

# Impaired tracheobronchial clearance in patients with mild stable asthma

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**ABSTRACT** Tracheobronchial mucociliary clearance was measured with the radioaerosol technique in 25 patients with stable, mild asthma, none of whom was taking systemic corticosteroids. The results were compared with those obtained from a control group of 25 healthy subjects matched for age and sex. All patients and healthy subjects were non-smokers. Ventilatory function was significantly impaired in the asthmatic group, which resulted in a more central initial tracheobronchial deposition of inhaled radioaerosol than in the control group. Despite the shorter transit path along the ciliated airways for the tracer radioaerosol in the asthmatic group, mucociliary clearance was found to be significantly poorer than in the healthy control group. This may be important with respect to bronchial mucus plugging.

Asthma is a disease characterised by reversible airway obstruction<sup>1</sup> caused by mucosal oedema, bronchial smooth muscle contraction, and hypersecretion of mucus.<sup>2</sup> Death from "ciliary insufficiency" and mucus plugging of small airways in asthmatics has been known for many years.<sup>3</sup> When the asthma is mild but variable, however, the roles of the cilia and of mucus and its clearance are ill defined. Mucociliary function in asthmatics has been examined by only a few investigators,<sup>4-9</sup> who have confined their measurements primarily to the proximal airways of the lungs. The numbers of patients studied are small and the results are conflicting. We have therefore assessed tracheobronchial mucociliary clearance in a moderately large group of patients with mild, stable asthma and compared it with that in a group of matched healthy subjects.

## Methods

The objective non-invasive radioaerosol technique<sup>10</sup> was used to measure whole-lung mucociliary clearance. Polystyrene particles 5  $\mu\text{m}$  in diameter tagged with the radionuclide technetium-99m (<sup>99m</sup>Tc) ( $T_{1/2} = 6 \text{ h}$ ) were generated by means of a spinning top<sup>11</sup> generator located within an airtight tank. The radioaerosol was inhaled from the tank by each sub-

ject or patient via a mouthpiece (a nose clip being worn) in eight discrete breaths starting from functional residual capacity and limited to 450 ml in volume by a Krogh spirometer. Inspiratory flow was measured by a pneumotachograph interposed between the spirometer and the tank. Each inhalation was followed by a three-second breath-holding pause to enable particles to deposit in the lungs by sedimentation. At the end of the inhalation procedure a water mouthwash and drink were used to clear the oropharynx and oesophagus of deposited radioaerosol.

The initial topographical distribution of the radioaerosol within the right lung was ascertained with a rectilinear gamma scanner.<sup>12</sup> The left lung was not scanned because of radioactivity in the stomach resulting from swallowed particles. Quantitatively the initial lung radioaerosol distribution may be expressed as a penetration index (PI). This is arbitrarily defined by us as the amount of radioactivity present in the outer two-fifths divided by that present in the inner two-fifths of the lung and expressed as a percentage.

Clearance of deposited radioaerosol from the lungs was monitored by two scintillation counters located within lead collimators.<sup>13</sup> One was placed anteriorly and the other posteriorly to the subject's chest. The wide-angle field of view of each counter was such that most of both lungs was included but the stomach was excluded. Counts were made at regular hourly intervals for the first six hours after radioaerosol inhalation. All counts, corrected for

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radioactive background and decay, were expressed as a percentage of the initial count. A final count at 24 hours served as a measure of the alveolar deposition of the particles.<sup>13</sup> There is considerable evidence<sup>10 14 15</sup> that particles deposited on the tracheobronchial airways are cleared within 24 hours, except in a few patients with severe airways obstruction.<sup>16</sup> Thus the proportion of particles retained at 24 hours represents those not deposited on airways mucus. Therefore the alveolar deposition (24-hour retention) reading was subtracted from the whole-lung retention curve of each patient or subject to give a tracheobronchial curve describing only clearance of particles deposited on airways mucus.<sup>17-19</sup>

During the six hours' observation all coughs were noted and sputum samples collected and weighed. All medication was withheld from the patients for at least 12 hours before the inhalation of radioaerosol.

Ventilatory function of patients and healthy subjects was measured about half an hour before the inhalation of the radioaerosol. Forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), and maximum mid-expiratory flow rate (MMFR<sub>25-75</sub>) were measured with a dry bellows spirometer (Vitalograph). The peak expiratory flow rate (PEFR) was measured with a Wright peak flow meter and flow rates at 25% and 50% of vital capacity from maximal expiratory flow-volume (air) curves were obtained with an Ohio 840 spirometer and a Bryan's X-Y recorder. The best result out of three technically acceptable attempts was taken for all indices measured.

Twenty-five patients (15 men and 10 women) with mild, stable asthma entered the study. Maintenance treatment ranged from regular inhaled bronchodilators and steroids to the occasional use of an inhaled bronchodilator only. None was receiving systemic steroid treatment. The data from the patients were compared with those obtained from 25 healthy subjects matched for age and sex. All patients and healthy subjects were non-smokers. Written informed consent was given by both patients and healthy subjects. The investigations were approved both by the ethical practices committee of the hospital and by the Radioisotope Panel of the Department of Health and Social Security.

Student's *t* test for two samples was used for the analysis of the results.

## Results

The physical characteristics and ventilatory function of both the asthmatic group and the healthy subjects are summarised in the table. Appreciable large and small airway obstruction was present in the asthmatic group at the time of study.

Physical characteristics and ventilatory function (means  $\pm$  SEM) of 25 patients with stable, mild asthma and 25 healthy control subjects

	Asthmatic group	Healthy subjects	<i>p</i>
Age (y)	32 $\pm$ 3	32 $\pm$ 3	NS
Height (m)	1.72 $\pm$ 0.02	1.72 $\pm$ 0.02	NS
Weight (kg)	68 $\pm$ 3	67 $\pm$ 3	NS
FEV <sub>1</sub> (% pred*)	85 $\pm$ 6	119 $\pm$ 4	<0.01
FEV <sub>1</sub> /FVC observed (%)	74 $\pm$ 4	88 $\pm$ 2	<0.01
PEFR (% pred*)	76 $\pm$ 5	99 $\pm$ 3	<0.01
MMFR <sub>25-75</sub> (% pred*)	63 $\pm$ 7	109 $\pm$ 4	<0.01
V <sub>max-50</sub> (% pred*)	47 $\pm$ 6	84 $\pm$ 4	<0.01
V <sub>max-25</sub> (% pred*)	39 $\pm$ 5	75 $\pm$ 6	<0.01

\*% pred—percentage of predicted values from Cotes.<sup>20</sup>

PEFR—peak expiratory flow rate; MMFR—maximum mid-expiratory flow rate; V<sub>max-50</sub>—maximum expiratory flow rate when 50% of the vital capacity remains to be expired; V<sub>max-25</sub>—maximum expiratory flow rate when 25% of the vital capacity remains to be expired; NS—not significant.

## RADIOAEROSOL DEPOSITION

Both penetration index and alveolar deposition were significantly less in the asthmatic group than in the healthy subjects. The penetration index (%) was 51  $\pm$  5 (SE) in the asthmatic group and 68  $\pm$  4 in the healthy subjects (*p* < 0.01). Alveolar deposition was 37  $\pm$  3 in the asthmatic group and 61  $\pm$  2 in the healthy subjects (*p* < 0.01). The radioaerosol was thus deposited in more proximal lung regions in the asthmatic group. The site of deposition of an inhaled aerosol within the lungs is determined by three factors: (a) the physical properties of the aerosol, (b) the mode of inhalation, and (c) the patency of the airways. We strictly control (a) and (b) with one exception—the inspiratory flow rate. This, however, was measured and was virtually identical for the groups (asthmatic group mean 27  $\pm$  1 l min<sup>-1</sup>; healthy subjects' mean 26  $\pm$  1 l min<sup>-1</sup>). The more proximal deposition of radioaerosol within the lungs of the asthmatic group therefore reflects their airway obstruction relative to the healthy control subjects. All other things being equal, this should result in a more rapid whole-lung clearance of particles in the asthmatic group because of the shorter transit pathway along the ciliated airways.

## CLEARANCE OF DEPOSITED AEROSOL

Figure 1 shows the mean whole-lung retention curves of deposited radioaerosol for the two groups. Retention was significantly greater after six hours in the healthy subjects than in the asthmatic group, because of their higher alveolar deposition. Figure 2 shows the mean tracheobronchial retention curves after subtraction of the alveolar deposition from the whole-lung data for each subject or patient. Six hours after inhalation retention in the healthy sub-

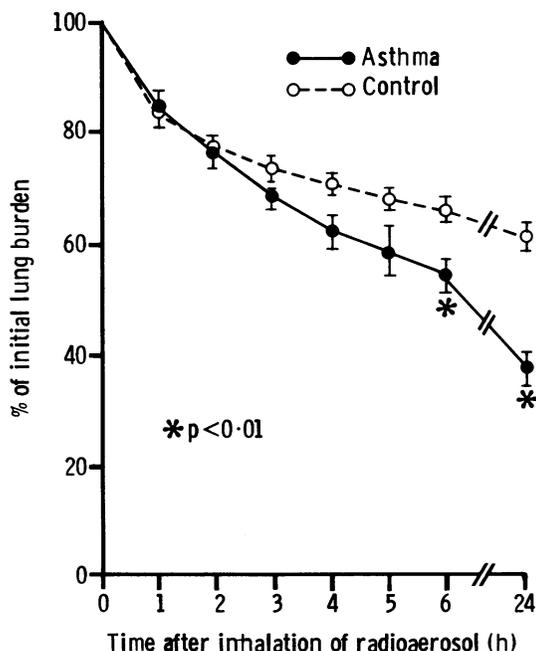


Fig 1 Whole-lung retention curves for 25 patients with stable, mild asthma and 25 healthy control subjects (values are means  $\pm$  SEM).

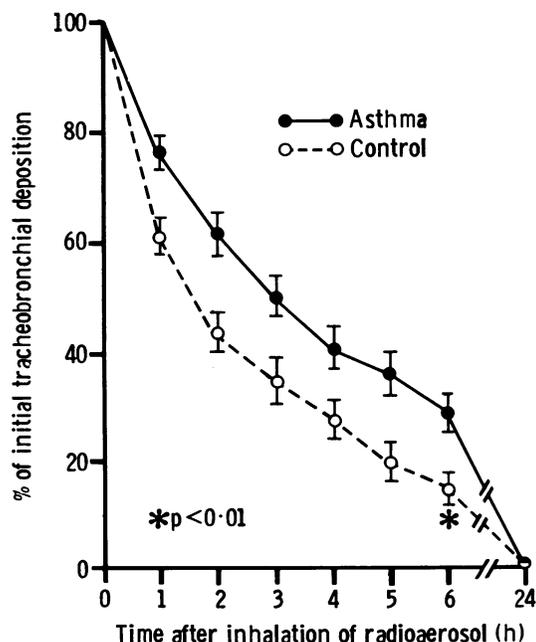


Fig 2 Tracheobronchial retention curves for 25 patients with stable, mild asthma and 25 healthy control subjects (values are means  $\pm$  SEM).

jects was significantly less than in the asthmatic group, reflecting impaired clearance of mucus from the airways in the asthmatic group.

COUGH AND EXPECTORATION

The healthy subjects seldom coughed and produced no sputum. Coughing was more frequent in the asthmatic group and a small number of patients expectorated. Neither cough nor expectoration could be shown to have a significant effect on mucociliary clearance.

Discussion

Both Hilding in 1943<sup>3</sup> and Dunnill in 1960<sup>2</sup> suggested that one major factor in the pathogenesis of asthma was a failure in mucociliary function. Only a few studies have examined mucociliary transport mechanisms in bronchial asthma. Santa Cruz *et al*<sup>4</sup> in 1974 found appreciable slowing of tracheal mucus velocity in three elderly patients with stable asthma. Age, however, adversely affects mucociliary clearance<sup>21</sup> and tracheal mucus velocity does not necessarily parallel mucus clearance in the smaller peripheral airways. Mossberg *et al*<sup>5</sup> in 1976 found that tracheobronchial clearance of rapidly inhaled 8- $\mu$ m <sup>99m</sup>Tc-labelled Teflon particles in 12 patients was the same as that in healthy non-smokers. In 1978 Foster *et al*<sup>6</sup> noted considerable reductions in both mucus clearance and tracheal mucus velocity in asthmatic patients with symptoms. Finally, Mezey *et al*<sup>7</sup> in 1978 and Ahmed *et al*<sup>8</sup> in 1981 studied small numbers of patients with a history of bronchial asthma and ragweed hypersensitivity. At the time of study all were symptom free, but tracheal mucus velocity was found to be impaired.

All these reports are on small numbers of patients and mucociliary function has been assessed in central rather than peripheral airways. Furthermore, no account has been taken of the initial particle distribution within the lungs. The last two reports were on a special subgroup of asthmatic patients with a specific allergy to ragweed and may not apply to asthma in general.

We have measured tracheobronchial clearance in both large and small airways in 25 patients with mild, stable asthma. The patients were relatively young (age range 17-61 years) and were a mixture of extrinsic and intrinsic asthmatics. All medication had been withdrawn at least 12 hours before the study and the effect of initial particle distribution on clearance was taken into account. Despite the shorter transit path because of airway obstruction we found that tracheobronchial mucociliary clearance was significantly worse in patients with asthma than in healthy subjects. This direct evidence of mucocili-

ary dysfunction in asthma supports the hypothesis of Hilding<sup>3</sup> and Dunnill.<sup>2</sup> Our data are in agreement with all previous reports except for that of Mossberg *et al.*<sup>5</sup> Their failure to report a significant retardation of mucociliary clearance from proximal ciliated airways in patients with asthma may reflect either a carry-over stimulatory effect of the concomitant medication or the possibility that the radioaerosol deposition was more central in their patients than their healthy subjects, or both.

The reasons for the observed mucociliary dysfunction are unclear and several mechanisms are likely to be responsible. Dulfano *et al* found that sputum taken from asthmatic patients during exacerbations contains a factor inhibiting ciliary beat.<sup>9</sup> On recovery and when the asthma is stable, however, this factor lessens or disappears. Ahmed *et al* have shown that impaired tracheal mucus velocity in antigen-induced bronchoconstriction was the net result of chemical mediators released during the allergic reaction.<sup>8</sup> Slow-reacting substance of anaphylaxis appears to be a potent inhibitor of mucus clearance whereas other mediators, such as histamine and acetylcholine,<sup>22</sup> enhance clearance. Further evidence for antigen-mediated mucociliary dysfunction was given in a preliminary report by Maurer *et al.*<sup>23</sup> These workers found that ciliary beat frequency was reduced in sheep trachea after antigen exposure. In a recent study, however, the same group reported that a reduction in sheep tracheal mucus velocity after antigen challenge was accompanied by a slightly increased ciliary beat frequency.<sup>24</sup> Efficient mucociliary transport depends on optimal elasticity and to a lesser extent viscosity of the mucus. Bronchial secretions are often tenacious and, while not qualitatively abnormal, have a high albumin, lipid, and mucus glycoprotein content.<sup>25</sup> The mucus glycoprotein is present only in gel form and the lipids are strongly bound to the glycoprotein. These biochemical features may be responsible for the tenacious nature of the bronchial secretions in asthma<sup>26,27</sup> and resultant changes in elasticity and viscosity may lead to ineffective ciliary action.

Cough is said to act as a back-up mechanism for mucociliary clearance and is very effective in clearing secretions from large airways. Its role in mucus clearance in small airways is ill defined,<sup>28</sup> but in the present study no significant effect was detected.

Our observations in asthmatics have confirmed mucociliary dysfunction both in large airways and in airways more distal to the trachea than hitherto reported. We believe that these findings give further support to the hypothesis that failure of this clearance mechanism may contribute to mucus plugging of airways that cannot otherwise be cleared by the alternative mechanism of cough. Further studies are

required to determine the precise underlying mechanisms for this failure in mucociliary function.

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