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CLEARANCE OF TC-99M DTPA AEROSOL FROM COAL MINERS' LUNGS*

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Abstract - Alterations in regional epithelial permeability were assessed in 22 retired West Virginia coal miners' lungs by measuring the clearance of inhaled 0.5- μ m Tc-99m DTPA aerosol. Activity was measured in both lungs and in regions of interest placed over the lung periphery in the apical, middle, and basal portions of each lung. Clearance rates ($T_{1/2}$) for 5 nonsmokers, 8 ex-smokers, and 9 smokers were significantly faster ($p < 0.01$) than for comparable subjects measured elsewhere, who were not coal miners. Regional apex-to-base distributions of DTPA were measured as a function of clearance time and compared with regional ventilation and perfusion. Regional, as well as overall lung clearance curves of 8 smokers and 4 ex-smokers had two components, with overall $T_{1/2}$ of < 7 min for the faster one. No correlations were found between $T_{1/2}$ and DLCO or with $P(A-a)O_2$. The results of our study suggest that measurement of DTPA clearance is a potentially useful noninvasive technique to assess lung injury in miners exposed to coal dust.

INTRODUCTION

Alterations in epithelial permeability were assessed in a group of 22 retired West Virginia coal miners by measuring the clearance of inhaled 0.5- μ m Tc-99m labelled DTPA (diethylenetriamine penta-acetate) aerosol from their lungs. This method has the potential to assess the failure or altered ability

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of the alveolar-capillary membranes to act as a barrier to fluid extravasation and/or increased transport of particulates to the interstitium and vasculature (JONES et al., 1980; JONES et al., 1982; HUCHON et al., 1981; RINDERKNECHT et al., 1980). DTPA clearance was also compared with carbon monoxide diffusing capacity (DLCO), alveolar-arterial oxygen gradient ($P(A-a)O_2$), and regional ventilation ($\dot{V}$) and perfusion ($\dot{Q}$).

Clearance of small soluble hydrophilic molecules, such as DTPA (molecular weight - 492 Daltons), is limited by their rate of diffusion across the alveolar-capillary membranes. Up to 90% of the resistance to diffusion is in the epithelium of the alveoli and respiratory bronchioles of the normal lung (STAUB, 1974). DTPA, which passes across the membranes, immediately dissolves in blood. An equilibrium is then established between circulating blood and extravascular fluid. DTPA is finally removed from the body by renal clearance. Acceleration of solute clearance from the lungs is taken to indicate increased epithelial permeability related to lung injury, as, for example, from cigarette smoke.

METHODS

Twenty-two retired West Virginia coal miners participated in this study: 5 life-long nonsmokers, 8 ex-smokers and 9 smokers. BNL Human Studies Review Committee approval and informed subject consent were obtained prior to the studies. Pulmonary function measurements were complemented with nuclear medicine studies, using inhaled Kr-81m, iv-injected Tc-99m MAA, and inhaled Xe-127 to measure regional $\dot{V}$, $\dot{Q}$, and volume (V), respectively.

A nearly monodisperse Tc-99m DTPA aerosol with a count median diameter of 0.59 μm and geometric standard deviation of 1.19, measured with an optical aerosol analyzer (Model 208, Climet Instruments), was administered to each subject (Fig. 1). The aerosol was produced in a small venturi-type nebulizer

(Mark I SynteVent, Synaco, Inc.) with an 8-liter/sec oxygen flow through the reservoir filled with 45 mCi Tc-99m DTPA in a volume of 1-3 ml saline. Following aerosol inhalation for 2-3 min of quiet breathing, the lung burden was estimated to be 150 μ Ci, which corresponded to absorbed radiation doses of 12 and 17 mRads to the lungs and bladder (target organ), respectively. Static images of 50,000-100,000 counts were obtained during inhalation (Fig. 2), while the subjects were sitting with their backs against a LFOV scintillation camera (Series 110, Ohio Nuclear Inc.) interfaced to a dedicated computer system (PDP 11/34 Gamma-11, Digital Equipment Corp.). A low-energy, all-purpose collimator with a 25% window centered over the 140-keV Tc-99m energy peak was used. Our earlier studies (SUSSKIND et al., 1985) had shown that this 0.5- μ m size aerosol behaved like a gas and penetrated into all regions of the lung.

Tc-99m activity was measured on a pixel-by-pixel (6.5-mm x 6.5-mm lung area) basis every minute for 25 min, corrected for decay, and plotted against time on a semilog scale. The rate of clearance from the lungs was computed from the initial slope of the least-squares-fit regression line, and expressed as the half-time ($T_{1/2}$). Because early data were used to determine $T_{1/2}$, 5-10 min for subjects with fast clearances and up to 20 min for those with slower clearances, no corrections were made for the contribution of Tc-99m activity in the circulating blood. The change in Tc-99m DTPA activity was measured in both lungs, as well as in regions of interest placed over the lung periphery in the apical, middle, and basal portions of each lung. Regional distribution and clearance of DTPA were also measured in 6.5-mm horizontal lung slices between apex and base. The apex-to-base DTPA distributions per lung slice were then plotted as a function of lung position at various post-inhalation times.

The procedures for measuring $\dot{V}$ and V using Kr-81m and Xe-127, respectively, have been described previously (SUSSKIND et al., 1981). Measurements of DLCO, $P(A-a)O_2$, and pulmonary function were carried out by standard procedures (MORRIS et al., 1984). Pixel-by-pixel counts of Tc-99m MAA and of Kr-81m, acquired as 500,000-count static images for each subject, were corrected for lung volume by dividing each pixel value by the corresponding Xe-127 activity measured after equilibrating a Xe-127/air mixture. Mean values of Tc-99m/Xe-127 and Kr-81m/Xe-127 were approximately equal to $\dot{Q}/V$ and $\dot{V}/V$, respectively, and were calculated for each 6.5-mm horizontal lung slice between apex and base. The respective apex-to-base distributions per lung slice were then plotted as a function of lung position and compared with regional DTPA clearance.

RESULTS

The mean age of the 22 subjects was 56.2y (range: 45-66y) and the mean time since their last exposure to coal dust was 2y (range: 0-19y) (Table I). The respective smoking histories of the ex-smokers and smokers were 20 ± 11 (mean $\pm$ SD) and 31 ± 19 pack-years. Overall $T_{1/2}$ decreased from 62.1 ± 17.4 min for the nonsmokers to 18.1 ± 10.0 min for the smokers; values for the ex-smokers were intermediate at 41.7 ± 20.0 min (Table II). A typical activity-time curve is shown in Fig. 3 (top) for subject 9, a nonsmoker. The regional, as well as overall lung clearance curves of 8 of 9 smokers and 4 of 8 ex-smokers had two components, a very fast one with a mean overall $T_{1/2}$ of 3.0 min (range: 0.3-6.3 min), and a slower one with a mean overall $T_{1/2}$ of 40.8 min (range: 21.6-78.8 min) (Fig. 4). Differences between nonsmokers and ex-smokers and between nonsmokers and smokers were statistically significant at the level of $p < 0.01$ and $p < 0.001$, respectively, as determined by the unpaired Student's t test.

The initial regional deposition of DTPA particles corresponded to the regional distributions of $\dot{V}$ and $\dot{Q}$, corrected for lung volume (Fig. 5). The subsequent change of DTPA distribution with time of clearance is also shown. The $\dot{V}$ and $\dot{Q}$ deficit in the upper right lung of subject 11, resulting from a mass lesion, can be clearly seen. DTPA deposition likewise showed this decrease, which remained throughout the clearance period. Regional clearance was also demonstrated by expressing the results as apex-to-base distributions of the ratio of Tc-99m DTPA activity after 20 min of clearance to that at the end of inhalation (Fig. 6). In the right lung of subject 11, the ratio decreased continuously, while in the left lung the decrease occurred with two different rates. In both lungs, basal clearance was faster than apical. Even though there was an ~30% reduction in $\dot{Q}/V$ in the right lung, this was not sufficient to affect clearance. Subject 9 is shown as an example of a different regional clearance pattern (Fig. 6). His apex-to-base distribution of Tc-99m DTPA activity after 20 min of clearance to that at the end of inhalation increased continuously in the right lung and more abruptly in the lower part of the left lung. Apical clearance in this subject was, therefore, faster in both lungs than that at the base. DTPA cleared faster from the apical regions of the lung in 11 miners (Fig. 3, bottom). However, the difference was not statistically significant, as was the case for normals and some patients not exposed to coal dust (RINDERKNECHT et al., 1980; CHOPRA et al., 1979). Three miners had equal clearance throughout the lungs.

Mean DLCO of miners with two clearance components was lower than that for miners with a single clearance curve, 86 ± 28 vs $107 \pm 36\%$ of predicted. However, the differences were not statistically significant. No correlations were found between $T_{1/2}$ and DLCO or with $P(A-a)O_2$.

DISCUSSION

The most significant factor affecting the movement of air-borne tracers, such as DTPA, from the lung is their ability to dissolve in and then diffuse across lipid cellular membranes (EFFROS and MASON, 1983). It is generally believed that hydrophilic solutes of relatively low molecular weight are largely confined to the extracellular pathways and traverse the junctions between cells. Since it is presumably through these pathways that edema fluid leaks when capillary pressures are increased or injury occurs, these tracers are appropriate indicators of lung injury.

The clearance of DTPA from the lungs of smoking coal miners was significantly faster than that of nonsmokers. This was in agreement with the studies of JONES et al. (1980) and COATES et al. (1983). The overall $T_{1/2}$ of the coal miners were also compared with those measured by COATES et al. (1983) using the same nebulizer for smokers (25.8 ± 12.8 min) and nonsmokers (92.5 ± 15.6 min), who were not coal miners. DTPA therefore cleared significantly faster from coal miners than from both smoking and nonsmoking subjects who were not exposed to coal dust ($p < 0.01$). Consequently, an additional effect due to inhaled coal dust is superimposed on both smoking and nonsmoking subjects. In contrast to the monoexponential DTPA clearance curves of the nonsmoking coal miners, we found that most smokers and ex-smokers had regional, as well as overall lung clearance curves with two components. This presumably indicated more severe damage to the coal miners' alveolar epithelium, and was also found previously in patients with ARDS (JONES et al., 1981; JONES et al., 1983) and in neonates with hyaline membrane disease (JEFFERIES et al., 1984). In our subjects, however, we found no radiographic evidence of edema. DTPA clearance was previously found to be unchanged in patients with obstructive lung disease (RINDERKNECHT et al., 1980; HUCHON et

al., 1982), while it was accelerated in patients with a variety of chronic interstitial lung diseases, including idiopathic pulmonary fibrosis, sarcoidosis and pneumoconioses (RINDERKNECHT et al., 1980), and systemic sclerosis (CHOPRA et al., 1979). Thus, although interstitial lung disease tends to thicken the alveolar-capillary barrier, solute clearance is increased at the same time. This may be due to alterations in the number or size of interepithelial junctions having a more pronounced effect upon solute diffusion than the thickness of the interstitium (EFFROS and MASON, 1983).

We found no consistent difference between relative DTPA clearance from the apical or basal regions of our subjects and their other values of lung function. This was in agreement with the results of patients studied by RINDERKNECHT et al. (1980), but in contrast to those of CHOPRA et al. (1979), and in contrast to the results of normals studied by both groups. They found that DTPA cleared significantly faster from the apical lung regions, presumably because the more expanded apical alveoli provided a greater surface area for diffusion. In coal workers pneumoconiosis, on the other hand, the upper lung regions are often more affected by coal dust than the lower ones, which may explain the reduced upper lung clearance in some of our subjects.

The DTPA aerosol behaved like a gas because of its small particle size; its regional deposition in the subjects' lungs therefore corresponded to the regional distribution of $\dot{V}/V$ (Fig. 5). Uneven regional deposition had no effect upon DTPA clearance, even in the case of gross $\dot{V}$ and $\dot{Q}$ defects due to a mass lesion. Clearance was also relatively insensitive to changes in $\dot{Q}/V$. Even a regional decrease of ~30% was insufficient to change the rate of clearance (Fig. 5). RINDERKNECHT et al. (1980) calculated that perfusion must decrease by a factor of 10 or more before $T_{1/2}$ is significantly affected.

This would cause an increase in DTPA concentration in the local blood pool, with an apparently slower $T_{1/2}$.

Although DLCO was reduced in subjects with two-component clearance curves, the results were not significantly different from those obtained from subjects with single-component curves. Also the fact that no correlation was obtained between DLCO and $T_{1/2}$ was not surprising, since the two processes are different. CO readily penetrates cellular membranes and rapidly combines with hemoglobin in blood. Decreases in DLCO are therefore usually due to maldistributions of $\dot{V}$ and $\dot{Q}$ or to loss of alveolar surface area. Movement of DTPA, on the other hand, is limited to diffusion through interepithelial junctions, and is very sensitive to subtle changes in structure and permeability of the alveolar-capillary membranes. Since maldistributions of $\dot{V}$ and $\dot{Q}$ also determine $P(A-a)O_2$, this helps to explain the lack of a correlation with $T_{1/2}$.

In conclusion, our study has shown that inhaled DTPA clears faster in both smoking and nonsmoking coal miners than in subjects not exposed to coal dust. This appears to indicate the presence of an injury to their lung epithelium, which persists even after they are no longer exposed to coal dust. Measurement of DTPA lung clearance should therefore be evaluated as a potentially useful noninvasive technique to assess early injury in miners exposed to coal dust.

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TABLE I. SUBJECT CHARACTERISTICS

Subject	Age, y	Smoking History, pack-years	RESULTS		
			Chest Radiograph	Pulmonary Function Measurements*	Nuclear Medicine Studies
1	52	33	Old inflammatory disease RLL	OPD	Global nonhomogeneous dist'n of $\dot{V}$ and $\dot{Q}$; $\dot{V}\&\dot{Q}$ defect-RLL
2	45	--	Normal	SAO	Normal
3	58	21	Normal	OPD	Diffuse bilateral $\dot{Q}$ defects; normal $\dot{V}$
4	55	30	Emphysema	OPD	Multiple bilateral $\dot{V}\&\dot{Q}$ defects
5	56	8	q/q 1/2 nodules	Normal	Normal
6	55	13	p/p 2/3 nodules; bilateral emphysematous & fibrotic apical changes	Restrictive disease; SAO	Normal
7	66	72	Emphysema	OPD	Bilateral $\dot{V}\&\dot{Q}$ defects
8	53	5	q/r 2/2 nodules	SAO	Bilateral $\dot{V}\&\dot{Q}$ apical defects
9	63	-	Normal	SAO	Normal
10	57	12	Normal	OPD	Normal
11	56	18	Lesion-RUL; PMF B	OPD	$\dot{V}\&\dot{Q}$ defects-RUL
12	58	40	r/r 2/3 nodules	OPD	Diffuse $\dot{V}\&\dot{Q}$ defects
13	59	20	Emphysema	OPD	Multiple bilateral $\dot{V}\&\dot{Q}$ defects; no $\dot{V}\&\dot{Q}$ in RML
14	47	17	Increased bilateral markings	OPD	Bilateral $\dot{V}\&\dot{Q}$ basal defects; reduced bilateral $\dot{V}$
15	47	26	Normal	OPD	Irregular bilateral unmatched $\dot{V}\&\dot{Q}$ distribution
16	54	38	Normal	OPD	Bilateral $\dot{V}\&\dot{Q}$ apical defects; irregular bilateral $\dot{Q}$ dist'n
17	63	--	Normal	SAO	Matching $\dot{V}\&\dot{Q}$ defect-LLL
18	59	--	Normal	SAO	Matching $\dot{V}\&\dot{Q}$ defect-RUL
19	64	22	q/q 2/1 nodules; RMF B	SAO	Decreased bilateral apical $\dot{V}\&\dot{Q}$
20	53	--	r/r 2/2 nodules	SAO	Normal
21	61	44	Pleural thickening	OPD	Bilateral $\dot{V}\&\dot{Q}$ defects
22	55	20	r/r 1/2 nodules	SAO	Normal

* SAO - small airway obstruction

OPD - obstructive pulmonary disease

TABLE II. CLEARANCE RATES

Overall Lung T _{1/2} , min					
Subject	Single Phase	Two Components		DLCO, % predicted	P(A-a)O ₂ , mm Hg
		Fast	Slow		
<u>NONSMOKERS</u>					
20	40.9			43	16
2	47.7			163	25
9	66.8			120	19
17	72.2			96	25
18	82.9			157	32
Mean±SD	62.1±17.4			116±49	23± 6
<u>EX-SMOKERS</u>					
22	14.7*	2.2	25.4	65	21
11	27.1*	6.3	37.9	112	10
5	31.6*	0.3	43.4	128	38
3	37.9*	2.3	78.8	79	31
6	38.2			95	22
10	42.5			95	15
21	69.0			123	-
19	72.9			81	37
Mean±SD	41.7±20.0	2.8±2.5	46.4±22.9	97±22	25±11
<u>SMOKERS</u>					
15	10.4*	3.1	27.4	58	44
8	10.8*	1.9	33.3	72	33
7	12.2*	2.9	43.7	86	41
16	12.6*	2.1	22.4	99	27
13	13.4*	3.9	21.6	68	36
4	15.4*	2.4	28.5	130	34
12	17.7*	5.2	74.3	38	50
14	32.6*	2.8	52.6	92	32
1	37.8			94	28
Mean±SD	18.1±10.0	3.0±1.1	38.0±18.1	82±27	36± 8

*Slope of least-squares-fit regression line forced into a single curve

FIGURE CAPTIONS

Figure 1. Size distribution of inhaled DTPA aerosol.

Figure 2. Posterior Tc-99m DTPA image of subject 10.

Figure 3. Typical activity-time curves of nonsmoker, subject 9, showing overall lung clearance of DTPA (top) and clearance of individual apical and basal regions in the left and right lungs (bottom). Apical clearance was faster than basal clearance.

Figure 4. Typical activity-time curve of ex-smoker, subject 22, which could be resolved into two DTPA clearance curves.

Figure 5. Apex-to-base regional distribution of DTPA in subject 11, an ex-smoker with a mass lesion in his upper right lung, at the end of inhalation and two different lung clearance times. Topographical distributions of $\dot{V}/V$ and $\dot{Q}/V$ were superimposed.

Figure 6. Apex-to-base variation of the ratio of Tc-99m DTPA activity at 20 min to that at the end of inhalation for subjects 9 and 11. DTPA cleared faster from the basal regions of subject 11 and from the apical regions of subject 9.

^{99m}Tc DTPA ACTIVITY REMAINING IN LUNGS, counts