EVALUATION OF INHALED DRUG DEPOSITION DURING AN ASTHMA ATTACK USING A STOCHASTIC LUNG MODEL

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Abstract: *Objective: The objective of this study is to use a computerized lung model to quantify the deposition of inhaled drug particles in bronchial generations 9-16, during a severe asthma attack. Material and methods: The deposition of 1–6 μm particles in a healthy individual and during a severe asthma attack were modelled using a stochastic lung model and respiratory parameters characteristic for the two conditions. A second series of simulations were carried out using identical respiratory parameters. Results: Deposition fractions in generations 9–16 were significantly higher during the asthma attack in both series of simulations, being 100% higher for all particle sizes when using identical breathing parameters. Conclusions: Our results suggest that the deposition of inhaled particles during an asthma attack can present significant differences compared to a healthy individual, regardless of the respiratory parameters.*

Cuvinte cheie: *astm bronşic, modelare, stohastic*

Rezumat: *Obiectiv: Obiectivul acestui studiu este realizarea unui studiu de modelare pentru a cuantifica depunerea particulelor inhalate în generaţiile bronşice 9–16 în timpul unei crize severe de astm bronşic. Material şi metode: Depunerea particulelor cu diametrul cuprins între 1–6 μm, inhalate de către un individ sănătos şi un individ aflat într-o criză severă de astm bronşic a fost modelată cu ajutorul unui model pulmonar stohastic, folosind parametri respiratori specifici celor două condiţii. O altă serie de simulări a fost efectuată folosind parametri respiratori identici. Rezultate: Fracţiile de depunere din generaţiile 9–16 au fost semnificativ mai mari în timpul crizei de astm în ambele serii de simulări, fiind cu 100% mai mari în cazul parametrilor respiratori identici, pentru toate diametrele investigate. Concluzii: Rezultatele noastre sugerează că depunerea particulelor inhalate în timpul unei crize de astm bronşic poate prezenta diferenţe semnificative comparativ cu un individ sănătos, independent de parametrii respiratori.*

INTRODUCTION

Asthma bronchiale is one of the most common chronic respiratory diseases, affecting more than 50 million persons in the US, according to the American Academy of Asthma, Allergy and Immunology, and approximately 300 million persons worldwide.(1) The main physiological element of this diseases is represented by the episodic obstruction of the airways, which leads to a limitation of the airflow, while the pathological basis is represented by the inflammation of the airways, frequently associating structural modifications.

Medication used in the treatment of asthma bronchiale is currently administered mainly by inhalation, as this route presents several advantages: the administered dose is relatively low, the effect installs quickly and adverse reactions are reduced.(2,3) Particles used in inhalation devices typically have diameters between 3–6 μm (4,5,6), which corresponds to the findings of several studies suggesting that the ideal particle size for β2 agonists is between 1–6 μm.(5)

The β2 receptors targeted by asthma medication are present predominantly in the small airways, their density increasing towards the periphery of the lungs.(7) At the same time, smooth muscle cells responsible for the constriction of the airways during an asthma attack are present mostly in the conductive region of the airways, but it can also be found in smaller bronchi.(5,8) Thus, the treatment of asthma bronchiale should target those areas where β2 receptors and smooth muscle cells are present simultaneously (9), namely in the region situated between bronchial generations 9 and 16.

The transportation and deposition of inhaled particles in the human airways can be assessed using in vivo studies or computerized lung models. However, due to the ethical and technical limitations of the in vivo studies, currently there is a great emphasis on computerized lung models, which can simulate the transportation and deposition of a wide range of particles in a large number of respiratory conditions.

PURPOSE

The objective of this study is to use a computerized lung model to quantify the deposition of inhaled drug particles in bronchial generations 9-16, during a severe asthma attack.

METHODS

The deposition of inhaled particles was modelled using the current version of the stochastic lung model developed

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by Koblinger and Hofmann. The detailed description of the model can be found in several sources (10,11,12,13,14,15), therefore here we will only present its main features. The model simulates the transportation and deposition of inhaled particles in a stochastic, asymmetric lung structure, calculating the deposition probabilities of inhaled particles in a sequence of bifurcation units, which consist of a parent tube and two asymmetrically dividing daughter airways. The airways are reconstructed on the basis of real morphometric measurements, while the geometric properties of the airways and particle trajectories are selected randomly, to ensure that all paths of the inhaled particles are different from each other.

The stochastic lung model has the built-in ability to simulate the transportation and deposition of inhaled particles in asthmatic airways. The obstruction that occurs during an asthma attack is modelled by assigning an asthma factor, i.e. a minimum and maximum level of obstruction for each bronchial generation, the model selecting a random value from this interval according to the severity of the modelled asthma attack. Since there is no detailed information regarding the spatial distribution of airway obstruction during an asthma attack, the asthma factors were derived empirically from lung function measurement data. Based on these data, a severe asthma attack is characterised by an asthma factor interval of 8–80%, a higher value representing a higher level of obstruction. Besides the asthma factor, there is a possibility to define the probability of obstruction occurring in any given bronchial generation, in case of a severe asthma attack this probability being 100%.

We modelled the inhalation of 1–6 µm particles in case of a healthy adult vs. during a severe asthma attack, calculating the amount of particles deposited in bronchial generations 9–16. The input parameters characteristic for the two conditions are presented in table no. 1.

Table no. 1. Input parameters used in simulations

Parameter	Healthy adult	Asthma attack
Functional residual	3300 ml	4500 ml
Tidal volume (V_T)	750 ml	600 ml
Breathing frequency	12 / min	36 / min
Inhalation time (T_{inh})	2.5 s	0.55 s
Exhalation time (T_{exh})	2.5 s	1.1 s
Inhalation: exhalation ratio	1:1	1:2
Particle diameter	1–6 µm	
Number of inhaled particles	100,000	

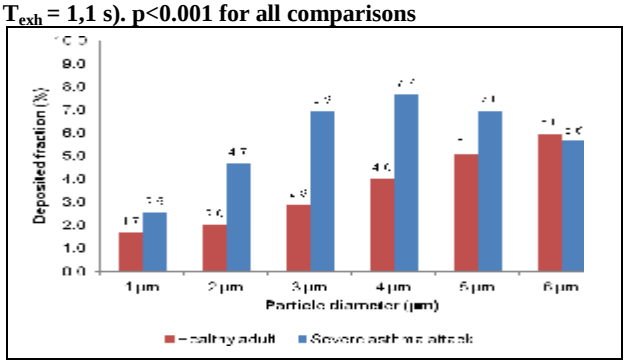
Assuming that an individual experiencing an asthma attack changes his inhalation mode when using a therapeutic inhalation device, we carried out a second series of simulations using identical breathing parameters, namely a 10 s symmetrical breathing cycle (T_{inh} = 5 s, T_{exh} = 5 s) and a 2000 ml tidal volume.

The simulations were carried out for one complete breathing cycle, in case of a male adult, assuming oral breathing and that the particles are inhaled uniformly during inhalation. Data processing and statistical analysis were performed using Microsoft Excel 2007. We used Student's t test to compare the results, and a p level below 0.05 was considered to be statistically significant.

RESULTS

In the first series of simulations we compared the deposition efficiency of 1–6 µm particles in bronchial generations 9-16, in case of a healthy adult and during a severe asthma attack. The results are presented in figure no. 1.

Figure no. 1. Deposition fractions of 1–6 µm particles in generations 9-16, in case of a healthy adult (FRC = 3300 ml, V_T = 750 ml, T_{inh} = 2,5 s, T_{exh} = 2,5 s) vs. during a severe asthma attack (FRC = 4500 ml, V_T = 600 ml, T_{inh} = 0,55 s, T_{exh} = 1,1 s). p<0.001 for all comparisons



The differences between the morphometric and respiratory parameters characterising the two conditions is clearly visible, and the obstruction of the airways during the asthma attack seems to favour the deposition of 1–6 µm particles exactly in the strategically important regions. The amount of particles deposited in generations 9–16 is higher for 1–5 µm particles (p<0.001), the highest deposition fraction being observed in the case of 4 µm particles, and the highest difference, of 138%, in the case of 3 µm particles (2.9% in the case of a healthy adult vs. 6.9% during the asthma attack, p<0.001).

Figure no. 2. Deposition fractions of 1–6 µm particles in generations 9-16, in case of a healthy adult vs. during a severe asthma attack, using identical respiratory parameters (V_T = 2000 ml, T_{inh} = 5 s, T_{exh} = 5 s)

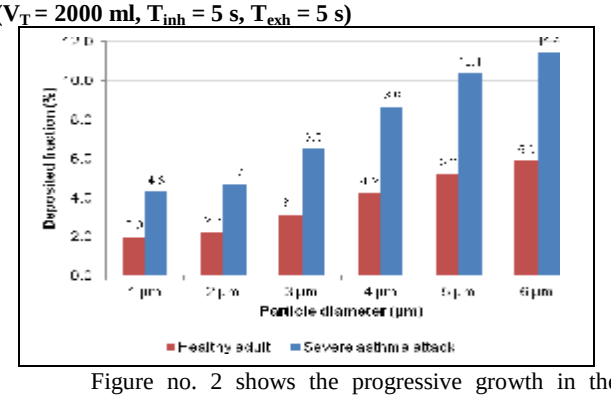


Figure no. 2 shows the progressive growth in the quantity of deposited particles for both conditions. The results suggest once more that the obstruction of the airways favours the deposition of inhaled particles in generations 9-16, deposition fractions obtained during the asthma attack being approximately 100% higher than the one obtained in a healthy individual, for all particle sizes (p<0.001). At the same time, the figure shows the clear superiority of 6 µm particles, compared to 1 µm particles (11.4% vs. 4.3%), during the asthma attack, p<0.001).

DISCUSSIONS

The deposition of inhaled particles in asthmatic patients has been described in the *in vivo* studies, using the imagistic quantification of the deposition of radiolabelled particles.(5)

These studies focused mainly on the effect of particle size, as previous studies have pointed out that this is the most

important factor that influences the deposition of inhaled particles.(16) Although *in vivo* studies reveal the general tendencies of particle deposition in the asthmatic lung, and these tendencies are confirmed by our results, they provide little insight regarding regional deposition fractions, due to their inherent technical limitations.

The characteristics of the obstructed airways and their effect on the deposition of inhaled particles were described in several modeling studies. Martonen et al developed an asthma model assuming that only a couple of bronchial generations are affected during an asthma attack and that the degree of obstruction is the same in all generations, demonstrating that the deposition of particles in the affected airways may change dramatically during an asthma attack.(17) Similar results were obtained by other studies.(18) Longest et al have also simulated the transportation and deposition of inhaled particles in a model of childhood asthma, obtained by decreasing the airway diameters with a constant factor.(19) This study obtained similar results to ours, concluding that bronchial obstruction leads to a significant increase in the deposition fractions of particles in this region.

Although the obstruction of the airways doubles the amount of particles depositing in this region during an asthma attack, the highest deposition fraction is only 11.4%, which can be considered far from efficient. There are studies that also suggest that inhalation treatment is not efficient enough and there is a need for a paradigm shift concerning the treatment of asthma bronchiale.(5) Further studies are needed to evaluate the effect of particle diameter and respiratory parameters on the deposition of inhaled particles during an asthma attack.

CONCLUSIONS

Our results suggest that the deposition of inhaled particles during an asthma attack can present significant differences compared to a healthy individual, regardless of the respiratory parameters. Deposition fractions in the therapeutically important areas of the airways may be up to 100% higher during an asthma attack, leading to a significant increase in the amount of medication depositing in this region.

REFERENCES

1. Global Inititiative for Asthma. Global strategy for asthma management and prevention. http://www.ginasthma.org/uploads/users/files/GINA_Report_2012.pdf.
2. Newman SP. Aerosol deposition considerations in inhalation therapy. Chest. 1985;88 (Suppl. 2):152S-160S.
3. Everard ML. Guidelines for devices and choices. J Aerosol Med. 2001;14 (Suppl. 1):S59-S64.
4. Mitchell JP, Nagel MW, Wiersema KJ, Doyle CC. Aerodynamic particle size analysis of aerosols from pressurized metered-dose inhalers: Comparison of Andersen 8-stage cascade impactor, next generation pharmaceutical impactor, and model 3321 aerodynamic particle sizer aerosol spectrometer. AAPS PharmSciTech. 2003;4(4):425-433.
5. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med. 2005;172(12):1497-1504.
6. Saini D, Biris AS, Srirama PK, Mazumder MK. Particle size and charge distribution analysis of pharmaceutical aerosols generated by inhalers. Pharm Dev Technol. 2007;12(1):35-41.
7. Barnes PJ, Basbaum CB, Nadel JA, Roberts JM. Localization of betaadrenoreceptors in mammalian lung by light microscopic autoradiography. Nature. 1982;299:444-447.
8. Haughney J, Price D, Barnes NC, Virchow JC, Roche N, Chrystyn H. Choosing inhaler devices for people with asthma: current knowledge and outstanding research needs. Respir Med. 2010;104(9):1237-1245.
9. Ebina M, Yaegashi H, Chiba R, Takahashi T, Motomiya M, Tanemura M. Hyperreactive site in the airway tree of asthmatic patients revealed by thickening of bronchial muscles: a morphometric study. Am Rev Respir Dis. 1990;141:1327-1332.
10. Koblinger L, Hofmann W. Analysis of human lung morphometric data for stochastic aerosol deposition calculations. Physics in Medicine and Biology. 1985;30:541-556.
11. Koblinger L, Hofmann W. Monte Carlo Modelling of aerosol deposition in human lungs. Part I: Simulation of particle transport in a stochastic lung structure. Journal of Aerosol Science. 1990;21:661-74.
12. Hofmann W, Koblinger L. Monte Carlo modelling of aerosol deposition in human lungs. Part II: Deposition fractions and their sensitivity to parameter variations. Journal of Aerosol Science. 1990;21(5):675-688.
13. Hofmann W, Koblinger L. Monte Carlo modelling of aerosol deposition in human lungs. Part III: Comparison with experimental data. Journal of Aerosol Science. 1992;23(1):51-63.
14. Hofmann W, Asgharian B, Winkler-Heil R. Modeling intersubject variability of particle deposition in human lungs. J. Aerosol Sci. 2002;33:219-235.
15. Hofmann W, Winkler-Heil R, Bálásházy I. The effect of morphological variability on surface deposition densities of inhaled particles in human bronchial and acinar airways. Inhal. Toxicol. 2006;18:809-819.
16. Dolovich M. Influence of inspiratory flow rate, particle size, and airway calibre on aerosolised drug delivery to the lung. Respir Care. 2000;45:597-608.
17. Martonen TB, Fleming J, Schroeter J, Conway J, Hwang D. In silico modelling of asthma. Advanced Drug Delivery Reviews. 2003;55:829-849.
18. Chalupa DC, Morrow PE, Oberdorster G, Utell MJ, Frampton MW. Ultrafine particle deposition in subjects with asthma. Environmental Health Perspectives. 2004;112:879-882.
19. Longest PW, Vinchurkar S, Martonen T. Transport and deposition of respiratory aerosols in models of childhood asthma. Journal of Aerosol Science. 2006;37:1234-1257.