Comparison of nasal and tracheobronchial clearance by similar techniques in normal subjects

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ABSTRACT Nasal and tracheobronchial mucociliary clearance have been compared in 10 healthy subjects. Nasal clearance was measured by monitoring the rate of removal of 2 μm diameter Teflon particles, labelled with ^{99m}Tc, which had been placed in the anterior part of the nose. Tracheobronchial clearance was measured with an objective radioaerosol technique, 5 μm diameter polystyrene particles being used. With these comparable techniques there was a close correlation between the nasal mucociliary clearance rate and both the area under the tracheobronchial clearance curve from 0 to 6 hours after radioaerosol inhalation ($r_s = -0.94$, $p < 0.001$) and the area under the tracheobronchial clearance curve from 0 to 2.5 hours after inhalation ($r_s = -0.79$, $p < 0.01$). The rate of clearance of small particles from the nose may thus be a useful guide to tracheobronchial clearance in healthy individuals.

Nasal mucociliary clearance has an important role as a defence mechanism for the upper airway.[1-3] The nose is an easily accessible organ and so in many centres the measurement of nasal mucociliary clearance has been used as a screening procedure for congenital abnormalities that would alter mucociliary clearance in the nose and lungs. The relationship between nasal and tracheobronchial clearance is not, however, clear. Previous studies[4 5] comparing the two have reported diverse results. This may be due to the different techniques used. In the present study we have used broadly similar techniques for the two measurements and so consider that we can determine the interrelationship between nasal and tracheobronchial clearance in normal subjects.

Methods

TECHNIQUE
Nasal clearance was measured with radiolabelled particles in a technique modified from that of Black *et al.*[6] Teflon particles (physical diameter 2 μm, aerodynamic diameter 3.2 μm) labelled with the radionuclide technetium 99m (^{99m}Tc) were produced by a spinning top generator,[7] and were collected and then washed twice in 40% ethanol before being suspended in 0.2 ml of 40% ethanol.[8] The subject's nose was examined and the inferior turbinate visualised, an auriscope being used as a speculum. The apparatus for the administration of the particle suspension consisted of a piece of narrow plastic tubing attached to a brass T piece. The latter was connected via a solenoid operated valve to a reservoir of compressed air at 7 kPa. Then 2 μl of the particle suspension containing 370 kBq (10 μCi) ^{99m}Tc were drawn into a plastic pipette tip with an automatic pipette. This pipette tip was attached on to the plastic tubing and over it a second pipette tip was placed to prevent any movement of the suspension by touching nasal hairs. The pipette tips were introduced through the auriscope and the suspension was blown via the operation of the solenoid valve on to the inferior turbinate of the right nostril.

The subject was positioned immediately with his or her head against a large field of view gamma camera (General Electric), which was connected on line to a Varian V-77 600 computer. Lateral views of the nasal region were taken at one minute intervals for 20 minutes and stored on magnetic tape. Each subject had radioactive markers (labelled with cobalt 57) on the chin, the nape of the neck and the forehead throughout the study for anatomical reference purposes. By using these fixed reference points a superimposed grid was placed identically on a computer
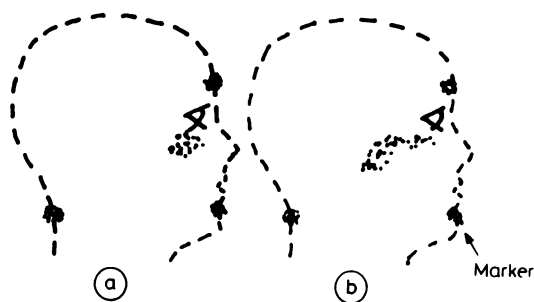
Fig 1 *Diagrammatic representation of computer printout showing nasal deposition pattern in relation to fixed markers: (a) initial deposition; (b) after 15 minutes.*

print out of each view as depicted in fig 1. The XY coordinates of the radioactive particle bolus were calculated from the fixed [57]Co markers for each view. Thus a graph of position of this bolus as a function of time was produced. The real chin to nape of neck measurement was compared with that on the printouts to give scale so that nasal clearance could be calculated in cm/min. Scans of the chest showed that no radioactive particles reached the lungs during the administrative procedures.

To assess the reproducibility of this technique we repeated the measurement of nasal clearance at an interval of 6–12 months after the initial studies.

On a separate day a non-invasive objective radioaerosol technique, described in detail previously,[9] was used to measure lung mucociliary clearance. Polystyrene particles of 5 μm diameter, again labelled with ^{99m}Tc, were produced inside an airtight tank by a spinning top generator.[7] The subjects, wearing a nose clip, inhaled the radioaerosol by taking eight single breaths via a mouthpiece from functional residual capacity to an automatically preset volume of 450 ml, followed by a three second breath hold before they exhaled. Oral rinsing and swallowing of water removed particles from the mouth and oesophagus. The amount of initially deposited aerosol within the lungs and its subsequent clearance were monitored by two collimated scintillation counters located anteriorly and posteriorly to the chest. Measurements were made at hourly intervals for six hours after inhalation of the radioaerosol and one final count was made at 24 hours—which was taken to be an estimate of alveolar deposition.[10] Count corrections were made for background radiation and physical decay of the radionuclide (T ½ 6 hours). The estimate of alveolar deposition was subtracted from the whole lung clearance curve to obtain the curve of tracheobronchial clearance. None of the subjects coughed during the six hours' observation period. The areas

under the tracheobronchial clearance curve for both 0–2.5 hours and 0–6 hours were calculated for each subject. The area under the tracheobronchial clearance curve is representative of the mean rate of clearance and inversely proportional to it. The first 2.5 hour period represents clearance from the more proximal airways and the 6 hour period includes clearance from virtually all the ciliated airways.

SUBJECTS

Ten volunteer subjects were recruited and gave informed consent to the procedures. Nine were non-smokers and one an ex-smoker.

None of the subjects had had an upper respiratory tract infection in the two months before assessment. The group comprised six men and four women—mean (SEM) age 28 (2) years, height 1·70 (0·04) m, and weight 65 (3) kg. Their pulmonary function indices, expressed as percentages of predicted values, were: FEV_1 120 (5), forced vital capacity (FVC) 118 (4), peak expiratory flow (PEF) 104 (4) (normal values are taken from Cotes (11)).

Results

The mean nasal clearance rate was 1·016 cm/min with a range of 0·5–1·7 cm/min. When the nasal clearance measurements were repeated 6–12 months after the initial studies the measurements were reproduced to within ±11%. The mean (SEM) area under the tracheobronchial clearance curve for 6 hours was 210 (22) arbitrary units (range 103·5–319·8) and the mean area under the tracheobronchial clearance curve for the first 2·5 hours was 149 (28) units (range 99·3–187·3).

Figure 2 shows the nasal clearance plotted against the area under the tracheobronchial clearance curve for up to 2·5 hours after inhalation of radioaerosol. The Spearman rank correlation test gave an r_s value of −0·79 (p < 0·01).

Figure 3 shows the nasal clearance plotted against the area under the tracheobronchial clearance curve for up to 6 hours after radioaerosol inhalation. The Spearman rank correlation test gave an r_s value of −0·94 (p < 0·001).

Discussion

Several methods have been used to evaluate nasal mucus transport. Initial studies used direct visualisation of various substances applied to the mucosal surface.[12 13] Subsequently three main forms of technique have been described: the saccharin test,[14] the use of radiolabelled markers, and the use of radio-opaque markers. Radiolabelled markers have been used as microdroplets[15] or single particles[16 17] with
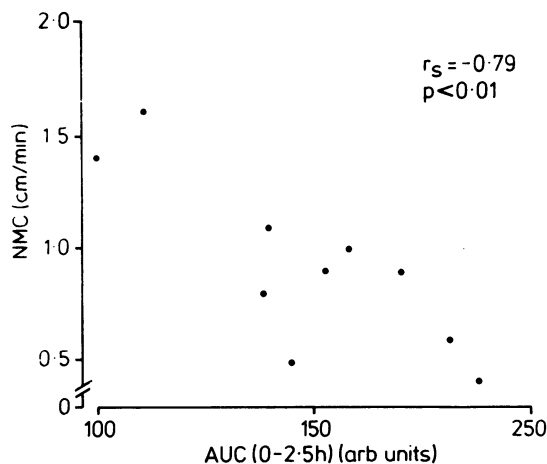
Fig 2 *Nasal mucociliary clearance (NMC) related to the area under the tracheobronchial clearance curve (AUC—in arbitrary units) in the first 2·5 hours: this represents clearance from the proximal airways.*
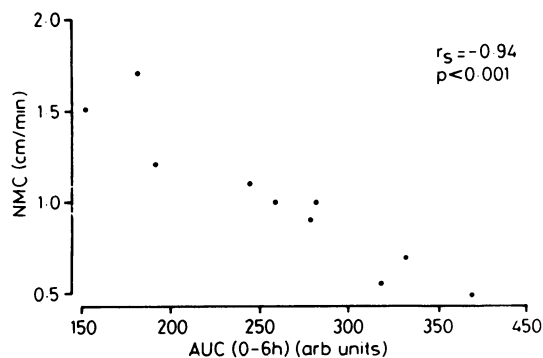

Fig 3 *Nasal clearance (NMC) related to the area under the tracheobronchial clearance curve (AUC—in arbitrary units) in the first 6 hours: this represents clearance from most of the ciliated airways.*

various types of detector. More recently a technique following the motion of radio-opaque discs with a fluoroscopic image intensifier[18] has been used. These techniques have been compared by several groups, with varying results.[14 18–20] Comparisons of nasal and tracheobronchial mucociliary clearance have shown in one study an inverse correlation[5] and in another study a weak association between tracheo-bronchial and nasal clearance as studied with a sac-charin particle,[4] and no correlation when nasal clear-ance was measured by single radiolabelled particles.[4] In all these studies both clearance measurements were made on the same day. Our measurements of nasal

and tracheobronchial clearance were made on different days, but we believe that this strengthens the relationship between our measurements. We could not measure both lung mucociliary clearance and nasal mucociliary clearance on the same day since radioactivity from one procedure might have inter-fered with measuring radioactivity from the other. As the reproducibility of the technique is within $\pm 11\%$, measurements made on the same day would not significantly alter our findings.

Another explanation for the discrepancies observed is that the techniques used for measurement may differ widely. All these studies have used a radio-aerosol technique for measuring lung tracheo-bronchial clearance. The nasal clearance test with sac-charin used a water soluble substance, which dissolves in the mucus and periciliary layer and so alters the way in which it is cleared from the nose. Previous radiolabelled particle techniques for studying nasal clearance used a single particle, of various sizes up to 600 μm, whereas radioaerosols used in the lungs are under 10 μm. We set out to measure tracheobronchial and nasal clearance with particles of similar size. For both clearance measurements we used small particles—5 μm polystyrene (equivalent to 5 μm unit density) for the lung and 2 μm Teflon (equivalent to 3·2 μm unit density) for the nose; they were in the form of an aerosol in the lung and a suspension in the nose. In the case of nasal clearance testing, it is difficult to assess how much localised retention of the radioactive material will depend on its initial distribu-tion within the nose. For this reason we believe that the rate of movement of a visualised bolus of radio-activity offers the best indicator of nasal mucociliary function. We also measured tracheobronchial clear-ance by the area contained under the tracheo-bronchial clearance curve, which is inversely propor-tional to the clearance rate. We consider that this gives the best overall indication of the tracheo-bronchial clearance rate and is more comparable with the nasal clearance technique than using the time for a fixed percentage clearance, as in other studies.[4 5]

The closer relationship of overall tracheobronchial clearance (measured for the first 6 hours) than more proximal clearance (measured for the first 2·5 hours) to nasal clearance was surprising. Ciliary beat fre-quency in normal epithelium is similar to that of the proximal ciliated airways, but differs from that found in subsegmental bronchi.[21] Ciliary beat frequency is only one element of mucociliary clearance. Other fac-tors are the differences between the nasal mucosa and the tracheobronchial tree in terms of nerve and blood supply and mucus production. The thickness of the nasal mucosa can alter by 2–3 mm with ordinary cli-matic changes, whereas the bronchial mucosa rarely exceeds 1 mm in the presence of inflammation.[3] This

is due largely to the extremely rich vascular supply of the nasal mucosa.[22] Differences between the nasal and bronchial mucosa in the response to environmental influences have been described in terms of the size and number of goblet cells and mucus glands.[23] The innervation of the bronchial tree continues to be elucidated. Some differences between the response and the presence of a cholinergic, an adrenergic, and a non-cholinergic, non-adrenergic component in the nerve supply of the bronchial[24] and nasal mucosa[25] have been determined. A combination of these factors influences mucus clearance rate in both the nasal and the tracheobronchial passages.

Our results for nasal clearance are similar to those previously reported, and show a wide normal range.[4–6 13–19] We have shown a close correlation between tracheobronchial clearance and nasal clearance in normal subjects, indicating that those factors that influence a particular individual's tracheobronchial clearance seem to exert the same influence on that individual's nasal clearance. As mucociliary clearance is such a highly developed and widespread mechanism for defence in the man this is not surprising. We conclude that using this technique nasal clearance is a useful guide to tracheobronchial clearance in healthy non-smoking subjects. It could be used as a screening procedure for congenital abnormalities of mucociliary clearance and for detecting those at particular risk from industrial exposure to inhaled carcinogens, such as in the woodworking industry.[6] Further studies may show that abnormalities of nasal clearance are important to diseases of the lung.[26 27]

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