

Variability and reproducibility in the measurement of tracheobronchial clearance in healthy subjects and patients with different obstructive lung diseases

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ABSTRACT: The purpose of this study was to establish the inter- and intra-subject/patient variability of tracheobronchial clearance, measured for 6 h, using a radioaerosol technique. Inter-subject variability was evaluated in five groups: 33 healthy non-smokers (NS); 19 asymptomatic smokers (S); 40 asthmatics (A); 27 chronic bronchitics (CB) and 12 bronchiectatics (B). Intra-subject variability was evaluated in 16 A and 27 CB who were studied twice. The inter-subject/patient coefficient of variation (CoV) of tracheobronchial clearance was 13% for NS and 28-39% for the remaining four groups. The intra-patient CoV was about half of the inter-patient CoV. Inter-subject CoV (for A and CB) appeared to be independent of initial tracheobronchial deposition of radioaerosol and frequency of cough. We were also able to estimate the approximate number of patients required for a crossover study in order to avoid statistical, type II errors when investigating the effect of a drug or of a therapeutic intervention on tracheobronchial clearance.

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In health, mucociliary transport is the main component of tracheobronchial clearance (TBC) [1], whereas in lung disease it is often impaired [2] and then aided by cough [3, 4].

The most popular method for assessing TBC [5] is the radioaerosol technique [6], for which several authors have reported the inter- and intra-subject variability [5, 7-11] but in relatively small numbers of subjects (mainly healthy non-smokers and chronic bronchitics) and over short observation periods.

In this study we report the intra- and inter-subject variability of this technique in relatively large numbers of healthy subjects (non-smokers and asymptomatic smokers) and in three groups of patients with airways disease of different aetiology (chronic bronchitics, asthmatics and bronchiectatics). The radioaerosol technique is often used in within-patient, cross-over studies to assess the efficacy of therapeutic interventions [12]. From the information obtained on the reproducibility of the measurement within patients we have produced tables indicating the approximate numbers of patients that need to be included in such studies in order to avoid statistical, type II errors [13, 14].

Subjects and methods

Subjects

We have studied five groups of subjects, 33 healthy non-smokers (NS), 19 asymptomatic smokers (S), 27

chronic bronchitics (CB), 40 asthmatics (A) and 12 bronchiectatics (B). The criteria used for the selection of the healthy subjects were: age < 50 yr, % predicted forced expiratory volume in one second (FEV_1) > 80% and radioaerosol inspiratory flow rate < 30 $l \cdot min^{-1}$. For the patients we used the baseline runs from several mucociliary clearance studies performed in our laboratories when investigating the effect of various drugs. All the CB and 16 of the 40 A were tested twice. The total number of experimental patient runs was 174.

The asthmatics were shown to increase their FEV_1 by > 15% after a bronchodilator. The chronic bronchitics were selected according to the criteria of the British Medical Research Council [15]; diagnosis of the bronchiectatics was confirmed by chest X-ray and bronchography and all subjects were expectorating purulent sputum daily. All patients were studied at a stable phase of their disease and at least one month after any acute episodes.

Smoking was not allowed on the day of the test for at least 1 h before inhalation of the radioaerosol and throughout the 6 h observation period. The maintenance therapy for the CB and A remained the same between their two assessments. Inhaled bronchodilators and corticosteroids were permitted up to 2 h and oral bronchodilators up to 12 h prior to the inhalation of the radioaerosol. None of the patients were on oral corticosteroids. Informed, written consent was obtained from all the subjects and patients and the

studies in which they participated were approved by the hospital's Ethical Practices Committee.

Pulmonary function tests

FEV₁ was measured using a dry bellows spirometer (Vitalograph) 10–20 min prior to each radioaerosol inhalation. The highest value of three technically acceptable measurements was recorded. All readings were corrected to body temperature and pressure and the results were expressed as percentages of predicted values [16].

Radioaerosol inhalation measurement

Tracheobronchial clearance (TBC) was studied using a non-invasive radioisotopic method [5]. 5 µm polystyrene particles, labelled with ^{99m}Tc and generated by a spinning top [17] were inhaled, in 8–10 breaths of 0.45 l each, from approximately functional residual capacity. After each inspiration there was a 3 s breath-hold pause, to allow particles to deposit by sedimentation in all airways <2 mm in diameter. The average flow rate during radioaerosol inhalation was measured by a pneumotachograph (connected in series to the tank from which the aerosol was inhaled) and recorded on a UV recorder. After the inhalation, the subjects washed out their mouths and then swallowed some water to remove deposited radioaerosol from the oropharynx and oesophagus. Immediately after this, readings were taken of lung radioactivity using suitably collimated axially opposed scintillation counters [18] and thereafter at 30 min intervals for 6 h, with a final reading at 24 h. The final reading was used to estimate 'alveolar deposition' (AD), *i.e.* the percentage of radioaerosol deposited distally in the small airways, at sites inaccessible to mucus clearance [19] by mucociliary action or cough. Subtracting AD from the initial radioaerosol deposition (*i.e.* 100%) yielded the percentage radioaerosol tracheobronchial (TB) deposition.

As an index of clearance we used the percentage TBC in 6 h (6 h TBC%). An alternative method of evaluating the TB retention curves is by measuring the area under the curve (AUC) from 0 to 6 h using the trapezoidal rule [20]. A small AUC denotes a fast TBC, and conversely a large AUC reflects a slow TBC.

During the first 6 h after aerosol inhalation, all coughs were recorded and sputum collected and weighed.

Statistical analyses

Student's t-test for unpaired groups was used when testing the difference of a parameter between two groups. Variability was expressed in terms of the coefficient of variation (CoV) defined as the ratio of the standard deviation to the mean value as a percentage.

The number of patients needed to be included in each limb of a cross-over design study, in order to

detect given differences at $p < 0.05$ with various powers of success, was calculated using the formula described by HILLS and ARMITAGE [21]:

$$n = (A^2 \times SD_d^2) / (2 \times D^2)$$

where, $A = (\text{actual difference}) / (\text{standard error})$ and varies for different powers of success. For example, $A = 2.8$ for detecting a difference at the $p < 0.05$ level with a power of 80%; $SD_d = \text{standard deviation for the paired differences between two periods}$; $D = \text{expected mean differences between the two periods}$.

The power of a study [22] is defined as the probability that the study will produce a difference between treatments, which is significantly different from zero at a certain statistical level of significance usually $p < 0.05$.

Since the cross-over study design consists of two limbs (*i.e.* placebo/drug and drug/placebo) the total number of patients necessary for such a study was taken as twice that given by the above formula, *i.e.* $2n$.

Results

Table 1 gives the mean \pm SEM physical characteristics, tobacco consumption, pulmonary function, radioaerosol inspiratory flow rate and TB deposition for the five groups of subjects/patients studied. The mean age for the healthy subjects (S and NS) was about half that of the patients (A, CB and B). The healthy subjects (NS and S) had, as expected, a markedly higher percentage predicted FEV₁ than the A, B and CB patients. The radioaerosol flow rate was the same for the healthy NS and asymptomatic S but was significantly higher ($p < 0.001$) in the CB, A and B groups. In the A, B and CB patients a larger proportion ($p < 0.001$) of the deposited radioaerosol was located in the tracheobronchial tree compared with the healthy NS or S.

Figure 1 shows the mean TB retention curves for the five groups. The asymptomatic smokers' clearance (AUC (0–6 h): 305 ± 24 SEM) was slower ($p < 0.005$) than that for the healthy non-smokers (AUC (0–6 h): 219 ± 13). All three patient groups had slower clearances (AUC (0–6 h): 303 ± 20 ; 345 ± 22 and 341 ± 35 for A, CB and B respectively), compared with the healthy NS ($p < 0.005$).

Figure 2 shows histograms of the inter-subject/patient CoV for two parameters: a) 6 h TBC% and b) AUC (0–6 h). The inter-subject CoV for 6 h TBC% for the asymptomatic S was approximately twice that for the healthy NS and, for the patients, about three times that for the NS. By contrast the inter-subject/patient CoV for the AUC (0–6 h) was roughly similar in all five groups. The actual SD values entering into the CoV calculations are illustrated in figure 3.

The inter-subject/patient CoV for 6 h TBC% for males and females respectively was 11 and 15% for the healthy NS; 31 and 24% for the asymptomatic S; 43 and 33% for the A group and 39 and 34% for the

Table 1. — Mean \pm SEM physical characteristics, smoking habits, percentage of predicted forced expiratory volume in one second (FEV_1), and radioaerosol inspiratory flow rate (\dot{V}_I) and initial tracheobronchial (TB) deposition expressed as a percentage of whole lung deposition for five groups of subjects/patients

Group	n	Sex M/F	Age yr	Height m	Smoking pack-years	FEV_1 %pred	Radioaerosol \dot{V}_I $l \cdot min^{-1}$ %	Radioaerosol TB deposition
Healthy non-smokers	(NS) 33	20/13	27.2 \pm 1.5	1.73 \pm 0.02	0	117 \pm 3	22.5 \pm 0.7	39.8 \pm 1.7
Asymptomatic smokers	(S) 19	11/8	27.4 \pm 1.8	1.70 \pm 0.02	10.9 \pm 3.3	110 \pm 3	23.7 \pm 1.1	43.4 \pm 2.6
Asthmatics	(A) 40	20/20	46.5 \pm 2.7	1.67 \pm 0.02	16.3 \pm 3.8*	71 \pm 4	36.2 \pm 1.6	68.4 \pm 2.3
Bronchiectatics	(B) 12	7/5	54.9 \pm 2.6	1.70 \pm 0.04	23.4 \pm 7.4@	47 \pm 7	42.4 \pm 2.9	70.9 \pm 5.5
Chronic bronchitics	(CB) 27	24/3	66.7 \pm 1.5	1.69 \pm 0.01	54.8 \pm 6.7†	42 \pm 4	30.9 \pm 1.7	77.0 \pm 2.5

* 11S/14ES; @ OS/7ES; † 11S/16ES; S: smokers; ES: ex-smokers.

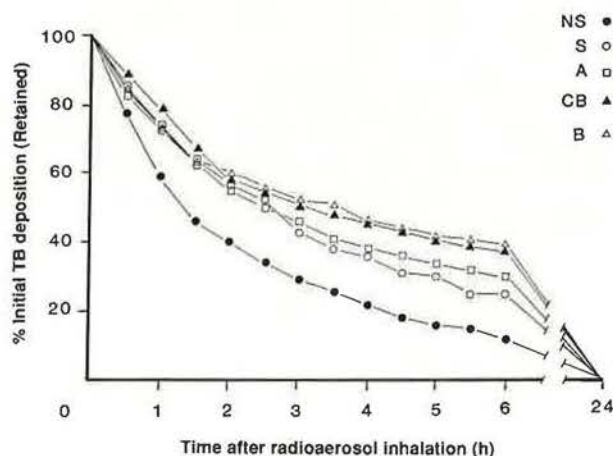


Fig. 1. Mean tracheobronchial retention curves showing retardation in clearance in 19 asymptomatic smokers (S), 40 asthmatics (A), 27 chronic bronchitics (CB) and 12 bronchiectatics (B) compared to 33 healthy non-smokers (NS).

B group. There were too few females in the CB group to permit such an analysis. These differences between the sexes were not consistent nor could they be accounted for by differences in TB deposition, age or tobacco consumption; as such, males and females were grouped together.

Figure 4 shows a) the distribution of the percentage TB deposition and b) frequency of coughs, for the three patient groups. Because the wide range of TB deposition observed in the asthmatics might influence their variability of clearance, we also investigated this factor in two sub-groups corresponding to narrow ranges of TB deposition (namely 40–59% and 70–89%). For the chronic bronchitics sufficient data were available only for one sub-group – with TB deposition in the range 70–89%. In table 2 the values of CoV for the 6 h TBC% and AUC (0–6 h) for the two asthmatic sub-groups and the one chronic bronchitic sub-group are compared with those for the

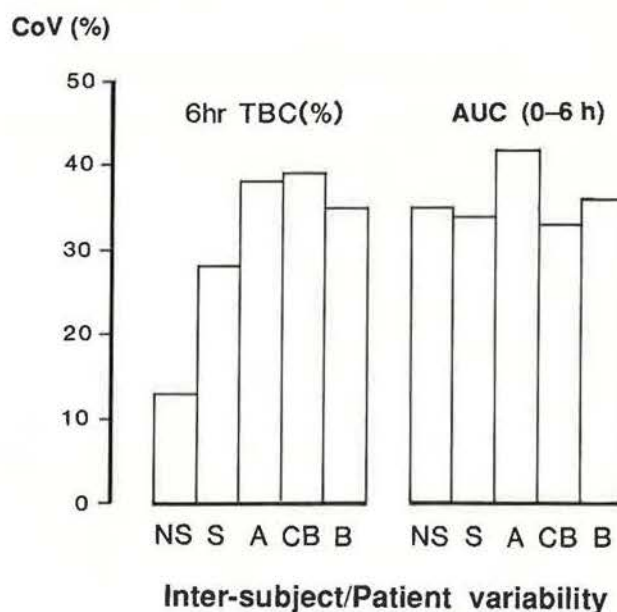
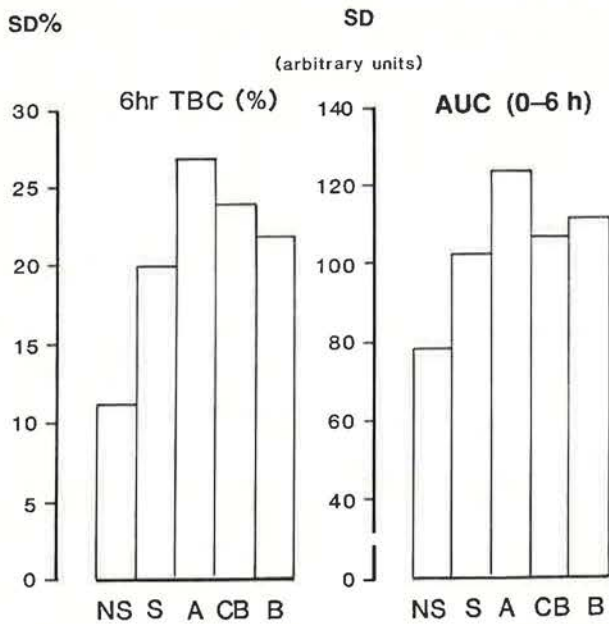


Fig. 2. Inter-subject/patient coefficient of variation (CoV) for 6 h tracheobronchial clearance (6 h TBC%) and area under the tracheobronchial retention curve between 0 and 6 h (AUC (0–6 h)) for 33 healthy non-smokers (NS), 19 asymptomatic smokers (S), 40 asthmatics (A), 27 chronic bronchitics (CB) and 12 bronchiectatics (B).

main groups. Since a wide range of cough frequency could influence variability of clearance, data were inspected for both asthmatics and chronic bronchitics coughing no more than 19 times over the 6 h observation period. Clearance variability for these sub-groups is also shown in table 2. In each case clearance variability of the sub-groups was similar to that in the corresponding main group. The bronchiectatics were not analysed in sub-groups because of their small number.

The mean \pm SD difference in days between the two



Inter-subject/Patient variability

Fig. 3. Standard deviation (SD) for 6 h tracheobronchial clearance (%) and area under the tracheobronchial retention curve between 0 and 6 h (in arbitrary units) for 33 healthy non-smokers (NS), 19 asymptomatic smokers (S), 40 asthmatics (A), 27 chronic bronchitics (CB) and 12 bronchiectatics (B).

assessments of TBC were 20 ± 17 and 49 ± 24 for the CB and A groups respectively.

The mean \pm SD paired differences for the 6 h TBC% between the two runs for the CB and A groups were: 5.5 ± 20.3 and $3.5 \pm 16.4\%$ respectively; and for the AUC (0-6h) 11.2 ± 86.5 and $22.9 \pm 67.3\%$ h.

Figure 5 shows the inter- and intra-patient variability for the 27 CB and 16 A studied twice. The intra-patient CoV for the two groups was approximately half the inter-patient CoV.

Table 3 gives the number of A and CB patients that are required to be entered into a cross-over study design in order to detect given differences in the 6 h TBC% or AUC (0-6 h), with various powers of success at $p < 0.05$.

Discussion

Mucociliary transport may be described in terms of clearance or of retention. For our CB group, the inter-patient CoV for 6 h % tracheobronchial clearance (TBC) may be calculated as $(SD/mean\ clearance) \times 100 = 23.8/61.7 \times 100 = 39\%$. Alternatively the same information may be expressed in terms of the inter-patient CoV for 6 h % tracheobronchial retention = $23.8/38.3 \times 100 = 62\%$. Thus, a seemingly simple choice between two different ways of recording data, may substantially influence the CoV value obtained.

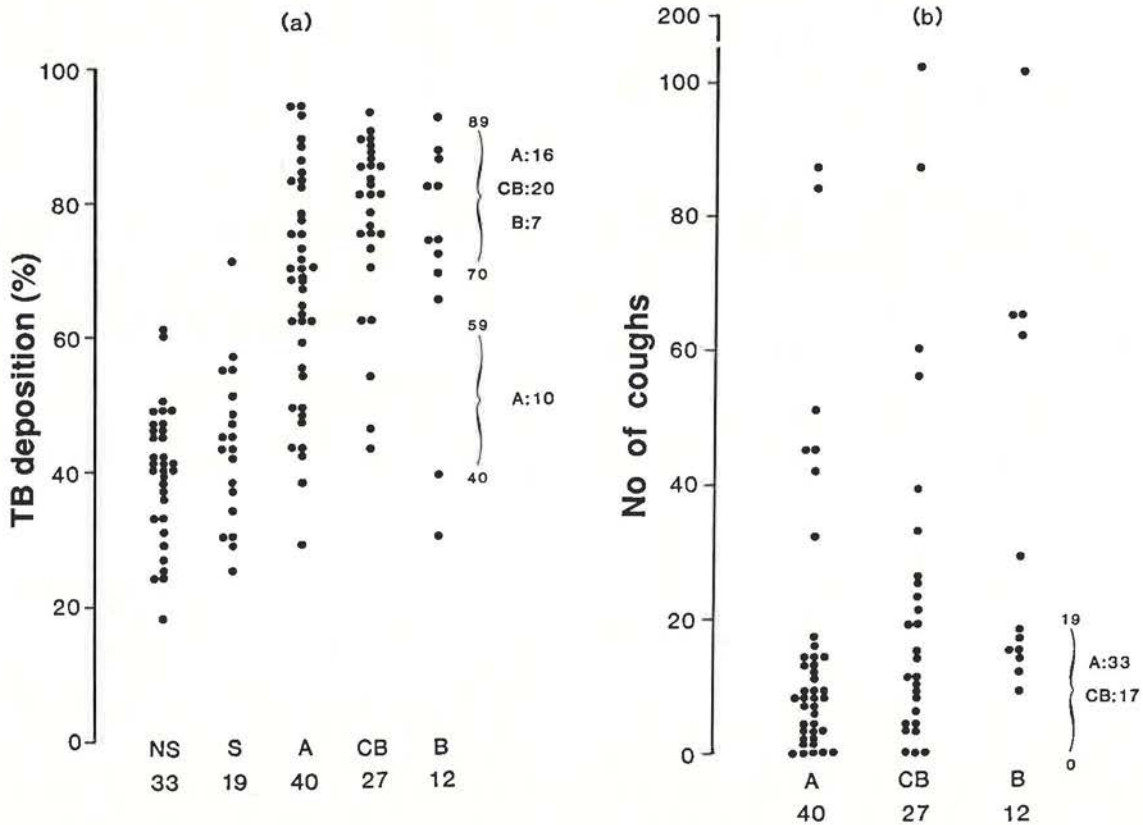


Fig. 4. Scatter diagram for a) initial radioaerosol tracheobronchial deposition and b) number of coughs in the 6 h observation period for healthy non-smokers (NS), asymptomatic smokers (S), asthmatics (A), chronic bronchitics (CB) and bronchiectatics (B).

Table 2. - Inter-patient coefficient of variation (CoV) for 6 h tracheobronchial clearance (%) and area under the tracheobronchial retention curve (AUC (0-6 h)) for all the chronic bronchitic (CB) and asthmatic (A) patients. Also shown are the CoV for those patients within given ranges of a) cough frequency in 6 h and b) initial tracheobronchial (TB) deposition when examined independently or in combination

	No. of observations		CoV 6 h TBC%		CoV AUC (0-6 h)	
	CB	A	CB	A	CB	A
Whole study group	27	40	39	38	33	42
TB deposition: 70-89%	20	16	38	26	32	44
TB deposition: 40-59%	-	10	-	39	-	38
Cough range: 0-19	17	33	39	38	32	40
Cough: 0-19 and TB deposition:70-89%	13	12	47	29	34	42

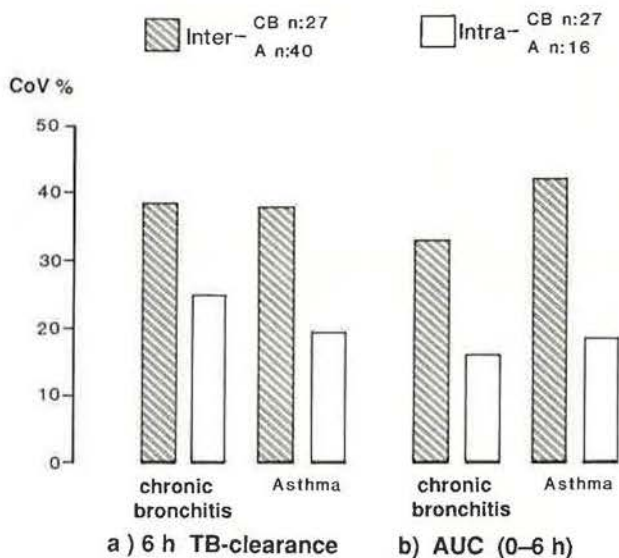


Fig. 5. Inter-patient coefficient of variation (CoV) for 27 chronic bronchitics (CB) and 40 asthmatics (A) for 6 h tracheobronchial clearance (6 h TBC%) and area under the tracheobronchial retention curve between 0 and 6 h (AUC (0-6 h)). Also shown are the intra-patient CoV for the 27 CB and 16 of the 40 A who were studied twice.

To facilitate detailed comparisons with other data we have expressed our own data in two different ways: a) an index of clearance, total tracheobronchial clearance over the 0-6 h period; and b) an index of retention, the summated area under the 0-6 h retention curve. The AUC is at present less widely used in published reports than are TBC values at one or another time post-inhalation. It does however have the advantage of reflecting clearance over the whole observation period.

In agreement with other reports [2, 23, 24], significant slowing of clearance was observed in A, CB and B despite more proximal radioaerosol lung deposition and coughing. This more proximal deposition of the radioaerosol should have resulted in a faster TBC [25] in the patients relative to the healthy subjects. The slowing of TBC in the patients must

therefore underestimate their true impairment of TBC. Furthermore, in some patients TBC is not complete within 24 h leading to inadvertent underestimation of TB deposition and overestimation of TBC [25]. On the other hand, the three patient groups were older than the healthy NS and S and therefore, all other things being equal, one would have expected a slower TBC in the patients [26]. The differences in clearance between the groups in figure 1 must, therefore, not be taken as absolute. One can only make comparison if both the initial topographical distribution of the tracer radioaerosol in the lungs and the age is similar between groups such as between NS and S. The TBC for the NS and S, who did not cough, reflects lung mucociliary clearance *per se*, that for the patients represents clearance by ciliary action plus cough and expectoration.

In the case of the AUC (0-6 h) the inter-subject/patient CoVs appear to be the same for all five groups (fig. 2). AUC (0-6 h) measures retention and thus the smaller value which is encountered in healthy subjects compared to patients would give rise to a larger value of CoV even for similar SD. However, when expressing the spread of the data in terms of SD (fig. 3) it can readily be seen that the SD is less for the NS compared to the S and the patient groups for both 6 h TBC% and AUC (0-6 h), thus giving rise to the apparent similarity in the values of CoVs for AUC (0-6 h) between the five groups. The higher SD in 6 h TBC% for the S and the patient groups coupled with the lower mean 6 h TBC% resulted in apparently higher CoVs in these groups for this measurement compared to the NS than would otherwise have been the case if all groups had similar mean AUC.

The reproducibility in the measurement of TBC within the CB and A groups was good and, as expected, the intra-patient CoV for 6 h TBC% and AUC (0-6 h) were less (by some 50%) than the inter-patient CoV (fig. 5).

Various indices have been used for describing the efficiency of lung mucociliary/tracheobronchial clearance. Table 4 compares our intra- and inter-subject/patient CoV with those reported by other

Table 3. — Number of chronic bronchitic and asthmatic (in brackets) patients needed to be entered in a crossover radioaerosol tracheobronchial clearance study in order to detect given absolute differences in 6 h tracheobronchial clearance or area under the tracheobronchial retention curve at $p < 0.05$ with various probabilities of success (power)

Δ 6 h TBC %	Power %						Δ AUC (0–6 h)
	70	75	80	70	75	80	
5 (68)	101 (77)	115 (87)	129 (67)	115 (76)	130 (85)	146	20
10 (17)	25 (19)	29 (22)	32 (22)	37 (25)	42 (28)	48	35
15 (8)	11 (9)	13 (10)	14 (11)	18 (12)	21 (14)	23	50
20 (4)	6 (5)	7 (6)	8 (5)	9 (6)	11 (7)	12	70

Δ 6 h TBC%: expected difference in 6 h TBC%.

Table 4. — Comparison of our intra- and inter-subject/patient coefficients of variation for various measurements of tracheobronchial clearance with those reported by other studies

Source	No. of subjects	Subjects patients	Type of measurement	Intra-CoV %	Inter-CoV %
Our study	33	NS	6 h TBC %	-	13
LOURENÇO <i>et al.</i> [7]	10	NS	6 h TBC %	-	17*
YEATES <i>et al.</i> [9]	22	NS	2 h TBC %	20	43
PUCHELLE <i>et al.</i> [26]	16	NS	1 h TBC %	16	42
YEATES <i>et al.</i> [10]	74	NS	TMV	-	48
Our study	33	NS	AUC (0–6)	-	35
LOURENÇO <i>et al.</i> [7]	10	NS	AUC (0–6)	-	29*
VAN HENGSTUM <i>et al.</i> [11]	10	NS	AUC (0–6)	8.5	36
Our study	19	S	6 h TBC %	-	28
LOURENÇO <i>et al.</i> [7]	9	S	6 h TBC %	-	27*
Our study	19	S	AUC (0–6)	-	34
LOURENÇO <i>et al.</i> [7]	9	S	AUC (0–6)	-	17*
Our study	27	CB	6 h TBC %	25	39
YEATES <i>et al.</i> [9]	19	COPD	2 h TBC %	67	86
CAMNER <i>et al.</i> [24]	15	COPD	2 h TBC %	-	28*
Our study	40	A	6 h TBC %	19	38
MOSSBERG <i>et al.</i> [27]	12	A	1 h TBC %	-	76*
Our study	12	B	6 h TBC %	-	35
LOURENÇO <i>et al.</i> [23]	13	B	6 h TBC %	-	27*
Our study	12	B	AUC (0–6)	-	36
LOURENÇO <i>et al.</i> [23]	13	B	AUC (0–6)	-	37*

NS: healthy non-smokers; S: asymptomatic smokers; CB: chronic bronchitics; COPD: chronic obstructive pulmonary disease; A: asthmatics; B: bronchiectatics; TMV: tracheal mucus velocity; AUC (0–6h): area under the tracheobronchial retention curve between 0 and 6 h radioaerosol inhalation; 1 h, 2 h, 6 h TBC%: % of tracheobronchial deposition cleared after 1, 2 and 6 h post radioaerosol inhalation; * derived from published data.

studies using techniques sufficiently similar to permit a direct comparison. It can be seen that our values of CoV are broadly comparable with those reported by other centres.

Variability in the measurement of lung mucociliary clearance using the radioaerosol technique arises from i) biological variability in the function of the mucociliary escalator and ii) methodological variability arising from differences in initial topographical distribution of the radioaerosol within the lungs. Variations in topographical distribution in our study reflect variability in flow rate and airway patency.

Surprisingly, perhaps, when the inter-patient CoV (table 2) were examined in patients within fairly narrow ranges of cough frequency and initial tracheobronchial deposition (fig. 4) independently or in combination, in an attempt to reduce the observed variability in the measurement of TBC, little or no difference was found. YEATES *et al.* [10] have reported that the intra-subject variation of mucociliary clearance in healthy subjects was equally partitioned between variances due to initial tracheobronchial deposition and variances due to transport. Our results may indicate that the dysfunction in lung mucociliary clearance due to airway disease is sufficiently great to mask the expected additional effects of cough and initial topographical distribution of the radioaerosol on the variability in the measurement of TBC.

It must be stressed that many factors inevitably contribute to the variability of mucus clearance measurements. The present study focuses particular attention on differences between different subject groups (table 1) and on the different methodologies available (table 4). These factors must, however, be related in a more general context. The principal factors contributing to variability in mucus clearance measurements (*e.g.* TBC%, AUC, tracheal mucus velocity) are the methodology used (*e.g.* size of radioaerosol, mode of inhalation) the aetiology and pathology of the disease process and sites of abnormality in patients with lung disease.

Clinical trials are often conducted to ascertain whether there is a statistically significant difference in TBC following therapeutic intervention. Such studies are invariably of the cross-over (within patients) design type, justified on the grounds of a smaller intra- than inter-patient variation in the measurement of TBC. A study which concludes that there is a highly statistically significant difference between therapeutic intervention and placebo is adequately sensitive for its purpose. However, if a study concludes that there is no statistically significant difference in TBC following therapeutic intervention compared to placebo, a further question must be asked. Was the number of patients entered into the study too small to detect an important difference and, therefore, did it give rise to a type II error [28, 29] or was there a genuine lack of difference? Table 3 indicates that a) the smaller the expected difference in TBC that needs to be detected and b) the bigger the power of success required for detecting this difference

(and thus the smaller the probability of generating a type II error) then the greater is the number of patients that needs to be studied. The wider question remains as to when a small but statistically significant difference in TBC also constitutes a clinically meaningful difference.

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RÉSUMÉ: Le but de l'étude est l'établissement de la variabilité de la clearance trachéo-bronchique inter- et intra-individuelle, mesurée pendant 6 heures par une technique de radio-aérosol. La variabilité inter-individuelle a été évaluée dans 5 groupes: 33 non fumeurs bien portants (NS), 19 fumeurs asymptomatiques (S), 40 asthmatiques (A), 27 bronchitiques chroniques (CB) et 12 bronchectasiques (B). La variabilité intra-individuelle a été évaluée chez 16 A et 27 CB étudiés à deux reprises. Le coefficient de variation inter-individuelle (CoV) pour la clearance trachéo-bronchique pendant 6 heures, a été de 13% pour NS et pour les quatre autres groupes de 28 à 39%. Le coefficient de variation intra-individuelle atteignait environ la moitié du coefficient de variation inter-individuelle. Le coefficient de variation inter-individuelle pour A et CB apparaît indépendant du dépôt initial du radio-aérosol dans la région trachéo-bronchique et de la fréquence de la toux. De plus, nous avons pu estimer le nombre approximatif de patients nécessaires pour entrer dans une étude avec permutation, afin d'éviter le type II d'erreurs statistiques lorsque l'on investigate l'effet d'un médicament ou d'une intervention thérapeutique sur la clearance trachéo-bronchique.