Imaging of the airways by bronchoscintigraphy for the study of mucociliary clearance

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ABSTRACT A method for functional imaging of the large airways (bronchoscintigraphy) has been developed. It is based on the administration of aerosolised albumin labelled with technetium-99m using a special inhalation technique to produce central airway deposition. The method was evaluated as a measure of mucociliary clearance by recording the movement of radioactivity in the airways of 11 healthy, non-smoking subjects on two separate days. A series of bronchoscintigrams was acquired at five minute intervals for two hours after termination of the inhalation. After the first bronchoscintigram 1.25 mg terbutaline or placebo was administered from a metered dose inhaler (five puffs) according to a randomised, double blind, crossover design. The scintigrams were evaluated blind. After terbutaline the segmental bronchi were no longer visible after a median time of 10 minutes, the lobar bronchi after 20 minutes and the main bronchi after 30 minutes. In six cases the trachea was cleared after two hours. After placebo the segmental bronchi disappeared after a median of 15 minutes, but at two hours half the lobar bronchi remained visible. In only two cases was it no longer possible to see the main bronchi or the trachea. It is concluded that bronchoscintigraphy can be used to examine regional mucociliary clearance in healthy subjects and that terbutaline significantly increases the clearance of the deposited radioactive aerosol.

Mucociliary clearance, one of the most important defence mechanisms of the airways, is usually measured by non-invasive external detection of the clearance rate of an inhaled radioaerosol.¹ For this measurement it is often recommended that the individual inhales the radioaerosol by tidal volume breathing so that lung deposition is diffuse rather than selectively reaching the large airways. Hence mucociliary clearance is usually calculated for the whole lung or for arbitrarily determined lung regions. As mucociliary clearance occurs in bronchi and bronchioles the possibility of making such measurements in selected morphologically defined airways is desirable.

The aim of this study was to determine whether a special inhalation technique consisting of slow inspirations and forced expirations, performed as close to

residual volume as possible, might cause a selective deposition of a radioaerosol on the airways, thus providing a morphological scintigraphic image and measurement of mucociliary clearance. Evaluation of the validity of this inhalation technique was combined with a study to determine whether terbutaline has an acute effect on mucociliary clearance in healthy non-smoking subjects. The change in radioactivity with time was taken as a measure of mucociliary clearance and was monitored by repeated scintigraphic acquisitions over two hours.

Methods

SUBJECTS

Eleven healthy subjects who had never smoked participated in the study, which was approved by the local ethical committee. Their median age was 21 (range 18-42) years. All subjects had a normal forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC), the median FEV₁ being 94% (range 82-108%) predicted and the median FVC 101% (range 87-128%) predicted.²

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BRONCHOSCINTIGRAPHY AND MUCOCILIARY CLEARANCE

Radionuclide Sodium pertechnetate ($^{99m}\text{TcO}_4$) was eluted in isotonic saline from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator. The pertechnetate was tagged to human albumin (Venticoll, Solco) by injecting 350–700 MBq of the pertechnetate into a phial containing albumin. Isotonic saline was added to make the volume up to 5 ml.

Aerosol generation, administration, and inhalation technique The aerosol was generated in an ultrasonic nebuliser (DeVilbiss 35B) containing the 5 ml ^{99m}Tc albumin. The aerosol was inhaled directly from the nebuliser via a tube 10 cm long with a T valve at the mouth. The T valve ensured that expired aerosol was trapped. The median mass particle diameter was 5 (range 1–7) μm . The subject inhaled while sitting and wearing a nose clip, with the nebuliser in series with a spirometer to allow inspiratory volume and flow rate to be monitored. Subjects were instructed to inspire slowly (inspiratory flow rate ≤ 30 l/min) from residual volume until 600 ml had been inspired and to follow this with a maximal forced expiration to residual volume. Subjects made a total of 10–20 inhalations using this pattern of ventilation. This usually resulted in a count rate of around 2000 counts/second on the gamma camera.

Data acquisition Immediately after inhaling the aerosol subjects were placed in the supine posture with their backs against a gamma camera (Maxi Camera, General Electric) with a large field of view size crystal and a parallel hole 140 KeV collimator. Initial scintigrams were made from the static acquisition of a 200 000 count image. The acquisition was repeated every five minutes until 120 minutes after the inhalation to follow mucociliary clearance of the ^{99m}Tc albumin. Each image was made at the same intensity as the initial one and, apart from being corrected for the physical decay of ^{99m}Tc , the acquisition time also remained unchanged. The acquired number of counts was disregarded. In this way it was intended that change in scintigrams contained biological information only. The background radioactivity of the room (5–16 counts/s) was negligible by comparison with the subject's radioactivity.

EFFECT OF TERBUTALINE ON MUCOCILIARY CLEARANCE

On two separate days at least one week apart five puffs of terbutaline (1.25 mg) or placebo were administered by inhalation from a conventional metered dose inhaler. The drugs were administered immediately after the first gamma camera acquisition, five minutes after the end of the inhalation of the ^{99m}Tc albumin. Inhalation of terbutaline and placebo was performed

Fig 1 An example of the morphological information that may be obtained by bronchoscintigraphic imaging.

as recommended by Newman,³ according to a double blind crossover design.

DATA ANALYSIS

The number of bronchi that could be identified on the bronchoscintigrams was counted and the time after inhalation when they could no longer be seen was noted. The effect of terbutaline and placebo on mucociliary clearance was compared by the sign test. The scintigrams were evaluated independently by two specialists who were unaware of whether placebo or terbutaline had been given.

Results

An example of the morphological information obtained by the bronchoscintigraphic imaging technique is shown in figure 1. Individual bronchi are easily identified; peripheral to the segmental bronchi the structures merge with the background. In most cases a substantial part of the radioactivity was deposited in the mouth. Most of the radioactivity in the stomach comes from the aerosol originally

Table 1 Last time (min, ≤ 120 min) at which it was possible to identify the anatomical structures on the bronchoscintigrams after administration of placebo (P) or terbutaline (T)

Subject No	Trachea		Main bronchi				Lobar bronchi	
			Left		Right		Left superior	
	P	T	P	T	P	T	P	T
1	120	120	120	40	120	40	80	30
2	120	120	120	25	120	25	120	20
3	120	55	120	25	120	25	10	5
4	120	120	120	25	120	20	90	15
5	120	120	120	40	120	30	45	25
6	120	80	120	40	120	30	120	25
7	120	70	120	40	120	30	45	20
8	80	45	70	30	80	30	120	25
9	120	120	120	40	120	20	120	35
10	120	80	120	55	120	50	120	40
11	90	70	120	35	75	20	40	20
Median	120	80	120	40	120	30	90	25
Range	80–120	45–120	70–120	25–55	75–120	20–50	10–120	5–40

*Number of identified segmental bronchi.

†Not visible.

deposited in the mouth. The oesophagus is seen faintly.

As a result of mucociliary clearance there was a gradual decrease in radioactivity to background levels, and the morphological structures became increasingly indistinct. This effect spread from the smallest visible airways (segmental bronchi) to the larger airways (lobar and main bronchi), as table 1 shows. This does not necessarily imply a greater mucociliary clearance in peripheral airways, because when central airways are considered separately there is a fairly constant decrease in radioactivity, despite the continuous admixture of radioactivity from the periphery.

The stimulatory effect of terbutaline on mucociliary clearance was evident for all visible airways and in all 11 cases the day with the faster clearance as identified by the readers, was the day when terbutaline had been given ($p < 0.01$). After terbutaline almost all the main and lobar bronchi were cleared to scintigraphic invisibility at a rate three times greater than on the placebo day ($p < 0.01$). Table 1 presents average values for the last points (≤ 120 min) given by the two readers at which it was still possible to identify the anatomical structures on the bronchoscintigrams after placebo and after terbutaline.

A typical example of the series of bronchoscintigrams is shown in figure 2. The uppermost scintigrams on both panels show the initial distribution of radioactivity in the lung immediately after inhalation. The images were similar on the two days, the major part of the retained activity being deposited in the large airways. Mucociliary clearance was considerably greater after terbutaline than after placebo.

None of the subjects coughed during the examinations, so no correction for coughing as an independent clearance mechanism was required.

Fig 2 An example of the effect of placebo (left) and terbutaline (right) on mucociliary clearance as seen from series of bronchoscintigrams.

Lobar bronchi (continued)

Left inferior		Right superior		Lingula		Right inferior		Segmental bronchi	
P	T	P	T	P	T	P	T	P	T
120	30	120	30	15	10	120	30	90 (10*)	20 (10*)
120	20	120	25	120	†	120	20	30 (3*)	†
20	10	30	10	†	5	45	15	10 (4*)	5 (4*)
15	15	10	15	40	15	120	20	5 (2*)	5 (2*)
120	15	70	10	120	5	120	15	15 (7*)	5 (5*)
120	25	70	15	10	5	85	30	10 (6*)	10 (7*)
120	20	70	20	35	25	120	25	15 (7*)	15 (7*)
120	25	80	20	85	20	120	25	35 (9*)	10 (11*)
120	15	35	15	35	10	80	25	35 (7*)	10 (7*)
120	35	120	35	25	†	120	40	15 (5*)	20 (9*)
120	20	120	35	85	35	120	35	10 (9*)	10 (10*)
120	20	70	20	37.5	10	120	25	15 (7*)	10 (7*)
15-120	10-35	10-120	10-35	10-120	5-35	45-120	15-40	5-90 (2-10*)	5-20 (0-10*)

Discussion

The results of this study show that inhalation of a radioaerosol by a slow small inspiration followed by a forced expiration made as close as possible to residual volume provides selective deposition of the aerosol in the airways, allowing scintigraphic imaging and measurement of mucociliary clearance.

The choice of pattern of inhalation is based on the behaviour of aerosol particles in tubing systems.^{4,5} If a subject inspires an aerosol at a low flow rate, a substantial part of it should be carried by the predominant laminar airflow into the lungs without premature deposition in the mouth or pharynx. If at the same time expiration is forced, the aerosol would tend to be retained in the airways by impaction due to

the effect of turbulence. If the inhalation is as close to residual volume as possible alveolar deposition should be reduced, as a consequence of the relative increase in deadspace ventilation. In addition, the deposition of aerosol in the airways should be enhanced, since the probability that the aerosol particles will strike the small airways should increase, when the small airways close.

Since 1955⁶ several methods have been introduced for the measurement of mucociliary clearance. None of the methods, however, has been widely accepted for routine clinical use. The radioactivity retained in the non-ciliated airways behaves as background noise and may interfere with the measurements of mucociliary clearance. A few studies have tried to solve this problem, usually by obtaining a selective deposition of

Table 2 Results of previous studies on the effect of β_2 agonists on mucociliary clearance (MC) in healthy individuals

Authors	Year	No of individuals	β_2 agonist	Dose and route		Study design	Effect on clearance
Konietzko <i>et al</i> ¹¹	1975	11	Terbutaline	Oral	5 mg	DB o	+ LMC
Camner <i>et al</i> ¹²	1976	8	Terbutaline	Sc	0.25 mg	DB o	+ LMC
Foster <i>et al</i> ¹³	1976	10	Isoprenaline	Inh	0.005 M	p	+ LMC
		3	Adrenaline	Inh	0.01 M	—	+ LMC
		4	Isoprenaline	Subl	10 mg	—	(+) LMC
Yeates <i>et al</i> ⁷	1976	8	Fenoterol	Inh	0.4-0.8 mg	p	+ TMC
Foster <i>et al</i> ¹⁴	1980	7	Isoprenaline	Inh	2.5 mg	p	+ LMC
			Isoetharine	Inh	2.5 mg	—	+ LMC
Yeates <i>et al</i> ¹⁵	1981	12	Orciprenaline	Oral	20 mg	p	+ TMC
						—	— LMC
Foster <i>et al</i> ¹⁶	1981	5	Isoetharine	Inh	0.005 M	p	+ LMC
			Isoprenaline	Inh	0.005 M	—	+ LMC
LaFortuna <i>et al</i> ¹⁷	1984	3	Salbutamol	Inh	0.5 mg	DB	+ LMC
		3	Placebo				—
Foster <i>et al</i> ¹⁸	1985	5	Isoetharine	Inh	2.5 mg	p	+ LMC
Yeates <i>et al</i> ¹⁹	1986	12	Orciprenaline	Oral	20 mg	p	+ TMC
						—	— BMC

Sc, subcutaneous; inh, inhalation; subl, sublingual; DB, double blind; o, crossover; p, placebo control; +, significant increase; (+), non-significant increase; —, no increase; LMC, lung mucociliary clearance; TMC, tracheal mucociliary clearance or velocity; BMC, bronchial mucociliary clearance.

the radioactivity in the airways with guided ventilation.¹⁷ Normally monodisperse particles of 5 μm or more are used. Because of their uniform size they often ensure a reproducible deposition. The resulting scintigrams do not, however, allow identification of even the large bronchi. No matter how large the particles, when tidal volume breathing is used much of the radioactivity will be deposited in airways with diameters smaller than the resolution power of the gamma camera. This results in a blurring of details of the image. Conventional techniques are not normally required to identify larger bronchi, and when precise measurements of background activity are achieved alveolar deposition may be useful as an index of the initial topographic distribution of radioactivity in the lungs. It may reflect patency of the airways when the mode of inhalation has been kept constant. When particles are under 5 μm tidal volume breathing causes an initial background count rate that may constitute as much as 40–60% of the total initial count rate.^{3,4,8} With particles of 5 μm or more the background count rate may be reduced.^{9,10}

The main purpose of our study was to determine whether the pattern of ventilation we chose could provide scintigraphic visualisation of the bronchial tree. The reason why the trachea was not always seen on the initial picture is probably that the forced expirations were initiated at lung volumes as little as 500–600 ml above residual volume (fig 2). If expiration had been initiated at TLC, the maximal flow would have been far greater than at low lung volumes, when it was presumably too low to cause effective impaction of the aerosol in the trachea. A deeper inspiration might have reduced bronchial deposition owing to a decrease in the relative deadspace ventilation. As the mucociliary beating gradually moved the radioactivity towards the mouth, radioactivity accumulated in the trachea (fig 2). It was not our aim, however, to determine the importance of the individual components of our ventilation technique for aerosol deposition. Perhaps the information obtained from the scintigrams could be increased by identifying and subsequently enhancing the effect of the most important components of the ventilation manoeuvre.¹⁴

In this study data were analysed by a blinded semiquantitative approach. If this method of analysis is applied in clinical trials with paired data, it will be sufficiently sensitive to identify significant changes in mucociliary clearance when the signals are as strong as those produced by terbutaline on mucociliary clearance in this study. The information will be strengthened if the quality of the imaging can be improved and if a kinetic model of absolute and regional mucociliary clearance is created.

In normal subjects some previous studies have found an effect of subcutaneous or oral terbutaline on

mucociliary clearance and others have found no effect^{7,11–19} (table 2). Six previous trials, all using an open design, have looked at the effect of inhaled β_2 agonists on mucociliary clearance in normal subjects.^{7,13,14,16–18} Yeates *et al*⁷ found an increase in tracheal mucociliary clearance in eight subjects after inhalation of fenoterol. Foster *et al*^{13,14,16,18} found an increase in mucociliary clearance after inhalation of a single dose of various β_2 agonists in 30 subjects and Lafortuna *et al*¹⁷ found similar changes after salbutamol when three subjects were compared with three others who did not receive salbutamol. Our study is the first controlled study to show unambiguously a stimulatory effect of an inhaled β_2 agonist on mucociliary clearance in normal subjects.

In view of the striking effect of terbutaline on mucociliary clearance in healthy non-smokers it is surprising that the results of previous trials on the effect of terbutaline on mucociliary clearance in chronic obstructive lung disease are so conflicting. In patients with chronic bronchitis some authors have found an increase in mucociliary clearance after β_2 agonists,^{11,17,20–22} but others have not.^{23–25} In asthmatic patients^{8,26–30} an increase in mucociliary clearance has been found in three of six trials.^{28–30} There is therefore no well established consensus that β_2 agonists increase mucociliary clearance in pulmonary disease.

In most normal individuals and patients maximal or near maximal bronchodilatation can be achieved with 0.5 mg terbutaline from a metered dose inhaler. In this study we used a higher dose of terbutaline (1.25 mg); so it remains to be established whether similar effects on mucociliary clearance would be produced by doses of terbutaline used in clinical practice.

Because of the conflicting and often negative results of previous investigations on the effect of β_2 agonists in patients with chronic bronchitis and asthma, it would be too early to extrapolate our results to such patients. Further investigations must determine whether our method for semimorphological imaging of bronchi will provide similar convincing information about regional mucociliary clearance in patients with obstructive lung disease.

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