

Impaired tracheobronchial clearance in bronchiectasis

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ABSTRACT Tracheobronchial clearance was measured by a radioaerosol technique in 12 patients with bronchiectasis, seven patients with chronic obstructive lung disease expectorating mucoid sputum daily (group X), eight patients with chronic obstructive lung disease but negligible sputum expectoration (group Y), and 10 healthy subjects. The patients with bronchiectasis all expectorated purulent sputum daily (mean wet weight 47 g/day), had reduced forced expiratory volume in one second (FEV₁) (mean 47.5% predicted), and were unable to avoid coughing during the six hour observation period. None of the patients with bronchiectasis or the healthy subjects were current smokers. There were five current smokers in group X and six in group Y. The mean FEV₁ in group X was 41% predicted and in group Y 52% predicted, both values similar to that of the patients with bronchiectasis.

Tracheobronchial clearance in the first six hours after inhalation of radioaerosol was significantly ($p < 0.01$) slower in patients with bronchiectasis than in matched healthy subjects despite more proximal deposition of radioaerosol ($p = 0.01$) and more coughing ($p < 0.01$) in the former. Tracheobronchial clearance in patients with bronchiectasis was impaired to a similar degree to that in patients with chronic obstructive lung disease but no bronchiectasis.

Clearance of microbes and host derived inflammatory products from the lungs of patients with bronchiectasis is important if the vicious circle of microbial colonisation and host response that may lead to progression of lung damage is to be avoided.¹

Only one previous study² has reported impaired lung mucociliary clearance in patients with bronchiectasis (these did not have clinical Kartagener's syndrome but were not tested for a primary ciliary dyskinesia). The clearance rates of inhaled particles in that study were similar to those in patients with chronic bronchitis. Clearance was impaired in six of the patients with bronchiectasis and mild airways obstruction (mean FEV₁ 70% predicted) by comparison with that in normal subjects but, surprisingly, in the other eight patients with bronchiectasis, who had more severe symptoms and greater airways obstruction (mean FEV₁ 50% predicted), it was not shown to be significantly impaired.

Because of this discrepancy we measured the lung deposition and clearance on inhaled radioaerosol in a

group of 12 patients with bronchiectasis and considerable airways obstruction and compared these with the deposition and clearance in patients with chronic obstructive lung disease but no bronchiectasis and in healthy subjects.

Methods

PATIENTS

Three groups of patients and one control group were studied.

Group B—Twelve patients (seven of them men) with radiologically definite bronchiectasis who were expectorating purulent sputum daily. Seven were ex-smokers and had not smoked for 8–25 years and five were lifelong non-smokers.

Group X—Seven men with chronic obstructive lung disease with no evidence of bronchiectasis on plain chest radiographs who were expectorating mucoid sputum daily. Five were smokers and two were ex-smokers.

Group Y—Eight patients (six of them men) with chronic obstructive lung disease but negligible sputum expectoration, with no evidence of bronchiectasis on plain chest radiographs. Six were smokers and two ex-smokers.

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Table 1 Characteristics of patients and controls (means for whole groups with standard errors in parentheses)

Group	Age (yr)	Weight (kg)	Height (m)	Tobacco consumption (pack y)	24 h sputum (g)	FEV ₁ (% predicted)	Inspiratory flow rate (l min ⁻¹)
B (Bronchiectasis—n = 12)	55 (3)	70 (4)	1.69 (0.03)	14 (5)	47 (11)	47 (7)	42 (3)
X (COLD with sputum—n = 7)	62 (2)	72 (2)	1.67 (0.03)	61 (14)*†	28§	41 (8)†	40 (3)
Y (COLD without sputum—n = 8)	67 (3)*†	66 (3)‡	1.74 (0.04)	56 (13)*†	0.25	52 (8)†	35 (2)
Controls (n = 10)	51 (5)	74 (4)	1.68 (0.03)	1	0	113 (6)*	40 (5)

*p < 0.01: significant difference from group B.

†p < 0.01, ‡p < 0.05: significant differences from controls.

§Measured in only four patients.

COLD—chronic obstructive lung disease.

Control group—Ten healthy subjects (five of them men) matched with group B for age, sex, height, weight, and inspiratory flow rate of radioaerosol. Two were ex-smokers and eight were lifelong non-smokers.

The characteristics of each group are shown in table 1.

The patients in group B had moderately severe bronchiectasis as judged by the extent of their disease on computed tomography scans³ (median 3 lobes), 24 hour sputum production (range 20–120 g) and reduced FEV₁ (range 17–91% predicted).⁴ The median duration of daily sputum production was 45 years (range 10–>60). *Haemophilus influenzae* was isolated from the sputum in 11 of the patients, *Pseudomonas aeruginosa* in three patients, and *Staphylococcus aureus* in one patient. One patient had associated rheumatoid arthritis, two had azoospermia and 10 reported nasal symptoms. Nasal mucociliary clearance by the saccharin method⁵ was longer than 60 minutes in three patients and a mean of 28 minutes in the remainder. The three patients with prolonged clearance all had normal ciliary beat frequencies.

TECHNIQUE

A non-invasive radioaerosol technique was used to measure tracheobronchial clearance.⁶ The subjects inhaled polystyrene particles of 5 µm diameter, labelled firmly with technetium-99m (^{99m}Tc), according to a standard protocol.⁷ The radioaerosol initially deposited in the lungs was measured and its subsequent clearance was monitored by two scintillation counters located opposite each other anterior and posterior to the chest. All radiation counts were corrected for background radiation and physical decay of the radionuclide. A final count was carried out at 48 hours in 10 of the 12 patients with bronchiectasis and at 24 hours in the remaining subjects. The amount of alveolar deposition was defined as the amount of radioactivity remaining at the time of the last count (24 or 48 hours). These particles were

assumed to be unavailable for tracheobronchial clearance, and were subtracted from the total lung burden to yield the total amount of radioaerosol available for tracheobronchial clearance. All counts were expressed as percentages of the initial count to overcome unavoidable differences between subjects in the initial total lung burden of radioaerosol. The remaining amount of radioaerosol available for tracheobronchial clearance was measured at regular intervals for the first six hours. The reading at six hours (TBC₆) was used as a measure of this clearance. These data were also displayed graphically and a second measure of total clearance of radioaerosol was obtained by calculating the area under the curve (AUC), with the use of the trapezoidal rule, for the six hours. The lower the value of TBC₆ or AUC the greater the tracheobronchial clearance (for example, with no clearance TBC₆ = 100, AUC = 600).

Informed written consent was obtained from all the subjects before the test. They were asked to omit all theophylline preparations and oral β₂ agonists for the 12 hours before the test. The initial lung burden per study amounted to about 30 µCi (1.1 MBq) of ^{99m}Tc, resulting in an absorbed radiation dose to the lungs of the order of 12 mrem (0.12 mSv). The mean inspiratory flow rate for each group of patients was similar (table 1).

The number of coughs, wet weight of sputum expectorated, and amount of radioaerosol in the expectorated sputum during the six hour test period were measured. The amount of radioaerosol in the sputum was expressed as a percentage of the initial radioaerosol available for tracheobronchial clearance. The data were not normally distributed and statistical significance was assessed by the non-parametric Wilcoxon rank sum test for unpaired data.⁸

Results

The results for the three groups of patients and the

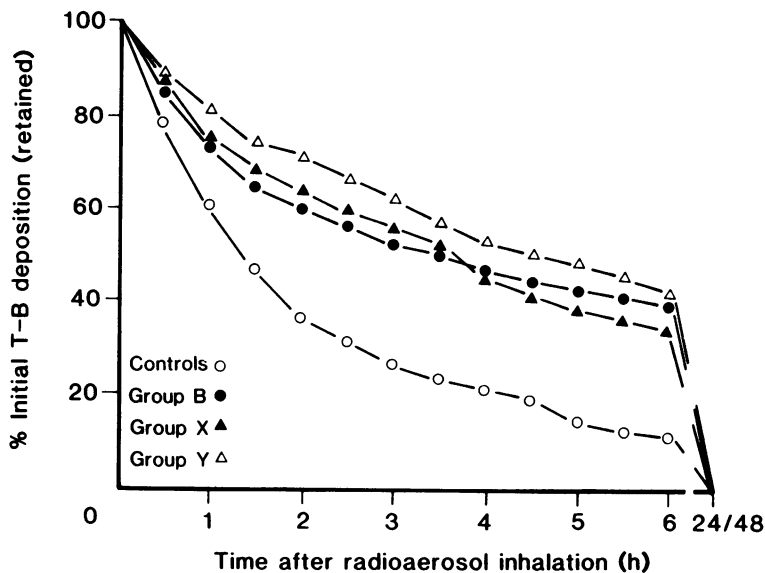
Table 2 Results (means with standard errors in parentheses)

Group	AD (%)	TBC ₆ (%)	AUC (% h)	Cough (No)	Sputum (g)	Sputum (% radioaerosol)
B (Bronchiectasis)	24 (5)	39 (6)	333 (36)	36 (10)	16 (4)	33 (7)
X (COLD with sputum)	32 (5)§	34 (5)†	343 (24)†	30 (9)†	5 (2)†	19 (8)†
Y (COLD without sputum)	30 (6)§	42 (4)†	383 (13)†	5 (1)*	0*	0*
Controls	44 (4)†	11 (2)*	210 (20)†	0*	0*	0*

AD—alveolar deposition as percentage of total lung burden; COLD—chronic obstructive lung disease; TBC₆—percentage of initial radioaerosol available for tracheobronchial clearance (TBC) remaining at six hours. During the six hour observation period: AUC—area under TBC curve; Cough—number of coughs; Sputum—grams of sputum. Sputum: % radioaerosol—percentage of the initial radioaerosol available for TBC expectorated in sputum.

* $p < 0.01$, † $p = 0.01$: significant differences from group B.

‡ $p < 0.01$, § $p < 0.05$: significant differences from controls.



Mean tracheobronchial clearance curves for 12 patients with bronchiectasis (group B), seven patients with chronic obstructive lung disease and daily sputum (group X), eight patients with chronic obstructive lung disease alone (group Y), and 10 healthy control subjects. Clearance is expressed as retained radioactivity relative to initial tracheobronchial (T-B) deposition.

control group are shown in table 2 and the figure. TBC₆ was significantly greater in the group with bronchiectasis (B) and the groups with chronic obstructive lung disease with (X) and without sputum (Y) than in the control group. The mean tracheobronchial clearance curve of group B was similar to that of the groups with chronic obstructive lung disease with (X) and without (Y) sputum. Of the particles cleared by 6 hours in group B, just over half (0.54) were expectorated; the remainder were presumably swallowed.

In the bronchiectasis group (B) and group Y (chronic obstructive lung disease with mucoid sputum) there were significant correlations between tracheobronchial clearance and the amount of radioaerosol in the expectorated sputum during the six hours after inhalation (TBC₆ versus sputum % radioaerosol: group B, $r = -0.8$, $p < 0.001$; group

X, $r = -0.9$, $p < 0.001$) and negative correlations between clearance and age in group B (TBC₆ versus age: $r = 0.6$, $p < 0.02$) and FEV₁ in group X (TBC₆ versus FEV₁: $r = 0.7$, $p < 0.05$). No other significant correlations were found in any of the three groups (B, X, and Y) between TBC₆ and alveolar deposition, inspiratory flow rate, FEV₁, number of coughs during the six hours of the test, age, height, weight, or tobacco consumption. Furthermore, in group B there was no correlation between TBC₆ and indicators of severity of bronchiectasis (24 hour sputum wet weight and computed tomographic extent of disease) or duration of disease (years of daily sputum production).

Discussion

This study confirms Lourenço's finding of central

deposition of inhaled radioaerosol in patients with bronchiectasis.² The deposition of inhaled radioaerosol in man depends on: (a) the physical properties of the aerosol; (b) the mode of inhalation; and (c) the patency of the airways.⁹ The first two factors were rigorously controlled, so we may reasonably assume that the reduced alveolar deposition of radioaerosol in the patients with bronchiectasis is due to differences in the airway patency. The patients with bronchiectasis had extensive disease, copious sputum, and severe impairment of FEV₁, all of which could alter or reflect changes in airway patency and thus airflow dynamics. Previous studies have shown that an increase in airway obstruction will tend to produce enhanced deposition in central airways owing to impaction.¹⁰⁻¹³ The influences of extensive bronchiectasis and copious secretions on deposition are unknown. In view of the fact that appreciable tracheobronchial clearance may occur in the second 24 hours after inhalation of radioaerosol in patients with airflow obstruction¹⁴ (whereas tracheobronchial clearance is essentially complete by 24 hours in normal subjects¹⁵) the amount of alveolar deposition in the patients with bronchiectasis was measured at 48 hours.

The mean tracheobronchial clearance of patients with bronchiectasis (group B) was significantly less than in healthy controls despite more central aerosol deposition and the resulting shorter distance along the conducting airways for the particles to be cleared. Clearance was reduced to a similar degree in the two groups of patients with chronic obstructive lung disease with and without daily sputum. Mucociliary clearance equals tracheobronchial clearance in the healthy controls, because they did not cough during the test. Therefore the impaired mean tracheobronchial clearance for each group of patients indicates that the mucociliary clearance is also impaired. The three groups of patients had broadly similar physical characteristics and reduction in FEV₁. Individual values of FEV₁ in the patients in groups B and Y did not correlate with individual values for TBC₆, which argues against airways obstruction directly reducing tracheobronchial clearance. In fact, in group X individuals with better FEV₁ tended to have worse tracheobronchial clearance. The pathology of the bronchial tree and lung parenchyma in bronchiectasis and chronic bronchitis is probably an important factor in reducing tracheobronchial clearance. Cigarette smoking in the patients with chronic obstructive lung disease is unlikely to be exerting a direct effect on clearance. In a study¹⁶ of patients with chronic obstructive bronchitis, mean tracheobronchial clearance curves of 18 current smokers was found to be similar to that of 18 ex-smokers who had not smoked for more than one year but who otherwise had similar

characteristics.

The patients with bronchiectasis (group B) and those with chronic obstructive lung disease and regular sputum production (group X) were unable to avoid coughing during the test. Unfortunately the amount of radioaerosol expectorated in the sputum is simply a measure of the amount of airway mucus not swallowed and does not equal the proportion of the tracheobronchial clearance which is effected by coughing. Therefore the precise proportion of tracheobronchial clearance attributable to each of the two components of clearance—mucociliary clearance and cough—is unknown in these two groups (B and X), but, given that some of their tracheobronchial clearance is due to coughing, these two groups must have worse mucociliary clearance than the group of patients with chronic obstructive lung disease and negligible sputum (group Y).

The fact that patients with bronchiectasis have greater impairment of mucociliary clearance than older patients with chronic obstructive lung disease without sputum is probably due to differences in the type and pattern of bronchial damage and in the characteristics of the secretions—in particular the presence of irreversible bronchial dilatation and continuous purulent sputum production in our patients with bronchiectasis. Both anatomical disorganisation and possible damage to bronchial ciliated epithelium may impair clearance in patients with bronchiectasis. In patients with primary ciliary dyskinesia, no appreciable mucociliary clearance has been detected,^{17,18} and mucociliary clearance is impaired in Polynesian patients with bronchiectasis associated with apparent ciliary abnormalities.¹⁹ Pathological changes in the bronchi of non-bronchiectatic segments of the patients with bronchiectasis may also appreciably alter the clearance of radioaerosol. The regional clearance in these patients is being assessed. The purulent sputum produced by the patients with bronchiectasis contained copious white blood cells, bacteria, and their products (including elastase). Such secretions have been shown to impair normal human ciliary function *in vitro*.²⁰ Neutrophil elastase²¹ and bacterial products²² damage human ciliated epithelium and reduce ciliary beat frequency *in vitro*. Furthermore, nasal cilia bathed in purulent secretions *in vivo* from patients with sinusitis beat more slowly *in vitro* than those obtained from healthy subjects.²³ In contrast, the patients with chronic bronchitis had less bronchial damage and mucoid sputum.

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