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Lung clearance of soluble radioaerosols of different molecular weights in systemic sclerosis

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ABSTRACT Clearance rates of soluble radioaerosols of sodium pertechnetate ($^{99m}TcO_4$; mol wt 163) and diethylenetriaminepenta-acetate (^{99m}Tc-DTPA; mol wt 492) were determined in seven normal subjects and ten patients with systemic sclerosis affecting the lungs. Twenty millicuries (mCi) each of $^{99m}TcO_4$ and ^{99m}Tc-DTPA in 5 ml saline were aerosolised and inhaled using a disposable "Blount" nebuliser on two different days. Two regions of interest over each posterior lung field were monitored with a scintillation camera, and data were stored on magnetic tape using a Hewlett Packard Data Analyser. Decreasing levels of radioactivity were plotted semilogarithmically and half-time ($T\frac{1}{2}$) removal rates were calculated. The $T\frac{1}{2}$ values in normal subjects did not differ significantly from $T\frac{1}{2}$ values of the patients with TcO_4. However, the removal rates of the higher molecular weight solute were significantly faster from lower lung zones in patients with systemic sclerosis than in the normal subjects. The faster absorption of DTPA from lower lung zones of the patients could be due to regional abnormalities of alveolar epithelium at the lung bases, presumably as a result of greater retractive forces secondary to fibrosis.

Lung clearance after inhalation of various absorbable radioaerosols was first studied in 1968 as a method for detecting regional impairment of alveolar-capillary membrane diffusion (Taplin and Isawa, 1968). Initial trials were unsuccessful, and further studies were deferred pending the availability of suitable imaging equipment. Recent improvements in aerosol administration and the advent of scintillation cameras capable of rapid sequential lung imaging and data display from selected areas of interest led us to study the clearance of soluble radioaerosols of different molecular weights from the lungs of healthy subjects and patients with systemic sclerosis affecting the lungs.

Methods

SUBJECTS

Seven normal subjects (28–60 years of age, mean 45·1) and ten patients with systemic sclerosis (36–54, mean 47·6) with affected lungs were studied. All patients were non-smokers. The criteria for lung involvement was indicated by a vital capacity (VC) or total lung capacity (TLC) less than 80% of predicted, a single breath carbon monoxide transfer factor (TLCO) less than 75% expected, or roentgenographic evidence of a diffuse interstitial pulmonary process. All patients were currently participating in studies of systemic sclerosis at the UCLA Clinical Research Center. The study was approved by the human subject protection committee, and informed consent was obtained from each subject.

All subjects underwent spirometry, determination of the subdivisions of lung volumes by helium-dilution, TLCO, and static lung compliance using techniques described previously by Bjerke *et al* (1978).

On two separate days radioaerosol lung imaging was performed in the posterior projection after inhalation in the upright position of aerosols of sodium pertechnetate ($^{99m}TcO_4$) (mol wt 163) or

Table 1 *Pulmonary function tests*

Subject No	*Age (years)*	*Sex*	*Forced vital capacity (% pred)*	*Forced expiratory volume (1 sec) (% pred)*	*Total lung capacity (% pred)*	*Transfer factor (% pred)*	*Static compliance (l/cmH_2O)*	*Coefficient of retraction (cmH_2O/l)*
1	37	F	44	53	54	46	0·03	21·1
2	52	F	102	116	128	76	0·14	4·2
3	54	F	103	105	119	65	0·16	4·9
4	49	F	98	98	104	86	0·12	7·6
5	50	F	94	109	105	81	0·14	6·2
6	45	M	65	77	74	65	0·15	8·5
7	46	M	116	133	128	94	0·25	4·5
8	53	F	61	68	80	75	0·13	7·7
9	36	F	38	47	43	22	0·02	20·8
10	54	F	93	96	107	43	0·14	3·7
Mean	47·6		81·4	90·2	94·2	65·3	0·12	8·9
±SD	6·6		27·1	28·1	30·0	22·4	0·07	6·6

^{99m}Tc-diethylenetriaminepenta-acetate (DTPA, mol wt 492). Twenty mCi of either solute were placed in a disposable "Blount" nebuliser that was driven by compressed air or oxygen at a flow rate of about 10 l/min. A six litre plastic reservoir-settling bag was interposed in the inhalation line between the nebuliser and the subject's mouthpiece to remove droplets larger than 2·0 μm, and previous studies in our laboratory have shown the resultant aerosol to consist of 0·5 to 2·0 μm particles. The subjects inhaled the aerosol during normal tidal breathing for two to three minutes or until about 2·0 mCi were retained in the lung. During aerosol administration and for 20 minutes thereafter subjects were seated with their backs against the collimator of a gamma scintillation camera. Imaging data were stored on magnetic tape using a Hewlett Packard Data Analyser. Two regions of interest of equal size were selected over the peripheral portions of the upper and lower lung fields posteriorly on each side. Time-activity curves of decreasing levels of radioactivity were plotted semilogarithmically, and half-time lung removal rates ($T\frac{1}{2}$ values) were calculated during the first ten minutes after aerosol inhalation. These curves were derived from 1 cm×1 cm areas 0·5 cm above the base and below the apex.

Results

Table 1 summarises the results of pulmonary function tests in the ten patients with systemic sclerosis. Seven had a reduction in TLCO, eight had a decreased static lung compliance, and three had a decreased total lung capacity. The normal (control) subjects had completely normal tests of lung function. Patients 4, 5, and 7, whose lung function was not very abnormal, had clear radiographic signs of pulmonary fibrosis.

Table 2 lists the rates of clearance of the lower molecular weight solute, TcO_4, from the lungs.

Table 2 *Sodium pertechnetate (TcO_4) absorption rates ($T\frac{1}{2}$=min)*

Subject No	*Normal subjects*		*Patients with systemic sclerosis*	
	Upper zone	*Lower zone*	*Upper zone*	*Lower zone*
1	8·9	9·8	5·3	10·4
2	8·7	12·3	7·6	10·0
3	4·5	10·7	6·1	8·6
4	7·1	9·0	6·7	12·8
5	9·4	12·1	6·6	10·6
6	10·2	11·8	5·7	7·8
7	7·7	8·9	8·1	10·1
8			5·5	13·3
9			5·0	5·0
10			6·1	8·6
Mean	8·1	10·7	6·2	9·7
SD	1·8	1·4	0·99	2·4
SE	0·68	0·53	0·31	0·76
P value		<0·05*		<0·05*
			NS†	NS‡

*Compared with upper zone in each group (paired *t* test)
†Compared with upper zone of normal subjects (unpaired *t* test)
‡Compared with lower zone of normal subjects (unpaired *t* test)

The $T\frac{1}{2}$ values in normal subjects averaged 8·1±0·68 (SEM) min and 10·7±0·53 (SEM) min from the upper and lower zones respectively. The $T\frac{1}{2}$ values in patients with systemic sclerosis averaged 6·2±0·31 (SEM) min and 9·7±0·76 (SEM) min from the upper and lower lung zones respectively. In both groups the solute cleared significantly more quickly ($P<0·05$, paired *t* test) from upper than lower zones. Absorption rates, however, were not significantly different ($P>0·05$, unpaired *t* test) either from the upper zones of normal subjects compared with the upper zones of systemic sclerosis or from the lower zones of normal subjects compared with the lower zones of patients (fig 1).

Table 3 lists the rates of diffusion of the higher molecular weight solute, DTPA. Its $T\frac{1}{2}$ values averaged 35·1±5·6 (SEM) and 65·0±8·7 (SEM) min from the upper and lower lung zones, respectively, of the normal subjects, whereas $T\frac{1}{2}$ values

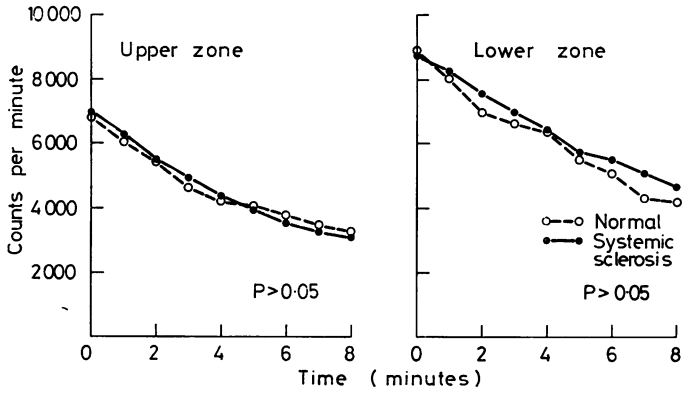

Fig 1 *Time-activity curves from upper and lower lung zones of normal subjects and patients with systemic sclerosis after inhalation of low molecular weight solute (TcO_4). Note that there are no significant regional differences in clearance of solutes in the two groups examined. Values given are mean ± standard error (SEM).*

Table 3 *Tc-DTPA absorption rates ($T\frac{1}{2}$=min)*

Subject No	*Normal subjects*		*Patients with systemic sclerosis*	
	Upper zone	*Lower zone*	*Upper zone*	*Lower zone*
1	29	89	14	30
2	37	91	68	49
3	44	99	8	11
4	26	20	18	64
5	22	38	30	35
6	34	96	14	20
7	19	45	33	64
8	81	66	40	32
9	32	59	24	40
10	27	47	13	34
Mean	35·1	65·0	26·2	37·9
SD	17·7	27·6	17·9	17·1
SE	5·6	8·7	5·7	5·4
P value		<0·05*		<0·05*
			NS†	<0·05‡←

*Compared with upper zone in each group (paired *t* test)
†Compared with upper zone of normal subjects (unpaired *t* test)
‡Compared with lower zone of normal subjects (unpaired *t* test)

averaged 26·9±5·7 (SEM) and 37·9±5·4 (SEM) min from the upper and lower zones, respectively, of the patients with systemic sclerosis. In both groups the absorption rates were significantly faster (P<0·05, paired *t* test) from the upper than the lower zones. The most important finding of this study was that the absorption rates were significantly faster (P<0·05, unpaired *t* test) from the lower lung zones of patients than from the lower zones of normal subjects (fig 2).

The $T\frac{1}{2}$ clearance values for DTPA from the lower zones in systemic sclerosis were not correlated with the lung compliance, coefficient of retraction, or percentage of predicted TLCO (fig 3).

Discussion

The mechanisms involved in the removal of aqueous solutes from the lung are not clearly understood. Particulate material can be removed from the lung by at least three mechanisms—namely, (*a*) mucociliary transport, (*b*) blood capillaries, and (*c*) lymphatics.

The maximum size of the aqueous aerosol droplets produced by the Blount nebuliser-delivery

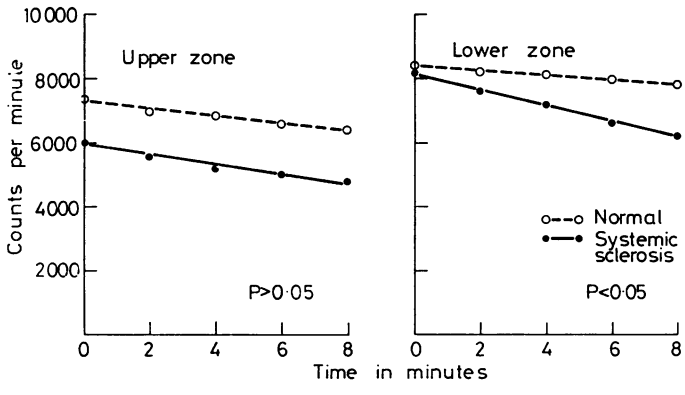

Fig 2 *Time-activity curves from upper and lower lung zones of normal subjects and patients with systemic sclerosis after inhalation of higher molecular weight solute (DTPA). Note that clearance of tracer is significantly faster from lower lung zones of patients. Values given are mean ± standard error (SEM).*

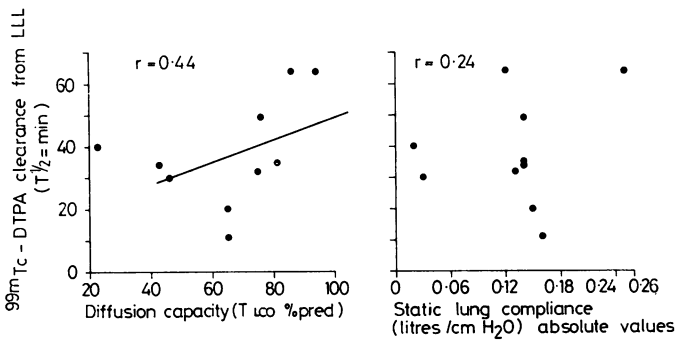

Fig 3 *Graphs showing relation between clearance of DTPA from lower lung zones of patients with systemic sclerosis and (a) transfer factor* (TLCO) *and (b) static recoil pressure. Note that there is a weak inverse correlation with* TLCO *and no correlation with Pst.*

system used in this study is most likely less than 2·0 μm. About 80% of initially deposited *insoluble* aerosols of this size penetrates beyond the ciliated airways and remains in the lungs longer than 24 hours in normal subjects (Morrow *et al*, 1967; Taplin and Chopra, 1978). The rapid removal of radiolabelled *soluble* aerosols from the lungs of our subjects ($T\frac{1}{2}$ values, 6–60 min) is most likely to be accomplished by mechanisms other than mucociliary transport, which requires a much longer time for clearance of activity from the distal tracheobronchial tree.

The faster clearance of both solutes (TcO_4 and DTPA) from the upper than the lower lung zones in normal subjects suggests that the removal of these solutes occurs by mechanisms other than perfusion (which is greater at the bases) and thus differs from the clearance of ^{11}CO, which is partly blood flow related (Taplin *et al*, 1976). The volume of alveolar spaces is fairly uniform throughout the lung at total lung capacity in normal subjects (Milic-Emili *et al*, 1966). At the end of both a normal expiration (functional residual capacity-FRC) and a maximal expiration (residual volume-RV), however, the alveoli in the apical lung regions are larger than those at the lung bases (Milic-Emili *et al*, 1966; Sutherland *et al*, 1968). During tidal volume breathing, the alveolar size decreases approximately linearly with distance down the lung. Therefore, the larger size of alveoli at the apex provides a greater surface area for diffusion of radioactive solutes and may be a factor in the faster diffusion from the upper than from the lower lung zones.

Absorption of radioaerosols may possibly occur via the lymphatics, which play an important part in the removal of many other agents (Leak and Burke, 1968; Meyer *et al*, 1969). The close proximity between the alveolar lymphatics and peribronchial lymphatic plexus as shown by electron microscopy (Casley-Smith, 1964; Leak and Burke, 1968; Lauweryns and Boussauw, 1969) also suggests that the lymphatics may play a part in lung removal of soluble aerosols.

The finding that a smaller molecular weight solute (TcO_4; 163) is cleared from the distal air spaces more rapidly than a larger molecular weight solute (DTPA; 492) in normal subjects is consistent with the hypothesis that the clearance of aqueous solutes through the alveolar epithelium is dependent on molecular size in relation to the size of the pores between the epithelial cells. The more rapid clearance of DTPA from the lower zones in systemic sclerosis compared with normal subjects might be caused by widening of interepithelial junctions, possibly from an increasing retractive force secondary to fibrosis, which predominantly affects the lung bases in systemic sclerosis. No correlation was shown to exist in this study, however, between the rate of DTPA clearance and degree of reduction in static lung compliance. This discrepancy may be explained in two ways—*regional* fibrosis may not give a measurable overall reduction in lung compliance or involvement of the oesophagus in systemic sclerosis may produce spurious abnormalities in the measurement of compliance.

These new observations with soluble agents open another area of investigation with radioaerosols—that is, "cold spot" imaging to detect regional lung abnormalities in patients with interstitial lung disease because clearance of the higher molecular weight solute is faster from diseased than from normal lung.

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