Additive effects of exposure to silica dust and smoking on pulmonary epithelial permeability: a radioaerosol study with technetium-99m labelled DTPA

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Abstract

Background Increased pulmonary epithelial permeability evaluated by the rate of clearance from lung to blood of the radioaerosol solute technetium-99m labelled diethylenetriamine pentacetate (^{99m}Tc -DTPA) has been reported in smokers and in workers exposed to silica dust. A study was carried out to determine whether there are additive effects of cigarette smoke and exposure to silica dust on clearance rates of ^{99m}Tc -DTPA in ceramic workers.

Methods Thirty one subjects with silicosis were studied, of whom 18 smoked cigarettes and 13 were non-smokers. They had similar histories of exposure to silica dust, and radiological alterations consistent with silicosis. The results from these patients were compared with those from normal subjects and smokers previously studied by the authors.

Results Pulmonary function values were normal in most patients and not significantly different among groups. The median (range) rate of clearance of ^{99m}Tc -DTPA in smokers with silicosis was 4.1 (1.9-12.7) %/minute, which was higher than the rates in non-smoking patients with silicosis of 2.2 (1.1-6.6) %/minute and in smokers without exposure to silica dust of 2.9 (1.6-4.5) %/minute. These differences were more evident and significant when the clearance rates of the lower lobes of the three groups were compared. Clearance rates higher than 3%/minute were much more frequent in smokers with silicosis (85%) than in non-smoking patients with silicosis (15%) and in smokers (40%).

Conclusion In ceramic workers with radiographic changes resulting from exposure to silica dust, there is an additive effect of inhalation of silica dust and cigarette smoking on clearance rates of ^{99m}Tc -DTPA.

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with acute and chronic respiratory disease. Increased rates of clearance of the radio-nuclide technetium-99m labelled diethylenetriamine pentacetate (^{99m}Tc -DTPA) have been reported in infants and adults with the respiratory distress syndrome^{1,2}; in patients with *Pneumocystis carinii* pneumonia,³ systemic sclerosis,⁴ sarcoidosis,^{5,6} and idiopathic pulmonary fibrosis,⁶ and after cytotoxic agents⁷ and amiodarone.⁸ Active cigarette smoking also causes an increase in alveolar epithelial permeability.^{5,10-12} We have recently reported that chronic exposure to silica dust may be related to accelerated clearance rates of this solute, even in the absence of radiographic changes.¹² Since smoking and exposure to respirable free silica dust appear independently to injure the lungs and cause accelerated solute clearance rates, our purpose was to determine if there is an additive effect on ^{99m}Tc -DTPA clearance rates in patients with silicosis who are smokers.

Methods

SUBJECTS

Subjects were selected from 150 ceramic workers^{13,14} who had had prolonged exposure to silica dust that exceeded the permitted threshold value for Brazil.¹⁵ In addition to the occupational history, chest radiographic abnormalities present in each patient confirmed the diagnosis of silicosis. Eighteen smokers with silicosis and 13 non-smoking patients with silicosis were studied, and were compared with a previously studied group of normal smokers and normal subjects not exposed to silica dust.¹² Dust exposure, smoking histories, and anthropometric data were compared between the groups.

PULMONARY FUNCTION TESTS AND CHEST RADIOGRAPHS

Spirometric measurements including forced vital capacity (FVC), forced expired volume in one second (FEV₁) and forced expired flow between 25% and 75% of FVC (FEF₂₅₋₇₅) were analysed as percentages of predicted values.¹⁶ Chest radiographs were classified according to the ILO guidelines¹⁷ by a radiologist experienced in this method and two chest physicians, resulting in a consensus interpretation. The severity of radiographic abnormality was graded as mild if profusion

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Accelerated clearance rates of small inhaled radioaerosol solutes from the lung to the blood have been used as an index of pulmonary epithelial permeability in patients

scores were 1 and moderate if profusion scores were 2 or more.

PULMONARY EPITHELIAL PERMEABILITY

Samples of ^{99m}Tc -DTPA were prepared from kits from IPEN-CENEN (Sao Paulo, Brazil) diluted in 2 ml saline containing more than 98% bound ^{99m}Tc -DTPA. The subject was seated with the back against an Anger gamma scintillation camera (Searle-LFOV) and 740×10^6 Bq (20 mCi) of the radioaerosol was inhaled.

The aerosol generating system has been described in detail previously.^{12,18} A jet nebuliser with a flow rate of 10 l/minute produces an aerosol that passes through a system of two plastic reservoirs that impacts and traps the large particles, resulting in droplets with a mean mass aerodynamic diameter of $1.1 \mu\text{m}$ and a geometric standard deviation of 2.69. Particle distribution was measured with a Battelle 5 stage cascade impactor.¹²

Pulmonary radioactivity was measured in counts per minute in 20 second sequential frames during the two minute inhalation period and for 10 minutes thereafter. Data were stored and processed by computer. Digital images were produced on a colour monitor and eight regions of interest were selected. Six of the regions of interest, representing 20% of the posterior portion of each lung, were selected from the periphery of the upper, middle, and lower regions of each lung.^{6,12} The whole right and left lung regions were also analysed. Regional radioactivity was then plotted against time, and the clearance rate of ^{99m}Tc -DTPA from lung to blood was calculated in units of percentage decline/minute for the first seven minutes of the post-inhalation (washout) period. The negative slope of the logarithm of radioactivity against time on a linear scale was expressed as the clearance rate, k , in units of percentage decline/minute.^{6,11,12} The clearance rate was calculated over a seven minute period to minimise the effect of rising activity in the lung tissue and blood pool.^{6,12} The total clearance rate of both lungs was calculated as the mean rates of the right and left lungs.

This study was approved by the Ethics Committee of Escola Paulista de Medicina

and informed consent was obtained from all subjects. The radiation dose received by each subject for the radioaerosol study and chest radiographic evaluation was 0.35 mSv.

STATISTICS^{19,20}

The anthropometric data and pulmonary function values were analysed by completely randomised analysis of variance (ANOVA) to compare the same variable in the three groups. The Scheffé multiple comparison test was then used to detect the mean values that contributed to the significant F values. Unpaired t tests were used to compare exposure to silica dust and to cigarette smoking between the groups.

As the data were not normally distributed in patients, non-parametric statistics were used in the analysis of regional lung activities and clearance rates of ^{99m}Tc -DTPA. The Kruskal-Wallis one way analysis of variance by ranks was used to compare the same variable in the three groups, and the Dunn multiple comparison test was then used to identify the differences between groups. The Wilcoxon signed rank test was used to compare paired data and the χ^2 statistic to test association. Values of $p < 0.05$ were considered significant. To determine whether the degree of abnormality on the chest radiograph was associated with more rapid clearance rates of ^{99m}Tc -DTPA results in both smoking and non-smoking patients with silicosis with mild chest radiographic scores were compared with patients in the same group with more abnormal chest radiographic findings.

Results

While the smokers were younger than the patients with silicosis, no differences in weight and height were found between the groups. The smoking habits of subjects with and without silicosis were similar at the time of the study (18.2 (1.6) and 21.0 (1.8) cigarettes/day respectively), although the former had a higher cumulative smoking history. Both groups had similar exposures to an atmosphere of respirable dust containing free silica. Spirometric variables were within the normal range, and no differences among groups were observed (table).

Small opacities up to 10 mm in diameter and profusion 1/1 to 3/3 were present on the chest radiographs in both smoking and non-smoking patients with silicosis. Mild abnormalities (p/p 1/1) were present in nine non-smoking and 10 smoking patients with silicosis, and moderate abnormalities occurred in four non-smoking patients with silicosis (p/q 2/2 (two patients), p/p 2/2, and p/p 3/3) and in eight smoking patients with silicosis (p/p 2/2 (three patients), q/r 3/3, t/t 2/2, q/r 2/2, p/q 2/2, and q/q 3/3).

Pulmonary radioactivity was higher in the lower than the upper region in all subjects. A similar regional radioaerosol clearance distribution (ratio of the radioactivity in each region of interest/total radioactivity) was found in the three groups (fig 1). The average

Mean (SE) anthropometric characteristics, smoking history, dust exposure, and pulmonary function tests in the three groups

	Smokers with silicosis	Non-smokers with silicosis	Smokers
Age (years)	40 (2.1)	41 (2.1)	27 (1.2)*
Weight (kg)	74 (1.4)	73 (2.7)	70 (3.8)
Height (cm)	172 (1.8)	169 (1.2)	174 (2.8)
Dust exposure (years)	16.1 (1.7)	19.4 (1.9)	—
Smoking history:			
cigarettes/day	18.2 (1.6)	—	21.0 (1.8)
packs/year	20.4 (2.6)	—	9.7 (1.7)**
FVC (% pred)	98 (2.0)	94 (4.4)	95 (3.0)
FEV ₁ (% pred)	99 (1.86)	98 (5.4)	94 (2.5)
FEF ₂₅₋₇₅ (% pred)	88 (5.8)	99 (11.0)	98 (10.0)

FVC—forced vital capacity; FEV₁—forced expired volume in one second; FEF₂₅₋₇₅—forced expired flow between 25% and 75% of the FVC; % pred—percentage of the predicted value.¹⁷

*Smokers < smokers with silicosis and non-smokers with silicosis (ANOVA).

**Smokers < smokers with silicosis (unpaired t test)

Figure 1 Regional radioactivity of ^{99m}Tc -DTPA defined as the activity in each region of interest/total activity in that lung. * $p < 0.05$, upper < lower region; $p < 0.05$ right versus left lung. ■—smokers with silicosis; ■—non-smokers with silicosis; ▨—normal smokers.

clearance rates of ^{99m}Tc -DTPA in smokers with silicosis were faster than in non-smoking patients with silicosis and in smokers. Smokers as a group, and all smokers with silicosis, were abnormal but not different from each other; however, the smokers with silicosis were significantly worse than the non-smokers with silicosis (fig 2).

The mean regional clearance rate of ^{99m}Tc -DTPA was significantly faster in the upper than the lower region in smokers, while there was no difference between upper and lower lung fields in either smoking or non-smoking patients with silicosis (fig 3).

The mean clearance rate in non-smoking patients with silicosis whose chest radio-

Figure 2 Individual and mean values of ^{99m}Tc -DTPA clearance rates, k (inclusive of all lung fields), in smokers with silicosis, non-smokers with silicosis and smokers compared with normal values.¹² The dashed line represents the highest rate of clearance of the normal group. * $p < 0.05$ compared with non-smokers with silicosis.

Figure 3 Upper (U) and lower (L) mean clearance rates of ^{99m}Tc -DTPA in the three groups. * $p < 0.05$ (upper region): smokers with silicosis and smokers > non-smokers with silicosis; * $p < 0.05$ (lower region): smokers with silicosis > non-smokers with silicosis and smokers; † $p < 0.05$: upper versus lower region.

graphic abnormalities were classified as mild was 2.7%/minute, which was not different from those classified as of moderate severity in whom the clearance rate was 2.0%/minute. Similarly, the mean clearance rate in smokers with silicosis with mild radiographic abnormalities was 5.0%/minute, which was not different from those with a classification of moderate severity, whose clearance rate was 4.6%/minute.

Discussion

Smokers have faster clearance rates of ^{99m}Tc -DTPA from the lungs than non-smokers, an effect which is more pronounced in the upper lung regions.^{9,11} We have previously shown that the aerosol clearance rate of ^{99m}Tc -DTPA in non-smoking normal subjects averages 1.2%/minute with a range of 0.8–1.7%/minute.¹² Workers exposed to silica dust may have accelerated clearance rates, with or without radiographic changes.¹² Gellert and coworkers reported similar findings in subjects exposed to asbestos.²¹ The present study indicates that these effects of smoking and silica dust are additive.

Approximately 80% of the particles inhaled by humans are deposited in the lung periphery—this has been interpreted to be the small airways and alveoli.²² Uncertainty remains about the precise deposition of aerosol droplets that are likely to gain water and increase in size. As our subjects had similar regional radioactivity distributions (fig 1) and there were no differences in pulmonary function indices between groups, different deposition is an unlikely explanation for our results. Differences in distribution of ventilation, blood flow, inequalities of ventilation/perfusion, and the level of alveolar deposition are not critical factors affecting the clearance rates of ^{99m}Tc -DTPA.^{6,9,23-25}

Recirculation of the radiotracer within the chest wall and vessels may lead to an underestimation of the clearance rate. This observation was reported when the calculation was performed 20–30 minutes after inhalation in

subjects with faster clearance rates.⁹ Background correction is used by some investigators by simultaneously determining relative activity of the thorax and thigh following intravenous administration of ^{99m}Tc-DTPA,^{10,26} or by measuring background activity in the interrenal area.^{21,27} We did not use background correction for recirculation, but determined the clearance over the first seven minutes after inhalation to minimise effects of rising radioactivity in the chest wall, lung tissue, and vascular tree.^{6,11,12}

Since the first report by Jones *et al*¹⁰ it has been shown that smokers have a faster pulmonary clearance rate of ^{99m}Tc-DTPA, which is not related to spirometric abnormalities or gas exchange.^{9,11,12} Accelerated clearance rate was related to the amount smoked in the preceding days^{11,28} rather than to the total tobacco consumption. Faster clearance rates occur in the upper than in the lower lung regions when studies are performed in the upright position,^{11,12} possibly as a result of greater "stretching" of epithelial pores in the lung apices. In smokers an additional consideration is the effect of inhaled smoke, which, according to the mechanisms of gas distribution, stays longer in the distended apical alveoli and may cause relatively greater changes in these membranes.^{9,29}

The pulmonary clearance rate of ^{99m}Tc-DTPA in patients with pneumoconioses was first evaluated by Rinderknecht *et al*,⁶ who found faster clearance rates in two of three patients exposed to silica dust. We reported abnormal clearance rates in non-smoking subjects exposed to silica with normal or abnormal radiographic findings.¹² Isolated exposure to silica is sufficient to cause abnormal clearance rates of DTPA as seven of 13 non-smoking patients with silicosis had clearance rates greater than the highest clearance rate measured in the normal group. Cigarette smoke and silica cause quite different pathological changes in the lung, and the former injury is rapidly reversible on stopping smoking. We therefore examined whether the patterns of clearance differed between these types of injury (fig 3). In contrast to normal subjects and smokers, both groups of patients with silicosis lost the normal pattern of greater upper lobe than lower lobe clearance. It may be that more widespread abnormalities of DTPA clearance patterns in smokers with silicosis (compared with cigarette smokers without silicosis) are the result of different disposition patterns of the inhaled silica dust particles.¹² Another possibility is disruption of the normal distribution of blood volume, with less recirculation in the apices when studies are performed on normal subjects when seated. In patients with silicosis, scarring of the lung parenchyma may result in the loss of the normally greater blood flow to the bases, a situation unlikely to occur in smokers.

Clinical and epidemiological studies have suggested that silica dust and smoking are additive risk factors leading to chronic bronchitis and chronic airways obstruction.³⁰ The analysis of individual data reinforces this

theory, showing that clearance values greater than 3%/minute were much more frequent in smokers with silicosis (83%) than in non-smokers with silicosis (15%) or in those not exposed to silica dust (40%) (fig 2).

This study shows an additive effect of smoking and exposure to silica dust in increasing epithelial permeability in patients with silicosis who smoke. There was a wide range of radiographic abnormalities, and it might have been expected that prior inflammatory changes may have led to more severe anatomical and physiological abnormalities. It is perhaps surprising therefore that the degree of abnormality found on radiographs was not correlated with the abnormalities of DTPA clearance seen in both smoking and non-smoking patients with silicosis.

Prospective studies will be necessary to understand the prognostic implications of these observations. If, as suggested in the literature,^{7,13,20,21} clearance rates of ^{99m}Tc-DTPA reflect injury to the pulmonary membranes from active inflammation and interstitial lung diseases, smokers with silicosis may be more likely to progress to a complicated form of the disease. This study reinforces the idea that control of smoking is important in minimising the respiratory consequences of silica related illness in exposed working populations.³⁰

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