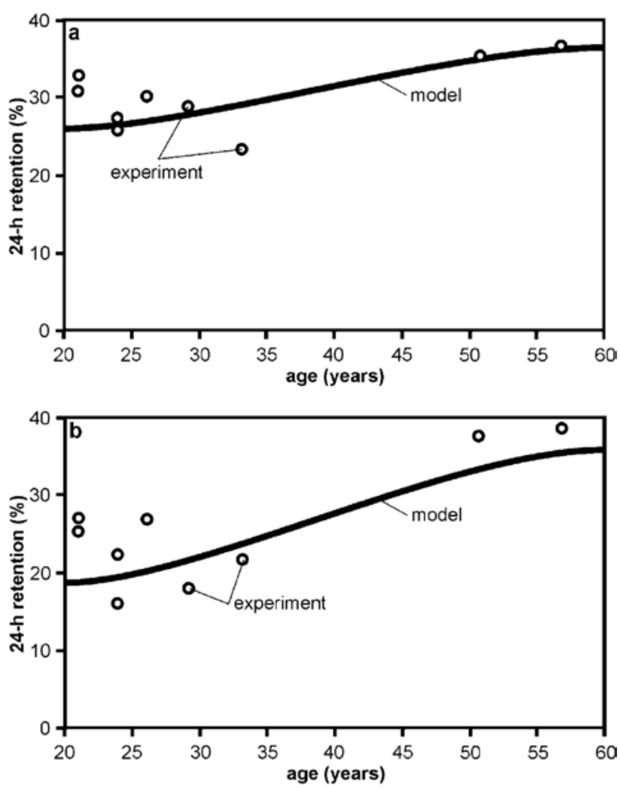

FIGURE 5. Simulation of the experimental data outlined by Philipson et al.[38] Modelling was carried out for a) polystyrene particles (d_g = 6.05 μm), and b) teflon particles (d_g = 4.47 μm).

experimental data and the model are most significant for young adults (20-40 %) and decrease with age. For the adults aged between 50 and 60 years, the differences fall to below 5 %. For the teflon particles, good agreement between the experimental and model data is observed in all the age groups. While in young adults the differences reach a maximum of about 20%, for the 50-60-year old adults the range is from 5 to 15%.

DISCUSSION

This study shows that, from a theoretical point of view, particle clearance from the tracheobronchial compartment is subject to marked variability between different age groups. This ispartly due to the age dependence of the tracheal mucus velocity, which reaches a maximum in adults at between 20 and 30 years (Figure 1).[24] Clearance is also affected by the continuous changes in the lung morphometry which take place between childhood and the adult state.[12] The increase in both airway mucus velocity and airway geometry during the human growth period enhances the clearance efficiency of distally deposited particles (e.g. 0.1 μm particles; Figure 4), but, on the other hand there is a loss of the filtering efficiency of the proximal airways that is a well-recognized characteristic of infant lungs. According to the results of clearance modelling, the smaller tracheobronchial tree of children prevents a significant deposition of particles in the alveolar region, because medium- to large-size aerosols are subject to inertial impaction in the bronchi, while small aerosols are also deposited in the proximal airways due to Brownian diffusion. For children with tracheobronchial disease such as asthma, bronchitis and cystic fibrosis (CF), this filtering effect is further increased and therefore guarantees high deposition of inhaled therapeutic aerosols in the target regions in the tracheobronchial tree.[36-38] Conversely to this optimal targeting of broncho-specific pharmaceuticals, the use of aerosolized drugs specifically targeting the alveoli (e.g. insulin, corticosteroids) is complicated in children, since deposition efficiency in this region is much lower. A solution to this problem could be the development of special breathing techniques (very slow inhalation to minimize inertial impaction[30]).

Within the adult group, the tracheal mucus velocity decreases again with age (Figure 1).[23] This phenomenon was documented by the studies of Goodman et al (1977)[21] who found that older (56-70 years) non-smokers had a significantly lower tracheal mucus velocity (5.8 ± 0.98 mm min^{-1}) than young (19-28 years) non-smokers (10.1 ± 1.1

mm min^{-1}). Possible explanations for this age-dependent decrease of mucus velocity in the adult trachea were not discussed by the authors, but could, for instance, include a continuous malfunction of single cilia or whole ciliated cells, or an increase in the thickness and viscosity of mucus with age. Increasing mucus viscosity could be similar to that in patients with CF, caused mainly by increased content of DNA fragments and actin filaments which are both released from necrotic cells. According to the modelling results presented here, the reduction in tracheal mucus velocity with age is accompanied by a general decrease in the clearance efficiency, and thus longer residence times of deposited particles in the tracheobronchial compartment. This deceleration of mucociliary clearance was found to range from 10 to 30 %, which corresponds with the investigations of Puchelle et al[39] who discussed an inverse relationship between bronchial clearance of particles and age in non-smokers. The reasons for this general decrease in clearance efficiency might be the same as those for the change in the tracheal mucus velocity. Age-dependent deposition patterns of specific particles due to slight modifications of the bronchial airway geometry need to be considered.[17,29] As outlined by Wolff,[24] the pattern of age-related change in mucus velocity is similar to the changes described for certain other pulmonary function measurements (e.g. VC, time-forced expiratory values, midexpiratory flow indices). This parallel could reflect a maturity and integrity of the lung that appears to reach a maximum in young adulthood. In contrast to the age dependence of mucociliary clearance in humans, possible intrasubject variability of this mechanism observed with specific physical exercise can be explained to a great extent as the consequence of differential particle deposition patterns. During heavy exercise, high rates of air flow enhance particle deposition by inertial impaction in the more proximal airways, while during light or sitting exercise the inhaled aerosols are in addition deposited in the more peripheral parts of the tracheobronchial compartment and thus need a longer time for their clearance. Improvements in mucociliary clearance produced by physical exercise have been reported by Gross et al[26] who found that high-frequency chest wall compression causes an increase in peripheral mucociliary clearance.

The results of modelling provide indications that the difference in tracheobronchial clearance between adult males and females ranges from 0 to 5 %, which is believed to be mainly due to individual airway geometry,[12] while basic clearance efficiency is assumed to be equal in males and females. The extensive studies of Pavia et al[40] and Yeates et al[20] have also shown that there is no solid evidence for different clearance efficiency between the males and females of any species. While in the juvenile age group (i.e., 15 years), the clearance in females exceeds that in males, in the adult group a reverse tendency can be observed. This phenomenon could be, again, explained by the relationship between lung morphometry and mucus velocity.

This study, based on clearance modelling, has yielded evidence that tracheobronchial clearance in humans is subject to certain age-related changes. In addition to refinement of the clearance models, such as application of fractal approaches for assessing clearance mechanisms based on non-linear model simulations, future research should also focus on clarification of the cellular and molecular mechanisms responsible for this phenomenon.[41,42]

REFERENCES

1. Lippmann M, Albert RE. The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. Am Ind Hyg Assoc J 1969;30:257-75.
2. Lippmann M, Yeates DB, Albert RE. Deposition, retention, and clearance of inhaled particles. Brit J Ind Med 1980;37:337-62.
3. Cuddihy RG, Yeh HC. Respiratory tract clearance of particles and substances dissociated from particles. In: Mohr U (editor). Inhalation toxicology: The design and interpretation of inhalation studies and their use in risk assessment. Springer, Berlin, 1988, pp. 169-193.
4. Oberdörster G. Lung clearance of inhaled insoluble and soluble particles. J Aerosol Med 1988;1:289-330.
5. Albert RE, Lippmann M, Briscoe W. The characteristics of bronchial clearance in humans and the effects of cigarette smoking. Arch Environ Health 1969;18:738-55.
6. Albert RE, Lippmann M, Peterson Jr HT, Berger J, Sanborn K, Bohning D. Bronchial deposition and clearance of aerosols. Arch Int Med 1973;131:115-27.
7. Stahlhofen W, Gebhart J, Rudolf G, Scheuch G. Measurement of lung clearance with pulses of radioactivity-labelled aerosols. J Aerosol Sci 1986;17:333-6.
8. Stahlhofen W, Koebrich R, Rudolf G, Scheuch G. Short-term and long-term clearance of particles from the upper human respiratory tract as a function of particle size. J Aerosol Sci 1990;21:S407-10.
9. Stahlhofen W, Scheuch G, Bailey MR. Measurement of the tracheobronchial clearance of particles after aerosol bolus inhalation. In: Dodgson J, McCallum RI (editors). Inhaled particles VII, Proceedings of an international symposium on inhaled particles organized by the British Occupational Hygiene Society. Oxford University Press, Oxford, 1994, pp. 189-196.
10. Stahlhofen W. Human lung clearance following bolus inhalation

of radioaerosols. In: Crapo JD, Smolko ED, Miller FJ, Graham JA, Hayes AW (editors). Extrapolation of dosimetric relationships for inhaled particles and gases. Academic Press, Washington, 1989, pp. 153-166.
11. Scheuch G, Kreyling W, Haas F, Stahlhofen W. The clearance of polystyrene particles from UO_2 fuel element fabrication. Health Phys 1993;48:29-48.
12. International Commission on Radiological Protection (ICRP). Human respiratory tract model for radiological protection. Publication 66. Ann. ICRP. Pergamon Press, Oxford, 1994.
13. Sturm R, Hofmann W, Scheuch G, Sommerer K, Svartengren M, Camner P. Particle clearance in human bronchial airways: Comparison of stochastic model predictions with experimental data. Ann Occup Hyg 2002;46(Suppl 1):329-33.
14. Iravani JD, Van As A. Mucus transport in the tracheobronchial tree of normal and bronchitic rats. J Pathol 1972;106:81-93.
15. Mercer RR, Russell ML, Crapo JD. Mucous lining layers in human and rat airways. Ann Rev Resp Dis 1992;145:A355.
16. Phalen RF, Oldham MJ, Beaucage CB, Crocker TT, Mortensen JD. Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Rec 1985;212: 368-80.
17. Hofmann W, Bergmann R, Ménache MG. The effect of intersubject variability in airway morphology on intersubject variations in particle deposition. J Aerosol Sci 1998;29:S943-4.
18. Abd El Hady M, Hofmann W, Bergmann R. The effect of intersubject variability in lung morphometry on particle deposition. J Aerosol Sci 1997;28:S623-4.
19. Asgharian B, Hofmann W, Bergmann R. Particle deposition in a multiple-path model of the human lung. Aerosol Sci Technol 2001;34:332-9.
20. Yeates DB, Aspin N, Levison H, Jones MT, Brian AC. Mucociliary tracheal transport rates in man. J Appl Physiol 1975;39:487-95.
21. Goodman RM, Yergin BM, Landa JF, Golvinaux MH, Sackner MA. Relationship of smoking history and pulmonary function tests to tracheal mucous velocity in nonsmokers, young smokers, ex-smokers, and patients with chronic bronchitis. Am Rev Resp Dis 1977;117:205-14.
22. Santa Cruz R, Landa J, Hirsch J, Sackner MA. Tracheal mucous velocity in normal man and patients with obstructive lung disease; effects of terbutaline. Am Rev Resp Dis 1974;109:458-63.
23. Mauderly JL, Hahn FF. Advances in Veterinary Science and Comparative Medicine: The Respiratory System. Vol. 26. Academic Press, New York, 1982.
24. Wolff RK. Mucociliary Function. In: Parent RA. (editor). Comparative Biology of the Normal Lung. CRC Press, New York, 1989, pp. 659-680.
25. Valberg PA, Wolff RK, Mauderly JL. Redistribution of retained particles: effect of hypernea. Am Rev Resp Dis 1985;131:273-80.
26. Gross D, Zidulka A, O'Brien C, Wight D, Fraser R, Rosenthal L, et al. Peripheral mucociliary clearance with high-frequency chest wall compression. J Appl Physiol 1985;58:1157-63.
27. Bateman JRM, Clarke SW, Pavia D, Sheahan NF. Reduction in clearance of secretions from the human lung during sleep. J Physiol Lond 1978;284:55.
28. Sturgess JM. Mucous secretions in the respiratory tract. Ped Clin N Am 1979;26:481.
29. Ménache MG. Conducting airway geometry in the human lung as a function of age: Development of airway geometry models for dosimetry calculations. UMI Dissertation Services, Ann Arbor, MN, 1997.
30. Philipson K, Falk R, Svartengren M, Jarvis N, Bailey M, Bergmann R, et al. Does lung retention of inhaled particles depend on their geometric diameter? Exp Lung Res 2000;26:437-55.
31. Koblinger L, Hofmann W. Monte Carlo modeling of aerosol deposition in human lungs. Part I: Simulation of particle transport in a stochastic lung structure. J Aerosol Sci 1990;21:661-74.
32. Hofmann W, Sturm R. Stochastic model of particle clearance in human bronchial airways. J Aerosol Med 2004;17:73-89.
33. Sturm R, Hofmann W. Mechanistic interpretation of the slow bronchial clearance phase. Radiat Prot Dosimetry 2003;105:101-4.
34. Sturm R, Hofmann W. Stochastic modeling predictions for the clearance of insoluble particle from the tracheobronchial tree of the human lung. Bull Math Biol 2007;69:395-415.
35. Asgharian B, Hofmann W, Miller FJ. Mucociliary clearance of insoluble particles from the tracheobronchial airways of the human lung. J Aerosol Sci 2001;32:817-32.
36. Hofmann W, Koblinger L. Monte Carlo modeling of aerosol deposition in human lungs. Part III: Comparison with experimental data. J Aerosol Sci 1992;23:51-63.
37. Winkler-Heil R, Sturm R, Hofmann W. Calculation of therapeutic aerosol deposition in cystic fibrosis patients. J Aerosol Med 2001;14:414.
38. Martonen T, Kratz I, Cress W. Aerosol Deposition as a Function of Airway Disease: Cystic Fibrosis. Pharm Res 1995;12:96-102.
39. Puchelle E, Zahm JM, Bertrand A. Influence of age on bronchial mucociliary transport. Scand J Resp Dis 1979;60:307-13.
40. Pavia D, Bateman JRM, Clarke SW. Deposition and clearance of inhaled particles. Bull Eu Physiopathol Respir 1980;16: 335-66.
41. Myrianthefs PM, Sznajder JI, Baltopoulos G. Lung Edema Clearance. Pneumon 2006;19:14-21.
42. Vittorakis S, Gaga M, Oikonomidou E, Samitas K, Xorianopoulos D. Immunological mechanisms in the lung. Pneumon 2007;20:274-278.