Eur Respir J 1998; 11: 1141–1146
DOI: 10.1183/09031936.98.11051141
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

A comparison of three methods of measuring ^{99m}Tc-DTPA lung clearance and their repeatability

D. Morrison*, K. Skwarski*, A.M. Millar**, W. Adams+, W. MacNee*

A comparison of three methods of measuring ^{99m}Tc-DTPA lung clearance and their repeatability. D. Morrison, K. Skwarski, A.M. Millar, W. Adams, W. MacNee. ©ERS Journals Ltd 1998.

ABSTRACT: The lung clearance of technetium-99m diethylenetriamine penta-acetic acid (^{99m}Tc-DTPA) is a measure of respiratory epithelial permeability. Many factors may contribute to the wide range of normal values, including the method of correction for background activity. The aim of this study was to compare three methods of analysis, including their repeatability.

^{99m}Tc-DTPA lung clearance imaging was performed on eight nonsmokers (age 32±2 yrs, forced expiratory volume in one second (FEV_1) 102.8±3.3% predicted yrs, mean±SEM and seven smokers (age 46±4 yrs, p<0.01, *versus* nonsmokers; FEV_1 88.9± 8.9%, p<0.05 *versus* nonsmokers) on two occasions each. The smokers were asked to refrain from smoking for 12 h. An uncorrected analysis was compared with two methods corrected for recirculating background activity using an intravenous correction and inter-renal and shoulder background regions of interest.

The uncorrected method gave higher mean values for 50% lung clearance of ^{99m}Tc-DTPA (t_{50}) values than the inter-renal (p<0.001) and shoulder (p<0.001) methods of correction in nonsmokers and the inter-renal method gave lower values than the shoulder-corrected method (p<0.05). In smokers there was no difference. There were no differences in mean t_{50} values obtained on two separate visits. There was no difference in the repeatability of the three methods of analysis.

The three methods of analysis produced comparable results with no differences in repeatability.

Eur Respir J 1998; 11: 1141–1146.

Depts of *Medicine and **Pharmacy, Unit of Respiratory Medicine, Royal Infirmary, Edinburgh, UK. +Dept of Medical Statistics, Edinburgh University, UK.

Correspondence: W. MacNee
Unit of Respiratory Medicine
Dept of Medicine
Royal Infirmary
Lauriston Place
Edinburgh
EH3 9YW
UK
Fax: 44 131 5363255

Keywords: DTPA
epithelium
method-related
permeability
pulmonary alveoli
repeatability

Received: November 15 1996
Accepted after revision January 20 1998

Supported by the British Lung Foundation

One of the earliest demonstrations of the permeability of the respiratory epithelium was made in 1857, when curare was seen to produce paralysis and death when introduced into the respiratory tract of a dog [1]. In recent years it has been extensively studied by measuring the lung clearance of inhaled 99m-technetium-labelled diethylenetriamine penta-acetic acid (^{99m}Tc-DTPA). This technique was first used as a means of assessing regional ventilation as a replacement for the radioactive gas ^{133}xenon [2]. The inhaled ^{99m}Tc-DTPA particles were noted to pass from the lungs to the blood at a rate of about 1%·min^{-1}. It was expected that diseases which thickened the alveolar-capillary membrane, such as interstitial lung disease, would exhibit a reduced rate of clearance. However, the converse was found to be true [3]. Increased rates of ^{99m}Tc-DTPA lung clearance occur in numerous conditions, including the adult respiratory distress syndrome [4], *Pneumocystis carinii* pneumonia [5], after exposure to cytotoxic agents [6], amiodarone [7] and ozone, [8] and in acute asthma [9]. Cigarette smoking produces a rapidly reversible increase in ^{99m}Tc-DTPA clearance [10–13]. Peripheral deposition is associated with faster clearance [14], as are positive end expiratory pressure [15] and raised lung volume [16].

Despite extensive use of this technique in studies of alveolar-capillary membrane integrity, no comparison has been performed of the different methods as they are employed in practice. A wide range of normal values for the time for lung activity of ^{99m}Tc-DTPA to fall to 50% of the initial value (t_{50}) has been quoted in the literature (44.4–117.5 min) (table 1). This is likely to reflect the sensitivity of ^{99m}Tc-DTPA clearance to changes in lung volume [15–17]. However, the method of correcting for background activity may also contribute to this range [3, 18, 19]. Two groups have compared uncorrected and corrected analyses

Table 1. – Values for ^{99m}Tc-DTPA clearance from lung to blood in nonsmokers and smokers, in previous studies

[Reference]	Nonsmokers	Smokers	Method
[10]	59±5	20±2	C
[12]	81±10	15±1	U
[13]	110±22	42±5	C
[15]	52±6	28±5	C
[16]	55±7	22±4	C
[17]	83±6	30±3	U
	70±6	20±3	C
[18]	66	33	U
	60	27	C
	58	26	C
[19]	91±5	28 (range 22–46)	C

Values are mean±SEM of values of t_{50} (50% lung clearance of ^{99m}Tc-DTPA, min). C: corrected; U: uncorrected for recirculating background activity.

on clearance curves of 100 min [18] and 20 min [19]. However, uncorrected analysis is normally restricted to the first 7–10 min of the clearance curve [3, 12]. Eight nonsmokers and seven smokers were each studied on two occasions, with the aim of comparing three methods of analysis including their repeatability, as they are employed in practice.

Methods

Study subjects

The characteristics of the study subjects are given in table 2. The nonsmokers had normal ventilatory capacity and the smokers had mild airflow limitation. All were free of respiratory infection and had no significant medical problems. The study was approved by the local Medical Ethics Committee and all subjects gave written informed consent.

Study design

For the purposes of this study subjects attended an initial sham study, performed without isotope, in order to accustomize them to the test. Such a sham study is not normally performed in practice and was done to eliminate as much as possible any variations in tidal volume, inspiratory flow and functional residual capacity. They were then studied on two occasions (visits 1 and 2) over variable time intervals (1–30 weeks) with initial and return studies overlapping to help to negate any possible influence of changes in the test set-up with time. On each of the three occasions smokers were asked to refrain from smoking for 12 h. Spirometry (Vitalograph, Buckingham, UK) and carboxyhaemoglobin measurements (IL 282 Co-oximeter; Instrumentation Laboratory, Lexington, MA, USA) were performed on all visits prior to study.

Methods

Except for during the sham study, each subject inhaled 1,200 megabecquerels (MBq) of nebulized ^{99m}Tc-DTPA from an Ultravent nebulizer (Mallinkrodt Medical, Petten, The Netherlands) at a radioactive concentration of 1.8 GBq·2 mL^{-1}. It was prepared using sodium pertechnetate [^{99m}Tc] injection obtained from an Amertec II generator (Code MCC20; Amersham International, Bucks, UK) and a Pentetate II kit (Code N108, Amersham International). It was estimated by A.M. Miller that approximately 50 MBq was deposited in the lungs. The mass median aerodynamic diameter (MMAD) of the particles generated is 0.59±0.04 μm (SD), with a geometric standard deviation (GSD) of 1.79± 0.14 μm, as measured by a seven-stage cascade impactor [20]. A flow rate of 12 L·min^{-1} of oxygen was used to generate the aerosol, which subjects inhaled for 2 min, while supine and wearing a noseclip, during normal tidal breathing to prevent proximal deposition through turbulent air flow [21]. The respiratory frequency (f_R) was counted during the 2 min inhalation period. Subjects were then imaged supine using a Siemens gamma camera positioned posteriorly with a 140 keV low-energy, all-purpose collimator (Siemens, Bracknell, UK) linked to a Bartec computer (Bartec Medical Systems, Farnborough, UK) and Unix Sun work-station (Sun Microsystems, Camberley, UK) with Micas System V software (Nodecrest, Byfleet, UK). Counts were acquired in 30 s time-frames for 30 min at a resolution of 128×128. An *i.v.* injection of 20 MBq ^{99m}Tc-DTPA at a concentration of 50 MBq·2.5 mL^{-1} was given at 20 min to allow correction for background activity.

A region of interest (ROI) was drawn with a cursor around each lung field at peak activity, approximately two pixels within the outermost lung contour, avoiding the mediastinum. Each ROI was normalized for area and corrected for ^{99m}Tc decay. A semilogarithmic plot of time *versus* activity was then made for all ROIs (fig. 1). Three separate analyses were performed. Uncorrected analysis was made on the first seven min after peak activity. This method is used by certain groups as it is assumed that no significant background accumulation of isotope occurs within this period [3, 12]. Other groups, including JONES *et al.* [10], who first described the technique, believe that a correction for recirculating background activity is required [11, 18, 19]. For the two different methods of corrected an-alysis under study, background ROIs were drawn, following the *i.v.* injection, over the inter-renal area for one [19] and over

Table 2. – Subject characteristics in nonsmokers and smokers

	Nonsmokers n=8		Smokers n=7		p-value
	Visit 1	Visit 2	Visit 1	Visit 2	NS *vs* S
Age yrs	32±2		46±4		<0.01
FEV_1 L	4.5±0.2	4.5±0.2	3.1±0.5	3.1±0.5	<0.001
% pred	102.8±3.3	102.5±3.4	88.9±8.9	89.1±7.9	<0.05
FVC L	5.4±0.2	5.5±0.2	4.3±0.5	4.2±0.6	<0.01
COHb %	0.9±0.1	1.1±0.1	2.5±0.5	2.8±0.4	<0.001
f_R RR min^{-1}	10±1	9±1	12±1	12±1	<0.01

Values are mean±SEM. NS: nonsmokers; S: smokers; FEV_1: forced expiratory volume in one second: FVC: forced vital capacity; COHb: carboxyhaemoglobin; f_R: respiratory frequency.

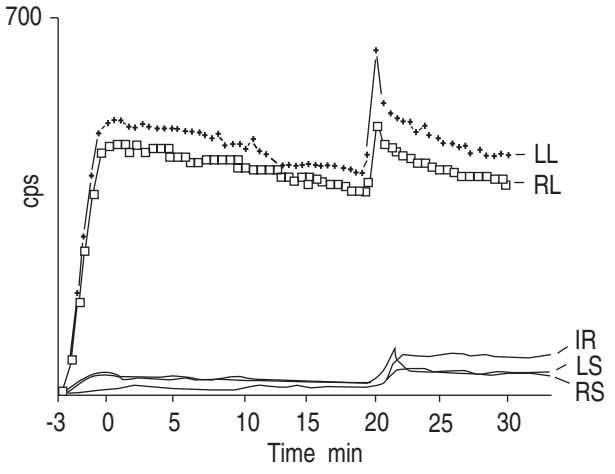

Fig. 1. – Semilogarithmic plot of time *versus* counts per second (cps) for uncorrected right lung (RL) and left lung (LL) curves, and inter-renal (IR), right shoulder (RS) and left shoulder (LS) background regions. An *i.v.* injection of 20 MBq ^{99m}Tc-DTPA was given at 20 min to correct for background activity.

each shoulder, excluding lung tissue, for the other [18]. A correction factor for recirculating background activity was calculated from the ratio of the increase in counts, following the *i.v.* injection, over each lung field and the increase over the appropriate background ROI. Each point in the initial background curves was multiplied by the appropriate ratio. The corrected background curves were then subtracted from the initial uncorrected lung curves. Monoexponential lung clearance for the corrected lung curves was observed and t50 calculated by linear regression analysis of the first 20 min. This comparison is thus between three methods of analysis as they are employed in practice by different groups.

No activity was seen to accumulate in the region of the thyroid gland, which would have indicated the release of free ^{99m}Tc. In one nonsmoker and four smokers thin-layer chromatography of the residual ^{99m}Tc-DTPA in the nebulizer and urine demonstrated 0% and <0.2% dissociation, respectively, into free ^{99m}Tc and DTPA [22].

Statistical analysis

The subject characteristics in the nonsmokers and smokers were compared between the two groups by an unpaired t-test and within the groups, between visits 1 and 2, by a paired t-test.

For comparison, the three methods of analysis were combined, the data were transformed to natural logarithms and a hierarchical analysis of variance was performed. The mean values between visits 1 and 2 were compared for each techique by a paired t-test. Correlation between the uncorrected t50 values and the correction factors for the two corrected methods of analysis was performed by a parametric analysis.

Repeatability of the three methods of analysis was defined according to the single-determination standard deviation and the 95% range of the repeated measurements, as recommended by CHINN [23]. For each of the three methods of analysing the lung clearance of ^{99m}Tc-DTPA the difference between the individual values at visits 1 and 2 was found to be related to the mean of these values. The data were therefore log transformed. The standard deviation of the differences between the log values at visits 1 and 2 was calculated for each method and divided by ± 2 to give the single-determination standard deviation. The 95% range, expressed as $\pm k$, is derived from this as $\pm 2 \times$ the single-determination standard deviation. This may then be antilogged to $\times/\div$ antilog(k) to indicate the limits around a single measurement, on a numerical scale, that must be regarded as possible values for the true measurement [23].

The values expressed in all tables are numerical. A p-value <0.05 was considered statistically significant.

Results

Individual t50 values for right and left lungs are shown in figure 2. Mean t50, r and standard error values and correction factors (inter-renal and shoulder-corrected methods) for the time-activity curves are shown in table 3. The r-values are regression coefficients for the curves and are given to show the tightness of fit to a monoexponential

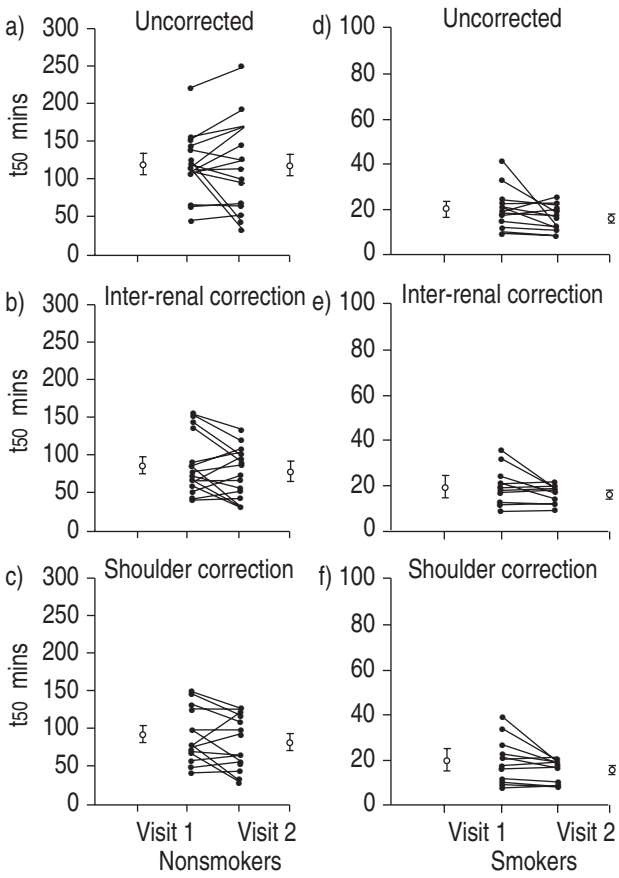

Fig. 2. – ^{99m}Tc-DTPA lung clearance (time to 50% clearance (t50) mean±SE) values at visit 1 and visit 2 in eight nonsmokers (a–c) and seven smokers (d–f) for the three methods of analysis.

line. They are, however, rather insensitive to different qualities of fit around curves with similar slopes and are more sensitive to increases in slope. Thus the r-values for the smokers are better than those for the nonsmokers, whose clearance curves have such a small slope. The combination of r-values and standard error values for the curve fitting provides a better indication of the variation in the data from which the time-activity curves were calculated.

Mean t50 values in nonsmokers were significantly higher than in smokers, with each of the three methods of analysis ($p<0.001$) (table 3). In nonsmokers the uncorrected method gave higher mean t50 values than the inter-renal ($p<0.001$) and shoulder ($p<0.001$) methods of correction. The inter-renal method gave lower values than the shoulder-corrected method ($p<0.05$). In smokers there was no difference between the values obtained between the three methods of analysis. There was no correlation between the uncorrected t50 values and the correction factors for the background-corrected methods of analysis either overall, or in nonsmokers and smokers separately.

There were no significant differences in t50 between the mean values obtained at visits 1 and 2 in either nonsmokers or smokers for any of the three methods of analysis. The repeatability of the three methods of analysis is given in table 4. There was no significant difference between the methods in all subjects or in nonsmokers and smokers separately.

Table 3. – ^{99m}Tc-DTPA clearance from lung to blood in nonsmokers and smokers

		Visit 1								Visit 2							
		Right lung				Left lung				Right lung				Left lung			
		t50	r	SEr	CF	t50	r	SEr	CF	t50	r	SEr	CF	t50	r	SEr	CF
Nonsmokers																	
Uncorrected	Mean	106	0.81	22.7		137	0.76	34.6		110	0.81	24.2		136	0.77	37.7	
	SEM	11.2	0.03	3.61		16.4	0.04	6.61		18.3	0.04	7.33		23.7	0.05	10.8	
Inter-renal	Mean	88.7	0.95	5.15	1.14	88.8	0.96	4.77	1.32	79.4	0.96	4.12	1.08	81.6	0.96	4.39	1.18
	SEM	14.1	0.01	1.54	0.08	14.1	0.01	1.18	0.11	11.3	0.01	1.10	0.04	11.7	0.01	1.24	0.03
Shoulder	Mean	94.8	0.92	7.25	1.34	92.7	0.90	7.37	1.61	84.5	0.94	5.74	1.46	86.0	0.92	6.83	1.59
	SEM	13.0	0.02	1.56	0.12	12.9	0.02	1.42	0.23	13.8	0.01	1.51	0.10	12.7	0.02	1.78	0.08
Smokers																	
Uncorrected	Mean	20.8	0.99	0.88		20.6	0.99	0.67		16.0	0.99	0.58		18.5	0.99	0.81	
	SEM	3.9	0.00	0.30		2.8	0.00	0.11		2.0	0.00	0.11		2.2	0.00	0.19	
Inter-renal	Mean	19.5	0.99	0.48	1.22	19.5	0.99	0.41	1.33	16.7	0.99	0.32	1.05	17.6	0.99	0.38	1.14
	SEM	3.3	0.00	0.16	0.07	2.8	0.00	0.12	0.06	1.7	0.00	0.06	0.08	1.8	0.00	0.05	0.04
Shoulder	Mean	20.3	0.98	0.60	1.78	20.4	0.98	0.62	1.73	16.7	0.98	0.55	1.70	18.0	0.98	0.65	1.74
	SEM	3.9	0.00	0.16	0.11	3.3	0.00	0.17	0.12	1.8	0.01	0.12	0.14	2.0	0.01	0.14	0.07

Values are shown as time (min) to 50% clearance (t50), regression coefficients (r) and their standard errors (min, SEr) for slope and tightness of monoexponential fit to the time-activity curves and the correction factor (CF) values for the curves. Each value is given as mean and SEM.

Table 4. – Single determination standard deviation (s) and 95% range for repeated measurements of t50 according to the three methods of analysis

	All			NS			Smokers		
	U	IR	S	U	IR	S	U	IR	S
s	1.30	1.23	1.24	1.33	1.27	1.29	1.27	1.18	1.19
95% range	1.69	1.51	1.54	1.77	1.61	1.66	1.62	1.40	1.41

The values have been transformed from natural logarithms. All: nonsmokers plus smokers; NS: nonsmokers; U: uncorrected analysis; IR: inter-renal correction; S: shoulder correction.

Discussion

Three methods of analysing the clearance of ^{99m}Tc- DTPA from the lungs to blood were compared, as they are employed in practice. Table 1 shows that the values obtained in previous studies have varied greatly. Although the mechanism of ^{99m}Tc-DTPA transport across the alveolar-capillary membrane is not known, the most important factor affecting ^{99m}Tc-DTPA clearance is thought to be its sensitivity to change in lung volume. It may be increased within 1–2 min of an increase in lung volume [15–17]. This may be due to an increase in the surface area available for clearance of ^{99m}Tc-DTPA, greater access to thinner alveolar capillary membrane, a change in lung surface characteristics, an increase in epithelial permeability, widening of intercellular junctions, recruitment of more permeable lung units, a change in the surfactant layer or increased negative pulmonary interstitial pressure [2, 20]. However, the method of correcting for background activity may also contribute to the wide range of normal values [3, 18, 19]. This study examined the effect of the method of analysis employed on the absolute values and repeatability of ^{99m}Tc-DTPA clearance, in particular the incorporation of a correction for recirculating background activity.

Lung clearance of ^{99m}Tc-DTPA is affected by many other factors. Bronchial absorption of ^{99m}Tc-DTPA is slower than alveolar absorption when mucociliary clearance is taken into account [24]. This may be due in part to binding of ^{99m}Tc-DTPA to mucus [25]. In some studies in humans, clearance has been found to be significantly faster from apical than from basal regions. This has been attributed to the larger alveolar surface area and thus increased permeability in the apices [3]. An anterior-posterior difference has been described in the supine position, with more rapid clearance posteriorly. This is thought to be due to the increased perfusion in the dependent dorsal regions [26]. ^{99m}Tc-DTPA clearance is also affected by increased blood flow [17] and is increased by exercise, perhaps through the recruitment of capillaries [27].

Initial studies in the UK incorporated a correction for recirculating background activity using a second scintillation probe placed over the thigh, with the first collecting activity over the lung [10, 11]. An *i.v.* injection was given to assess the contribution of soft tissue and blood activity. This form of correction assumes that activity collected over a nonthoracic area reflects the situation in the soft tissues and vessels of the thorax and that ^{99m}Tc-DTPA given *i.v.* in this way is distributed in the same fashion as that absorbed through the airspace epithelium. Time is required following the bolus for equilibration with the soft tissues. Background correction by monitoring accumulation in the thigh was validated by BARROWCLIFFE *et al.* [28] in pigs. The left lung was selectively intubated to receive ^{99m}Tc-DTPA and an *i.v.* bolus was given after 30 min. No difference was found in the corrected t50 from the left lung derived from background activity in either the right lung or thigh. Studies performed in North America have not used a correction, since analysis has been confined to the first 7–10 min of the clearance curve [3, 4, 12]. This assumes that insufficient background activity accumulates over this short period to constitute a problem. Measurement of urinary ^{99m}Tc-DTPA excretion or factor analysis can also provide background-free time-activity curves for lung to blood clearance [29].

O'DOHERTY *et al.* [18] used an *i.v.* correction employing a gamma camera technique and background regions over both shoulder areas. They found that the correction factor increased with the permeability of the alveolar capillary membrane. We found no such relationship, presumably because the contribution from the background curve is greater where there is increased lung clearance, regardless of whether a correction factor is applied to it. LANGFORD *et al.*

[19] modified this technique with a background region between the kidneys. They claimed to have found a technique that did not require an *i.v.* bolus, as the increase in activity in the background region was the same as that over the lungs, giving a correction ratio of one. This has, however, not been our experience with this method and we believe that an *i.v.* correction is required with this technique.

Lung clearance of ^{99m}Tc-DTPA may occur by either epithelial absorption or mucociliary transport. Certain methods of measuring epithelial absorption, such as the urinary excretion of ^{99m}Tc-DTPA after inhalation, or the application of factor analysis, may permit the study of the individual components, although clearance by mucociliary transport is too slow to have affected our studies. None the less, in our study we ensured that epithelial absorption was measured, as the optimal particle size for alveolar deposition was used [26, 29].

There was no difference between the three methods of analysis in the t_{50} values obtained in smokers. Previous studies comparing uncorrected and corrected analyses have shown the corrected t_{50} values to be significantly less in both smokers and nonsmokers. However, these studies did not compare the methods as they are used in practice. Uncorrected analyses were performed on clearance curves of 100 min [18] and 20 min [19], rather than the first 7–10 min only. It is likely that uncorrected and corrected t_{50} values for longer duration curves will differ, thus demonstrating the validity of making a background correction on such clearance curves. If uncorrected analysis is restricted to the first 7–10 min of the clearance curve and, as in our study, corrected analysis is performed on clearance curves of 20 min then t_{50} values obtained by the two forms of analysis should agree, if the basic assumptions behind the two techniques are valid. The results confirm that background correction is not necessary if analysis is confined to the first 7 min of the clearance curve, and support the findings of COATES and O'BRODOVICH [30] that background activity has a negligible effect, even on a very short t_{50}. It may, however, be useful to use a background correction in certain special situations, for example where clearance may be biexponential.

Nonsmokers have less background activity than smokers and thus differences between the uncorrected and corrected t_{50} values in the present study are likely to be due to technical factors. In the nonsmokers the clearance curves had such a small slope that the peak activity following inhalation was less sharply differentiated than in the smokers and was thus more difficult to identify. This may explain the higher values obtained by the uncorrected analysis of the first 7 min of the curve in nonsmokers, compared with the corrected values obtained from the first 20 min. The lower t_{50} values obtained from the inter-renal, compared with the shoulder method of correction in nonsmokers, was probably due to the greater vascularity of the inter-renal background.

Previous studies of intra-individual coefficients of variation (CV) have ranged from 7–18% [16, 20, 26, 31, 32]. RIZK *et al.* [17] studied five anaesthetized, paralysed and ventilated dogs using an uncorrected method of ^{99m}Tc-DTPA lung clearance. They found a mean t_{50} of 24.6±5.3 min (±SD), which was not significantly different when repeated at least 72 h later (26.7±7.9 min). There was substantial intra-individual variation but a CV was not quoted. O'DOHERTY *et al*. studied seven nonsmokers and six smokers on two occasions and found that the correction factors were not significantly different between visits [18]. SMITH *et al.* [20] found that the least variability between and within subjects with an uncorrected method was given by monoexponential analysis after inhalation of ^{99m}Tc-DTPA during tidal breathing, followed by scanning for 30 min, compared with vital capacity inhalation of isotope, shorter scanning times and bi-exponential analysis. They found that several vital capacity manoeuvres prior to measuring ^{99m}Tc-DTPA clearance resulted in faster clearance rates for 10–20 min. This was associated with a more rapid curvilinear clearance, suggesting a transient difference in pulmonary permeability, surface area or volume of epithelial lining fluid. They recommended that subjects rest for 20 min prior to inhaling the aerosol of ^{99m}Tc-DTPA to avoid alterations in clearance rates from deep breathing. In normal subjects, intersubject and probably also intra-subject variability is minimized with the delivery of the aerosol supine rather than sitting [20]. This is probably because it reduces the difference in regional clearance rates between upper and lower regions [3, 12]. It has also been reported that keeping the number of ^{99m}Tc-DTPA molecules per number of aerosol particles constant improves intrasubject repeatability [32]. SMITH *et al.* [20] recommended that submicronic particles with a GSD of less than 1.6 μm should be employed to minimize variability. Measurements of tot-al lung projections also improve repeatability [26].

In the present study there was no difference in the mean values for ^{99m}Tc-DTPA clearance between two visits in either nonsmokers or smokers for any of the three methods of analysis. Inhalation of ozone, 0.4 parts per million (ppm) for 2 h, in normal nonsmokers, for example, has been shown to change the t_{50} for ^{99m}Tc-DTPA clearance from 117±16 (SEM) to 40±10 min [8]. Repeatability in our study did not differ between the three methods of analysis or between nonsmokers and smokers. It would have seemed likely that smokers would have greater variability in epithelial permeability over time than nonsmokers, owing to variations in their smoking habit, but this was not observed.

In conclusion, values for technetium-99m diethylenetriamine penta-acetic acid clearance from lung to blood obtained from two background corrected methods of analysis were the same as those from an uncorrected analysis in a group of smokers with values for 50% lung clearance largely >10 min. There was no difference in the repeatability of the technique between the three methods of analysis in either smokers or nonsmokers. Background correction is therefore not necessary if analysis is confined to the first 7 min of a monoexponential clearance curve. It may, however, be useful in certain special situations and further attempts to standardize this and other aspects of the technique are likely to reduce the wide range of results in the literature.

Acknowledgements: The authors thank E. Neal for preparing the manuscript.

References

1. Bernard MC. Lecons sur Les Effete des Substances Toxiques et Medicamenteuses. Paris, Bailliere, 1857; pp. 286–288.

2. Taplin GV, Chopra SK. Inhalation lung imaging with radioactive aerosols and gases. *Prog Nucl Med* 1978; 5: 119–143.
3. Rinderknecht J, Shapiro L, Krauthammer M, *et al.* Accelerated clearance of small solutes from the lungs in interstitial lung disease. *Am Rev Respir Dis* 1980; 121: 105–117.
4. Barrowcliffe MP, Jones JG. Pulmonary clearance of ^{99m}Tc-DTPA in the diagnosis and evolution of increased permeability pulmonary oedema. *Anaesth Intens Care* 1989; 17: 422–432.
5. Robinson DS, Cunningham DA, Dave S, Fleming J, Mitchell DM. Diagnostic value of lung clearance of ^{99m}Tc-DTPA compared with other non-invasive investigations in *Pneumocystis carinii* pneumonia in AIDS. *Thorax* 1991; 46: 722–726.
6. O'Doherty MJ, Van de Pette JEW, Page CJ, Bateman NT, Singh AK, Croft DN. Pulmonary permeability in hematologic malignancies. *Cancer* 1986; 58: 1286–1288.
7. Terra Filho M. Estudo com radioaerosol de DTPA tecnecio 99m em pacientes portadores de pneumopatia por amiodarona. Ph.D. Thesis. Departmento de Cardio-Pneumologia da Faculdade de Medicinea da Universade de Sao Paulo, 1989.
8. Kehrl H, Vincent LM, Kowalsky RJ, *et al.* Ozone exposure increases respiratory epithelial permeability in humans. *Am Rev Respir Dis* 1987; 135: 1124–1128.
9. Lemarchand P, Chinet T, Collignon M-A, Urzua G, Barritault L, Huchon GJ. Bronchial clearance of DTPA is increased in acute asthma but not in chronic asthma. *Am Rev Respir Dis* 1992; 145: 147–152.
10. Jones JG, Minty BD, Lawler P, Hulands G, Crawley JCW, Veall N. Increased alveolar epithelial permeability in cigarette smokers. *Lancet* 1980; i: 66–68.
11. Minty BD, Jordan C, Jones JG. Rapid improvement in abnormal pulmonary epithelial permeability after stopping cigarettes. *BMJ* 1981; 282: 1183–1186.
12. Mason GR, Uszler JM, Effros RM, Reid E. Rapidly reversible alterations of pulmonary epithelial permeability induced by smoking. *Chest* 1983; 83: 6–11.
13. Kennedy SM, Elwood RK, Wiggs BJR, Pare PD, Hogg JC. Increased airway mucosal permeability of smokers. Relationship to airway reactivity. *Am Rev Respir Dis* 1984; 129: 143–148.
14. Oberdorster G, Utell MJ, Morrow PE, Hyde RW, Weber DA. Bronchial and alveolar absorption of inhaled ^{99m}Tc-DTPA. *Am Rev Respir Dis* 1986; 134: 944–950.
15. Nolop KB, Braude S, Royston D, Maxwell DL, Hughes JMB. Positive end-expiratory pressure increases pulmonary clearance of inhaled ^{99m}Tc-DTPA in nonsmokers but not in healthy smokers. *Bull Eur Physiopathol Respir* 1987; 23: 57–60.
16. Nolop KB, Maxwell DL, Royston D, Hughes JMB. Effect of raised thoracic pressure and volume on ^{99m}Tc-DTPA clearance in humans. *J Appl Physiol* 1986; 60: 1493–1497.
17. Rizk NW, Luce JM, Hoeffel JM, Price DC, Murray JF. Site of deposition and factors affecting clearance of aerosolized solute from canine lungs. *J Appl Physiol* 1984; 56: 723–729.
18. O'Doherty MJ, Page CJ, Croft DN, Bateman NT. Lung ^{99m}Tc-DTPA transfer: a method for background correction. *Nucl Med Commun* 1985; 6: 209–215.
19. Langford JA, Lewis CA, Gellert AR, Tolfree SEJ, Rudd RM. Pulmonary epithelial permeability: vascular background effects on whole lung and regional half-time values. *Nucl Med Commun* 1986; 7: 183–190.
20. Smith RJ, Hyde RW, Waldman DL, *et al.* Effect of pattern of aerosol inhalation on clearance of technetium-99m-labelled diethylenetriamine pentaacetic acid from the lungs of normal humans. *Am Rev Respir Dis* 1992; 145: 1109–1116.
21. Brain JD, Valberg PA. State of the art. Deposition of aerosol in the respiratory tract. *Am Rev Respir Dis* 1979; 120: 1325–1373.
22. Zimmer AM, Pavel DG. Rapid miniaturised chromatographic quality control procedures for Tc-99m radiopharmaceuticals. *J Nucl Med* 1977; 18: 1230–1233.
23. Chinn S. Statistics in respiratory medicine 2. Repeatability and method comparison. *Thorax* 1991; 46: 454–456.
24. Barrowcliffe MP, Jones JG, Agnew JE, Francis RA, Clarke SW. The relative permeabilities of human conducting and terminal airways to ^{99m}Tc-DTPA. *Eur J Respir Dis* 1987; 71: Suppl. 153, 68–77.
25. Barrowcliffe MP, Jones JG. Solute permeability of the alveolar capillary barrier. *Thorax* 1987; 42: 1–10.
26. Thunberg S, Larsson K, Eklund A, Blaschke E. ^{99m}Tc-DTPA clearance measured by a dual head gamma camera in healthy subjects and patients with sarcoidosis. Studies of reproducibility and relation to bronchoalveolar lavage findings. *Eur J Nucl Med* 1989; 15: 71–77.
27. Meignan M, Rosso J, Leveau J, *et al.* Exercise increases the lung clearance of inhaled technetium-99m DTPA. *J Nucl Med* 1986; 27: 274–280.
28. Barrowcliffe MP, Otto C, Jones JG. Pulmonary clearance of ^{99m}Tc-DTPA: influence of background activity. *J Appl Physiol* 1988; 64: 1045–1049.
29. Kohn H, Konig B, Klech H, Pohl W, Mostbeck A. Urine excretion of inhaled technetium-99m-DTPA: an alternative method to assess lung epithelial transport. *J Nucl Med* 1990; 31: 441–449.
30. Coates G, O'Brodovich H. Extrapulmonary radioactivity in lung permeability measurements. *J Nucl Med* 1987; 28: 903–906.
31. Oberdorster G, Utell MJ, Weber DA, Ivanovich M, Hyde RW, Morrow PE. Lung clearance of inhaled ^{99m}Tc-DTPA in the dog. *J Appl Physiol* 1984; 57: 589–595.
32. Groth S, Mortensen J, Lange P, Vest S, Rossing N, Swift D. Effect of change in particle number on pulmonary clearance of aerosolized ^{99m}Tc-DTPA. *J Appl Physiol* 1989; 66: 2750–2755.