

Influence of airway calibre on the intrapulmonary dose and distribution of inhaled aerosol in normal and asthmatic subjects

K.F. Chung, K. Jeyasingh *, P.D. Snashall

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ABSTRACT: We investigated the relationship between airway calibre and the dose and distribution of inhaled aerosol in ten normal and six asthmatic subjects. Subjects inhaled saline aerosol containing $^{99m}\text{TcO}_4$ delivered from a nebulizer connected to a dosimeter, and the lung fields were scanned with a gamma-camera. Right lung dose (RLD) was calculated as percentage of total dose. Intrapulmonary distribution was measured as penetration index (PI) (peripheral zone counts/central zone counts). Asthmatics had a significantly lower PI than normal subjects and there was a linear relationship between PI and baseline specific airway conductance (sGaw, $p < 0.001$), and forced expiratory volume in one second (FEV₁, $p < 0.05$). After bronchodilatation with salbutamol ($\Delta\text{sGaw } 101 \pm 31\%$, mean \pm SEM), PI increased from 0.73 ± 0.11 to 1.09 ± 0.15 ($p < 0.05$); after bronchoconstriction with methacholine ($\Delta\text{sGaw } 62.6 \pm 2.9\%$), PI decreased from 1.42 ± 0.24 to 1.06 ± 0.22 ($p < 0.05$). Changes of PI were correlated with changes in sGaw and FEV₁ ($n=20$, $p < 0.001$) but changes of RLD and changes in airway calibre were not. The distribution of inhaled aerosol, but not the dose, is largely dependent on airway calibre. The differences in PI between normal and asthmatic subjects may at best be explained by the differences in central airway calibre.

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The bronchomotor response to an inhaled aerosol of a bronchoactive drug depends upon the quantity of the drug reaching active sites in the tracheobronchial tree. Delivery of aerosol to these sites is a complicated function of particle size, inspiratory and expiratory characteristics and airway geometry [1, 2]. Differences in the pattern of deposition between normal and asthmatic subjects [3, 4] may partially explain the differences in response to inhaled drugs seen between and within these groups. However, the degree to which the pattern of aerosol deposition controls response remains controversial and poorly defined. RUFFIN *et al.* [5] deliberately and markedly changed deposition pattern by altering particle size and pattern of inspiration. When histamine was delivered preferentially to the central bronchi, up to twenty times less drug was required to produce a given degree of bronchial obstruction than when the drug was deposited evenly to the whole bronchial tree. It is more difficult to determine the importance of the more subtle differences in central to peripheral deposition seen between subjects using the same apparatus and inhalation techniques. Thus, we were unable to show any increase in the responsiveness to histamine in subjects whose bronchi we precontracted with methacholine, despite the likelihood that this would

cause the histamine to deposit more centrally [6].

In the present study we have used gamma-camera scanning techniques to visualize the pattern of aerosol deposition. We have employed the same techniques for particle generation and inhalation that we and others have used in previous studies [6-9]. We have examined the relationship between the dose deposited in the lungs, central to peripheral deposition patterns and airway calibre, and the effects of prior bronchoconstriction and bronchodilatation with pharmacologic agents.

Methods

Subjects

Ten normal and six asthmatic subjects gave informed consent for the study (table 1); one normal and two asthmatic subjects took part in two different parts of the study. All medications, including bronchodilator and steroid aerosols, were stopped 8 h prior to the study. No subject was on oral bronchodilator drugs. The study was approved by the Ethical Committee and the Radiation Safety Committee of Charing Cross Hospital.

Table 1. - Characteristics of subjects

Subjects	n	Age yrs	Smoking	FEV ₁ l (BTPS)	
				Observed	Predicted
Normal	10	26±4	1	4.07±0.69	4.02±0.51
Asthmatic	6	44±6	0	2.49±1.23	3.66±0.40

FEV₁: forced expiratory volume in one second; BTPS: body temperature, pressure (atmospheric), and saturation (water vapour).

Experimental design

Baseline pulmonary function was assessed by measurement of forced expiratory volume in one second (FEV₁) using a dry-bellows spirometer (Vitalograph Ltd, UK) and of specific airway conductance (sGaw) in a constant-volume body plethysmograph (Fenyves & Gut, Basel, Switzerland). The subject then inhaled an aerosol of 0.9% NaCl containing ^{99m}TcO₄ delivered from a Hudson's nebulizer connected to a dosimeter, and immediately after this a posterior thoracic scan was performed. Approximately 5 min later the subject was premedicated with aerosols of either: a) salbutamol sulphate to cause bronchodilatation or; b) methacholine to cause bronchoconstriction. In order to test the reproducibility of the distribution of radioactive aerosol, another group of subjects inhaled 0.9% NaCl only. Measurements of pulmonary function were repeated 30 min after premedication, and a second scan of the posterior thorax was obtained to estimate the residual background radioactivity. The subject then inhaled the same number of puffs of ^{99m}TcO₄ aerosol as before and immediately afterwards a further scan was obtained. In order to define the lung boundaries and to quantify the dose of aerosol in the lungs, a perfusion scan was performed at the end of each study by an intravenous injection of approximately 1.5 mCi ^{99m}TcO₄ labelled macroaggregated albumin (^{99m}Tc-MAA). The position of the posterior thorax relative to the gamma-camera was fixed for the four scans by marking the position of bony landmarks on the posterior chest wall with a radioactive pointer.

Aerosol production and delivery

Aerosols were generated from a Hudson's nebulizer driven by compressed air. Aerosol mass-median particle diameter, measured with a seven-stage Batelle cascade impactor, was 2.8±2.1 µm (geometric mean±GSD). The nozzle of the nebulizer was connected to the mouth-piece by a tube 36 cm in length and 3.8 cm in diameter. The nebulizer was triggered by means of a dosimeter, by the fall in the tube pressure at the onset of inspiration, and nebulization continued for 0.6 s. Subjects were asked to inhale at a slow rate from functional residual capacity (FRC) to total lung capacity (TLC) and to exhale slowly to FRC without breath-holding. This manoeuvre was practised by the subject before the start of each experiment.

Lung scans

Seven ml of ^{99m}Technetium pertechnetate (^{99m}TcO₄; approximately 40 mCi per ml) were placed in the Hudson's nebulizer which was kept in a lead container. The subject was seated upright with the posterior thorax resting against the parallel-hole collimator of a large field of view gamma-camera (Nuclear Enterprise NE 8970), and inhaled between 10 and 15 puffs of aerosol (depending upon the activity of ^{99m}TcO₄) over a period of 30 s. Immediately after this, a scan was performed over a period of 3 min. The data acquired were stored on magnetic tape for off-line computer processing (Nodecrest NMS80). The lung images were kept in a 64×64 matrix and each aerosol scan contained total counts ranging from 100,000 to 400,000 counts.

Preliminary studies failed to demonstrate significant uptake in the thyroid gland and therefore no attempt was made to block uptake.

Quantitative image analysis

A computer programme was used to define the boundaries of the lungs from the perfusion scan image [10]. The dividing line between the left and right lungs was first identified as the point of minimum count-rate in the horizontal plane between the two maxima. The image was then divided into two by a vertical line along this mid-line. To delineate the lung a contour line was drawn at 18% of the maximum count-rate in each half of the image. The value of 18% was chosen empirically; values from 12 and 25% gave similar results. The largest contiguous area in each half was taken as the lung. Because the image of the left lung was contaminated by counts from the stomach (from swallowed ^{99m}TcO₄), only the right lung data were analysed.

Also using the perfusion scan image of the right lung, another programme was used to define a central and peripheral lung zone. A horizontal line was extended from the mid-point of the vertical height of the lung to its medial border, and from this point lines were drawn to



Fig. 1. - Aerosol images obtained in one normal subject (left panel; FEV₁ 4.3 l) and one asthmatic subject (right panel; FEV₁ 1.55 l). These images have been subdivided for each lung into three zones as described in the methods section. The aerosol scan of the normal subject shows a relatively uniform distribution with a penetration index (PI) of 1.1; in the asthmatic subject, there is a patchy central deposition with PI 0.51. FEV₁: forced expiratory volume in one second.

the lung boundary starting from the vertical position and proceeding by steps of 10° up to 180° . The line joining the mid-points of these radiating lines defined the outer boundary of the central zone. A similar line was drawn to join points on the radiating lines 75% of the distance to the lung edge, defining the inner border of the peripheral zone. These lung contours were then superimposed on the two aerosol and background images obtained for each subject (fig. 1) in order to calculate: a) central zone deposition as a fraction of lung dose; and b) peripheral zone deposition as a fraction of lung dose. A penetration index (PI) defined as the ratio of the peripheral zone deposition to central zone was then derived.

All measurements of radioactivity in the lung were corrected for background activity and radioisotope decay. We have used the perfusion scan to allow us to relate emitted counts from the thorax to the dose of the isotope inhaled. The dose of injected ^{99m}Tc -MAA was accurately known and we assumed that all was trapped within the lung microvasculature. A calibration factor was derived to define the relationship between injected radioactivity and emitted counts (calibration factor=injected dose (mCi)/total lung counts), assuming that a similar relationship exists between inhaled dose and emitted counts. The calibration factor was used to calculate the right lung aerosol dose as a percentage of the dose delivered by the nebulizer at the mouth.

Based on a total dose of 0.5 mCi of $^{99m}\text{TcO}_4$ and on an intravenous dose of 1.5 mCi of ^{99m}Tc -MAA, the maximum possible exposure to radiation per subject was estimated to be 350 mrad to the lungs and 15 mrad to the whole body [11, 12].

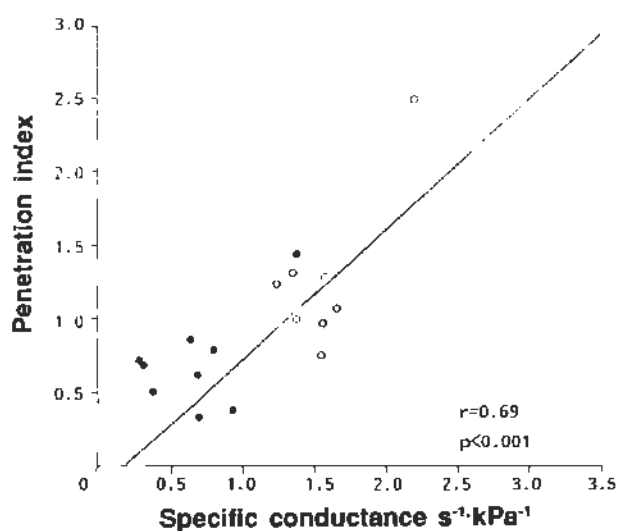


Fig. 2. — Relationship between penetration index and baseline specific conductance for 20 aerosol studies performed on 10 normal (○) and 6 asthmatic (●) subjects. There is a significant linear correlation ($r=0.69$; $p<0.001$).

Variability of the nebulizer output

The nebulizer output was checked *in situ*. The mouth-piece was connected to a 4 cm diameter and 8 cm long plastic tube stuffed with sponge foam in order to trap aerosol. A liter syringe was attached at its other end and the plunger was manually drawn at a constant rate for 2 s, causing the nebulizer to trigger for 0.6 s. Five such "inhalations" were performed for each sponge foam. This was repeated ($n=7$) with fresh tubing and sponge foam at 5-min intervals and the radioactivity from the $^{99m}\text{TcO}_4$ trapped in the sponge was determined.

Statistics

All values have been expressed as mean \pm SEM. Statistical significance was expressed using Student's *t*-test. Regression analysis was calculated by the least squares method. We accepted $p<0.05$ as indicating a significant difference.

Results

Baseline aerosol lung scans

Twenty baseline scans were examined (eleven from normal subjects and nine from asthmatic subjects). The proportion of nebulized ^{99m}Tc depositing in the right lung did not differ significantly between the two groups

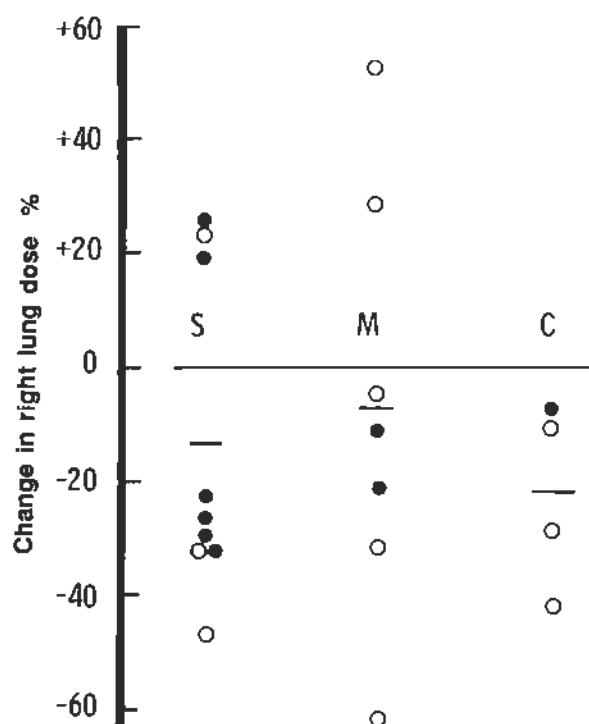


Fig. 3. — Change in lung dose in the right lung in each subject after salbutamol (S), methacholine (M) and saline (C) as a percentage of the lung dose in the baseline state in normal (○) and asthmatic (●) subjects. Horizontal bars indicate mean changes.

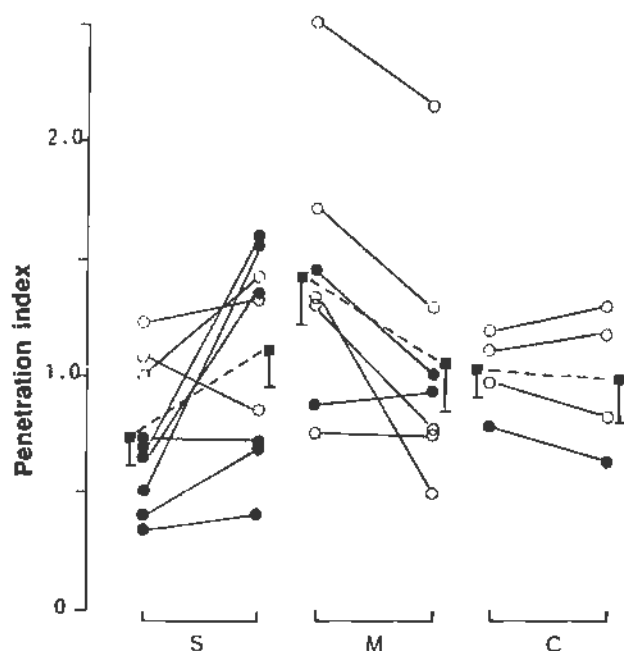


Fig. 4. — Effect of salbutamol (S), methacholine (M) and saline (C) premedication on penetration index in normal (○) and asthmatic (●) subjects. Mean values (■)±SEM are also shown. Salbutamol significantly increased the penetration index ($p<0.05$) and methacholine decreased it ($p<0.05$). However, saline had no effect.

(in normal subjects $8.1\pm1.1\%$; in asthmatic subjects $7.3\pm1.2\%$).

The distribution of inhaled aerosol within the lung appeared uniform in normal subjects, but in asthmatics who showed a marked degree of airways obstruction, there was a reduced amount of activity in the peripheral zone and a more patchy distribution in the central zone (fig. 1). PI was significantly lower in asthmatic subjects ($p<0.01$; fig. 2). There was a significant positive correlation between PI and baseline sGaw ($r=0.69$, $p<0.001$; fig. 2), and between PI and baseline FEV₁ ($r=0.51$, $p<0.05$).

Effects of changes in airway calibre

i) *Bronchodilatation.* Nine studies following salbutamol premedication were performed (three on normal subjects and six on asthmatic subjects). Mean sGaw and mean FEV₁ increased from 0.84 ± 0.31 to 1.46 ± 0.22 s⁻¹·kPa⁻¹ ($p<0.001$) and from 3.02 ± 0.46 to 3.54 ± 0.38 l (BTPS) ($p<0.01$), respectively. The change in right lung dose after bronchodilatation as a percentage of the dose in the baseline period varied from -47% to +24% (mean $14\pm9.9\%$) and was not statistically significant (fig. 3). There was no significant relationship between the change in sGaw or FEV₁ and the change in right lung dose. Mean PI increased from 0.73 ± 0.11 to 1.09 ± 0.15 ($p<0.05$; fig. 4).

ii) *Bronchoconstriction.* The effect of methacholine premedication was studied in five normal subjects and

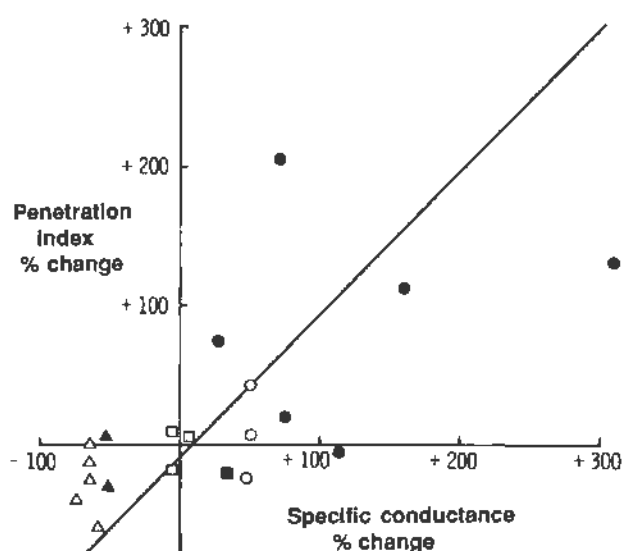


Fig. 5. — Relationship between the change in penetration index and the change in specific conductance induced by either salbutamol (○), or methacholine (▲) or saline (□) for 10 normal (open symbols) and 6 asthmatic (closed symbols). There is a significant linear correlation ($y=1.01x-4.64$; $r=0.68$; $p<0.001$).

two asthmatic subjects. Mean sGaw and mean FEV₁ decreased from 1.72 ± 0.36 to 0.63 ± 0.13 s⁻¹·kPa⁻¹ ($p<0.005$) and from 3.95 ± 0.32 to 2.96 ± 0.50 l (BTPS) ($p<0.001$), respectively. The change in the right lung dose varied from -62% to +52% of the dose delivered at the mouth (mean $-8\pm15\%$) and was not statistically significant (fig. 3). PI decreased from 1.42 ± 0.24 to 1.06 ± 0.22 ($p<0.05$; fig. 4).

iii) *0.9% NaCl.* Premedication with saline was given to three normal and one asthmatic subjects. Mean sGaw and mean FEV₁ showed no significant changes: from 1.78 ± 0.45 to 1.86 ± 0.43 s⁻¹·kPa⁻¹ and from 3.01 ± 0.60 to 3.01 ± 0.59 l (BTPS), respectively. Right lung dose decreased by $22\pm9.4\%$ after the second inhalation (range -6.7% to -42%; fig. 3) but this was not a significant change. PI was not significantly changed from 1.0 ± 0.10 to 0.98 ± 0.32 (fig. 4).

iv) *Changes in airway calibre and penetration index.* The change in sGaw following salbutamol, methacholine or saline was significantly correlated with the change in PI ($r=0.66$, $p<0.001$; fig. 5). A similar relationship was also found between changes in FEV₁ and changes in PI ($r=0.69$, $p<0.001$).

v) *Variability of nebulizer output.* The mean counts obtained over a period of 100 s for the seven "inhalations" in the dummy sponges, corrected for isotope decay, were $78,394\pm3,653$, giving a coefficient of variation of 12.3%.

Discussion

This study has quantified both total pulmonary aerosol deposition and its pattern of distribution within the lung under conditions standard to bronchial provocation studies. Total lung deposition was calculated using a perfusion lung scan to correct the thoracic gamma ray attenuation. We found that total deposition is highly variable between individuals and on different occasions with the same individual, but this variability was much greater than that of the nebulizer output. It is probable that the main source of intra-subject variability lies in the pharynx and larynx. RYAN *et al.* [8] found with the dosimeter method of delivering aerosols that the dose depositing in the throat is higher than that in the lung and is highly variable. We were unable to show any relationship between total deposition and airway calibre and there was no consistent difference between normal and asthmatic subjects. Neither acute bronchodilation nor acute bronchoconstriction altered total deposition.

Our findings on the intrapulmonary pattern of distribution of inhaled aerosol confirm and extend those of other workers [3, 13–18]. Thus, PAVIA *et al.* [13, 14] using a monodisperse aerosol demonstrated that alveolar particle deposition is a function of airway calibre, as measured by FEV₁. This was confirmed by LAUBE *et al.* [15] using a polydisperse aerosol. Similarly, DOLOVICH *et al.* [16] found a good relationship between intrapulmonary aerosol penetrance and maximal mid-expiratory flow rate. CHOPRA *et al.* [3] used a semi-quantitative approach to show that aerosol penetrance was a positive function of both FEV₁ and airway conductance. SVARTENGREN and co-workers [17, 18] showed that bronchoconstriction with methacholine resulted in a decrease in 24-h lung retention of 4 µm monodisperse Teflon particles in normal subjects, suggesting that methacholine constriction reduced penetration of particles into the alveoli. Our study has shown that intrapulmonary penetrance is a positive linear function of baseline airway conductance and also of conductance changes produced by methacholine, salbutamol and saline. Thus, normal subjects when bronchoconstricted demonstrate a pattern of aerosol deposition similar to that seen in asthmatic individuals.

The deposition of a large proportion of inhaled aerosol in central airways of asthmatics is probably largely due to narrowing of these central airways. Narrowing causes turbulent airflow, particularly at bifurcations and thus promotes deposition. Inhalation of salbutamol increased sGaw by 74% and penetration index by 49%. Since it was delivered by the same method as the ^{99m}Tc aerosol it probably deposited preferentially in the central airways of the asthmatic subjects and was, therefore, effective in promoting deeper penetration of subsequently administered aerosol.

One problem of our technique for measuring deposition is that central airways can only be visualized by scanning through the overlying "peripheral" lung. Penetration index is, therefore, an under-estimation of

actual penetration particularly where peripheral deposition is normal or high as in subjects with good airway function. Thus, our method may underestimate the differences seen between normal and asthmatic subjects with regard to aerosol penetration. Other workers [13–18] have quantified central airways deposition as that proportion of deposited aerosol which is removed by mucociliary clearance in a few hours, but this distinction between central and peripheral may be altered if disease affects central or peripheral rates of clearance. Another potential inaccuracy in our calculation of central and peripheral activities is in the use of the calibration factor to relate emitted counts to the administered dose of radioactivity. Strictly, this factor is only applicable to the counts from the whole lung when the distribution of the aerosolized isotope is the same as that of the perfusion scan isotope. Gamma rays emitted from different parts of the lung may be attenuated to differing extents. However, these potential errors are independent of airway calibre and state, and therefore are unlikely to undermine our conclusions.

Our results show that the pattern of deposition within the lung but not the total quantity deposited is largely determined by airway calibre. The effect of different patterns of aerosol deposition on airway responsiveness to inhaled bronchoconstrictor agents remains unclear. RUFFIN *et al.* [5] found that when histamine aerosol deposited predominantly in the large airways it was much more effective in causing airway obstruction than when it was deposited diffusely throughout the bronchial tree. However, in a previous study we showed that prior bronchoconstriction (reducing sGaw by approximately 50%) did not alter responsiveness to histamine despite the inference from the present study that this degree of constriction would have promoted central deposition of the histamine aerosol, with a reduction of penetration index by approximately 35% (fig. 5). Thus, taking our two studies together, central deposition is seen in asthma, but its effect on responsiveness is slight.

However, the total quantity of drug inhaled into the lungs may be more important in determining responsiveness. Thus, WANNER *et al.* [19] showed that some of the inter-subject variability in bronchial responsiveness to inhaled histamine was accounted for by differences in the dose of histamine retained in the airways. With inhaled atropine we have recently demonstrated that the amount of central airway deposition (which is largely determined by the total pulmonary deposition) is a major factor determining the degree of muscarinic antagonism produced by inhaled atropine [20].

In conclusion, large inter-subject differences are seen in total lung aerosol deposition, and these may reasonably be expected to influence responsiveness. However, mean total deposition is not different in normal and asthmatic groups and is, therefore, unlikely to explain asthmatic hyperresponsiveness. Preferential aerosol deposition in central airways does occur in asthma to an extent that depends on airway calibre but appears to have little effect on responsiveness.

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Influence du calibre des voies aériennes sur la dose intrapulmonaire et la distribution des aérosols inhalés chez les sujets normaux et asthmatiques. K. Chung, K. Jeyasingh, P. Snashall.

RÉSUMÉ: Nous avons investigué la relation entre le calibre des voies aériennes et la dose et la distribution d'aérosols inhalés chez 10 sujets normaux et 6 asthmatiques. Les sujets ont inhalé une solution saline d'aérosol contenant du $^{99m}\text{TcO}_4$ produit par un nébuliseur connecté à un dosimètre, tandis que les champs pulmonaires sont scintigraphiés à la gamma caméra. La dose du poumon droit a été calculée comme pourcentage de la dose totale. La distribution intrapulmonaire a été mesurée sous forme d'un index de pénétration (PI) (=comptage des zones périphériques/comptage des zones centrales). Les asthmatiques avaient un index de pénétration significativement plus bas que les sujets normaux, et il y a une relation linéaire entre l'index de pénétration et la conductance spécifique de base des voies aériennes, sGaw ($p < 0.001$) et VEMS ($p < 0.05$). Il n'y avait pas de relation entre le calibre des voies aériennes et la dose du poumon droit. Après bronchodilatation au salbutamol (sGaw+101±31%, moyennet erreur standard de la moyenne), l'index de pénétration passe de 0.73±0.11 à 1.09±0.15 ($p < 0.05$); après bronchoconstriction à la méthacholine (sGaw=62.6±2.9%), l'index de pénétration diminue de 1.42±0.24 à 1.06±0.22 ($p < 0.05$). Les modifications de l'index de pénétration sont en corrélation avec les modifications de la conductance spécifique des voies aériennes et du VEMS ($n=20$, $p < 0.001$), mais les modifications de la dose du poumon droit et les modifications du calibre des voies aériennes ne le sont pas. La distribution de l'aérosol inhalé, mais non la dose, est donc largement dépendante du calibre des voies aériennes. Les différences d'index de pénétration entre les sujets normaux et asthmatiques pourraient être expliquées au mieux par des différences dans le calibre des voies aériennes centrales.

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