

The bronchoalveolar epithelial permeability in house painters as determined by Tc-99m DTPA aerosol scintigraphy

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Purpose: Isocyanates are highly reactive chemicals used in a number of industries including paints. Therefore, house painters are known to be at risk for occupational exposure to isocyanates. Our objectives in this study were: (1) to investigate the possible effects of isocyanate exposition on the bronchoalveolar epithelial permeability in house painters by using Tc-99m DTPA radioaerosol lung scintigraphy; (2) to assess whether or not some differences exist between asthmatic and non-asthmatic house painters, and (3) to determine the relationship between Tc-99m DTPA radioaerosol lung scintigraphy and the spirometric measurements, and the work duration of house painters. **Materials and Methods:** Ten non-smoking house painters (28.8 ± 8.8 yrs) and ten healthy volunteers underwent Tc-99m DTPA radioaerosol lung scintigraphy. Following inhalation of radiotracer through a nebulizer for 5 minutes, dynamic scintigrams (1 frame/min, up to 10 min) were taken from both lungs. ROI's were drawn over the both lung area, and time-activity curves were obtained, from which the half-time ($T_{1/2}$) of Tc-99m DTPA clearance was calculated. Spirometric lung function test was measured in all house painters. **Results:** Mean $T_{1/2}$ values (min \pm SD) were 93.74 ± 32.79 for house painters, and 90.96 ± 40.02 for control subjects. There was no significant difference in $T_{1/2}$ values of Tc-99m DTPA clearance between house painters and controls, and between asthmatic and non-asthmatic house painters as well. No correlation was observed between $T_{1/2}$ values of Tc-99m DTPA clearance and spirometric measurements. In house painters, there was a positive correlation between $T_{1/2}$ values of Tc-99m DTPA clearance and work duration ($r = 0.73$, $p = 0.016$). **Conclusions:** Our findings indicate that in house painters, occupational exposure to isocyanates has no effect on bronchoalveolar epithelial permeability, and the rate of Tc-99m DTPA clearance shows no difference between asthmatic and non-asthmatic house painters. The positive correlation between the rate of Tc-99m DTPA clearance and work duration needs to be confirmed in larger cohorts.

Key words: house painters, Tc-99m DTPA aerosol scintigraphy, bronchoalveolar permeability

INTRODUCTION

ISOCYANATES are highly reactive, low-molecular-weight chemicals used in the manufacture of polyurethane foams, varnish, adhesives, automobile and spray paints.¹ Com-

monly used isocyanates are toluene diisocyanate (TDI), methylene diphenyldiisocyanate, and naphthalene diisocyanate. High concentrations of TDI cause an acute inflammatory reaction. Exposure to lower concentrations of TDI induces sensitization in a small percentage of exposed individuals. It has been suggested that repeated exposure to high levels during spills is associated with the development of asthma.² Isocyanates react with proteins to produce an isocyanate protein conjugate; high levels of IgE and IgG antibodies against diisocyanates were detected in the patient's serum; re-exposure to paint sprayed

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on hot metal reproduced the illness. Thus, exposure to isocyanates can elicit hemorrhagic pneumonitis, likely mediated by circulating antibodies (IgG or IgE) and immune complexes.³

The measurement of lung clearance of aerosolized technetium-99m diethylenetriaminepentaacetic acid ([Tc-99m] DTPA) has been used to assess the bronchoalveolar permeability in both smoking and nonsmoking normal subjects and patients.⁴⁻⁸ This hydrophilic molecule crosses the alveolar-capillary barrier and diffuses from the air space into the vascular space, probably passing through the tight epithelial intercellular junctions.^{9,10} The Tc-99m DTPA clearance rate thus provides an index of barrier integrity and has been shown to be in a wide variety of lung disorders.¹¹

The objectives of this study were as follows: (1) to investigate the possible effects of isocyanate exposition on the bronchoalveolar epithelial permeability in house painters by using Tc-99m DTPA radioaerosol lung scintigraphy; (2) to assess whether or not some differences exist between asthmatic and non-asthmatic house painters, and (3) to determine the relationship between Tc-99m DTPA radioaerosol lung scintigraphy and the spirometric measurements, and the work duration of house painters.

MATERIALS AND METHODS

Subjects

We studied ten nonsmoking house painters (mean age; 28.8 ± 8.76 years) and ten healthy volunteers as controls, who were all nonsmokers. Five out of ten house painters had normal findings, other five patients had wheezing, and three patients had sinusitis on questionnaire. Chest x-ray, spirometric lung function test and inhalation scans were performed from all house painters in the same day. Chest x-rays were interpreted by a pneumologist who was masked to the scan results. Average working duration of house painters was 14.9 ± 8.2 years. The study protocol was approved by the Ethical Committee of our hospital. All subjects gave informed and signed consent before entering the study.

The spirometric lung function assessment included the following parameters: (1-s forced expiratory volume [FEV₁], forced vital capacity [FVC], FEV₁/FVC, peak expiratory flow rate [PEF], reversible FEV₁, reversible PEF, and the diffusing capacity of the lung for carbon monoxide (DL_{CO}) measured using Single Breath method in all house painters. An increase in FEV₁ of 12 percent after bronchodilator administration, with a minimum volume change of 200 ml, and an increase in PEF of 15 percent were considered evidences of reversible airway obstruction. A value below 80% of the predicted value was considered abnormal for spirometric measurement. A value below 80% or above 120% was considered abnormal for DL_{CO}.

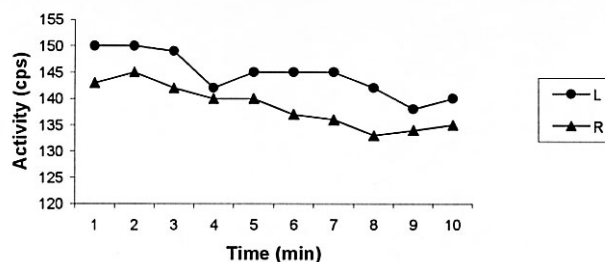


Fig. 1 The time-activity curves of Tc-99m DTPA radioaerosol scintigraphy from right (R) and left (L) lung field from house painter No. 3 was illustrated.

Tc-99m DTPA aerosol inhalation lung scintigraphy

Tc-99m DTPA aerosols were generated from commercial lung aerosol delivery unit (VENTICIS Biodex III) which produces submicronic particles (the mean particle size = $0.5 \mu\text{m}$) containing 1.295–1.48 GBq (35–40 mCi) Tc-99m DTPA in 2–4 ml saline. All subjects were positioned supine and while tidally breathing, each subject inhaled the radioaerosol through a mouthpiece with clipped nose, for 5 minutes. Data were collected for another 10 min by means of a large-field computerized gamma camera (Philips Diagnost, Holland), over the posterior view, which included the entire chest. Immediately after inhalation, dynamic scintigrams were acquired one minute per frame, up to 10 minutes, in 64×64 matrix with word mode. Upon completion of the data acquisition, ROI's were drawn around the periphery of the left and right lung, and the time-activity curves from each lung were generated (Fig. 1) and then the means of half-time ($T_{1/2}$) of Tc-99m DTPA clearance rate for both lungs were calculated.

Statistical analysis

Data are expressed as mean \pm SD. Mann-Whitney U test was used for the comparison of the $T_{1/2}$ values of Tc-99m DTPA clearance. Spearman rank correlation was used to test the relations between $T_{1/2}$ values of Tc-99m DTPA clearance and spirometric measurements, and the working duration of house painters. Significance was set at a $p < 0.05$.

RESULTS

Detailed data of house painters was shown in Table 1. All house painters had normal chest x-ray findings. FEV₁/FVC values were normal in all subjects. FEV₁ values in two patients and PEF values in five patients were abnormal. Three (pts. 7, 9, and 10) of house painters showed early reversibility criteria. The mean of DL_{CO} was $110.9 \pm 25.96\%$. An increase in DL_{CO} was showed in four patients (pts. 1, 3, 4, and 7) of all house painters. Two of them had asthmatic symptom. The mean $T_{1/2}$ values (min \pm SD) were 93.74 ± 32.79 for house painters, and 90.96 ± 40.02 for control subjects. There was no significant differ-

Table 1 Detailed data of house painters

No.	Age/Sex	Work duration (yr)	Symptom	FEV ₁ Lt/(%)	FVC (%)	FEV ₁ /FVC (%)	PEF (%)	rFEV ₁ Lt/(%)	rPEF (%)	DL _{CO} (%)	CR (T _{1/2} min)
1	28/M	13	—	4.04 (110)	105	89	112	4.03 (109)	105	141	69.69
2	45/M	30	Wheezing	2.45 (85)	86	84	87	2.49 (87)	87	94	168.16
3	38/M	22	—	3.35 (93)	95	82	97	3.38 (94)	98	123	101.74
4	29/M	15	Wheezing	2.64 (75)	83	78	61	2.56 (73)	61	127	85.3
5	17/M	4	Wheezing	3.20 (87)	86	79	87	3.21 (87)	85	82	58.77
6	23/M	10	—	4.13 (98)	104	80	77	4.10 (97)	82	103	88.31
7	25/M	10	Wheezing	3.36 (78)	80	83	67	3.57 (83)	67	158	46.17
8	30/M	18	—	3.17 (93)	94	85	72	3.29 (96)	77	110	89.79
9	18/M	5	—	3.66 (87)	87	85	77	3.86 (92)	77	80	94.33
10	35/M	22	Wheezing	3.19 (85)	92	79	96	3.39 (91)	105	91	100.19

rFEV₁; reversible FEV₁, rPEF; reversible PEF, CR; T_{1/2} values of Tc-99m DTPA clearance.

ence in the T_{1/2} values of Tc-99m DTPA clearance between the house painters and control subjects. The difference between asthmatic and non-asthmatic house painters was not significant. We observed a positive correlation between the T_{1/2} values of Tc-99m DTPA clearance and the working duration of house painters ($r = 0.73$, $p = 0.016$). No correlation was found between the mean T_{1/2} values of Tc-99m DTPA clearance and the spirometric measurements in house painters.

DISCUSSION

The lung parenchyma is essentially a three-compartment structure consisting of the alveolar space, the vascular space, and the interstitium. The integrity of these compartments is fundamental to the maintenance of normal gas exchange. Small aerosols can move across these compartments via transcellular and intercellular routes.^{12,13} The rate of clearance of Tc-99m DTPA aerosol was an index of lung epithelial permeability and the technique, although non-specific, is rapid, easy to perform and extremely sensitive in the detection of lung damage.

House painters are at risk for the occupational exposure to isocyanates. Exposure to TDI—the most chemically reactive isocyanate—is most frequently associated with the development of asthma. Overall 5 to 30 percent of exposed workers are reported to develop airway symptoms.¹⁴ In our study group, five house painters had airway symptoms and signs. Isocyanates cause asthma by inducing intense airway inflammation.¹⁵ Bronchoalveolar lavage studies have demonstrated increased numbers of neutrophils and eosinophils in the airways of subjects with asthma due to isocyanates, particularly those that manifest a late airway reaction upon controlled exposure. Bronchial biopsies of affected patients also show intense inflammation, much of which is lymphocytic. There are studies suggesting that isocyanates may interact directly with elements, which modulate inflammation. Because these compounds are very reactive, they may affect membrane receptors or enzymes involved in inflammatory

pathways.¹⁶ Bronchial biopsies of patients with isocyanate-induced asthma have demonstrated inflammatory changes, subepithelial fibrosis and thickening of the basement membrane by collagenization.¹⁷ The simplest and rapid technique to determine the bronchoalveolar permeability alterations is Tc-99m DTPA radioaerosol scintigraphy. In the present study, we observed that the rate of Tc-99m DTPA clearance was normal in all house painters. In addition, there was no significant difference in the rate of Tc-99m DTPA clearance between asthmatic and non-asthmatic house painters. But we found a positive correlation between the clearance rate of Tc-99m DTPA aerosol and work duration of the house painters. Although the clearance rate of Tc-99m DTPA aerosol was normal in house painters, the relationship between the clearance rate of Tc-99m DTPA aerosol and work may be explained environmental factors or long term effects of the other chemicals in paint material.

Our results are in agreement with previous studies in asthmatic patients used Tc-99m DTPA clearance. The pathophysiology of asthma has been investigated with the Tc-99m DTPA clearance technique.^{18–20} Although asthmatics have a marked increase in airway reactivity, the rate of Tc-99m DTPA clearance does not increase. In our study, moreover, the rate of Tc-99m DTPA clearance of five asthmatic house painters did not show any difference other than non-asthmatic house painters. This may be due to the fact that isocyanates cause bronchial changes rather than alveolar changes in house painters. Our results pointed out that the exposure to isocyanates in asthmatic and non-asthmatic house painters did not affect the bronchoalveolar epithelial permeability. Since in our study, there was no correlation between the rate of Tc-99m DTPA clearance and spirometric measurements in house painters, we thought that the increased reactivity of the airway was not associated with the increased bronchoalveolar epithelial permeability. Our results support previous studies in which it was found that an increase in lung epithelial permeability to small solute is not a major determining factor in the pathogenesis of nonspecific airway

hyperresponsiveness in asthma.¹⁹ Lung epithelial permeability can also be assessed by DL_{CO} which can provide an estimate of the rate transfer of that gas from the alveoli into capillary blood. DL_{CO} reflects an abnormality in gas transfer that may be indicative of abnormal diffusion, but it also reflect abnormalities in the gas carrying capacity of blood, the non-uniformity of distribution of physiological properties throughout the lung, the loss of lung tissue, or artifacts in measurement. DL_{CO} is usually normal in asthma.²¹ In this study, we found an increment in DL_{CO} in four house painters, and normal DL_{CO} in other subjects. DL_{CO} is affected by the hemoglobin concentration. In our study, since DL_{CO} was not corrected to hemoglobin concentration, an increase DL_{CO} in four house painters may be due to this reason.

Our findings indicate that occupational exposure to isocyanates in house painters has no effect on bronchoalveolar epithelial permeability, and the rate of Tc-99m DTPA clearance shows no difference between asthmatic and non-asthmatic house painters. The positive correlation between the rate of Tc-99m DTPA clearance and work duration needs to be confirmed in larger cohorts.

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