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Alveolar epithelial permeability in patients with primary spontaneous pneumothorax as determined by Tc-99m DTPA aerosol scintigraphy

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Purpose: Primary spontaneous pneumothorax (PSP) occurs subsequent to a disruption in the continuity of visceral pleura and escape of air into the pleural space. The cause of PSP is most often the rupture of subpleural blebs or bullae. It is usually difficult to detect evidence of pulmonary pathology. The purposes of the present study were (1) to investigate the changes of pulmonary alveolar epithelial permeability in patients with PSP as determined by Tc-99m DTPA aerosol lung scintigraphy, (2) to assess whether or not some differences exist between apical and basal parts of the lungs, and (3) to determine the relationship between the clearance rate of Tc-99m DTPA and the PFT results, the recurrence rate of PSP, and the percentage of pneumothorax in affected lung. ***Material and Methods:*** Thirteen PSP patients (two females, 11 males; mean age 32.5 ± 11.8 years) with normal chest X-ray were studied. Thirteen healthy non-smoking volunteers (1 female, 12 males; mean age, 35.8 ± 10 years) were selected as a control group. Tc-99m DTPA aerosol lung scintigraphy and PFT were performed in all patients and controls. Clearance rates (%/min) of Tc-99m DTPA aerosol in right and left lung field, and apical and basal parts of each lung were calculated from dynamic images for 15 min. ***Results:*** There was no significant difference ($p > 0.05$) between patients and controls, or between apical and basal parts of each lung. No correlation was found between the clearance rate of Tc-99m DTPA and PFT results, the recurrence rate of PSP, or the percentage of pneumothorax. ***Conclusion:*** This study demonstrates that pulmonary epithelial permeability is not altered in PSP patients; the clearance rate of Tc-99m DTPA shows no difference between apical and basal parts of each lung.

Key words: primary spontaneous pneumothorax, pulmonary epithelial permeability, Tc-99m DTPA aerosol lung scintigraphy

INTRODUCTION

PRIMARY SPONTANEOUS PNEUMOTHORAX (PSP) is relatively common disease with an incidence of 4 to 9 per 100,000 population per year in the USA.[1] Typically, young adults developing spontaneous pneumothorax are otherwise healthy with no clinically apparent lung disease. The cause of PSP is most often rupture of subpleural blebs or bullae, which are usually located in the apex of the lung.[2] They have been attributed to intrinsic abnormality of connective tissue (e.g., Marfan's syndrome), to inflammation of the bronchioles, or to overdistension of alveoli with poor collateral ventilation. In addition, it has been hypothesized that oxidative stress might have a role in the pathogenesis of PSP.[3] Radioaerosol inhalation lung imaging with Tc-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) is well recognized as a sensitive tool for the study of pulmonary epithelium integrity.[4,5] The clearance of Tc-99m DTPA across the epithelial surface of distal airways and the lung parenchyma was assessed non-invasively by external detection. The clearance rate of small radiolabeled solutes from pulmonary tissues under normal conditions is linear, with clearance half-times (t_{50}) of < 100 min. It has been generally assumed that the clearance Tc-99m DTPA follows a simple first-order process and solute clearance through the respiratory

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epithelium and into the blood and lymphatic channels is complete within a few hours.[6] The purposes of the present study were (1) to investigate the changes of pulmonary alveolar epithelial permeability in patients with PSP as determined by Tc-99m DTPA aerosol lung scintigraphy, (2) to assess whether or not any differences exist between apical and basal parts of the lungs, and (3) to determine the relationship between the clearance rate of Tc-99m DTPA and the PFT results, the recurrence rate of PSP, and the percentage of pneumothorax in affected lung.

MATERIAL AND METHODS

The study population consisted of 13 patients (two females, 11 males; mean age 32.5 ± 11.8 years), who had been diagnosed and treated for PSP in the past (of these 13 patients the most recent pneumothorax case was seen at least 12 months earlier) in the department of chest disease of our hospital. They had normal chest X-ray findings at the time of the study, and 9 non-smoking patients, and 4 patients ceased smoking for at least a year were recruited for the study. They had smoked for a mean 14 pack-years. Of these 13 patients, three patients had two times and one patient had three times recurrence after a PSP. The percentage of pneumothorax was estimated as the degree of collapse (PNX%) by measuring average diameters of the lung and hemithorax, cubing these diameters, and using the following equation: $PNX\% = 100[1 - lung^3/hemithorax^3]$. As a normal control group, 13 healthy non-smokers (one female, 12 males; mean age, 35.8 ± 10 years) and without a previous history of lung disease were studied. Chest X-ray, spirometric pulmonary function tests (PFT), and radioaerosol lung scintigraphy were performed for all PSP patients on the same day. The study protocol was approved by the Ethics Committee of the hospital. Informed consent was obtained from all individuals prior to participation in the study.

The spirometric PFT included the following parameters: 1-s forced expiratory volume [FEV_1], $FEV_1\%$, forced vital capacity [FVC], FVC%, FEV_1/FVC, mean forced expiratory flow during the middle of FVC [$FEF_{25-75}\%$], peak expiratory flow [PEF%], the diffusing capacity of the lung for carbon monoxide (DL_{CO}), and $DL_{CO}\%$ measured using Single Breath method in patients with PSP. 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}.

Tc-99m DTPA was prepared from a freeze-dried kit according to the manufacturer's instructions. The quality

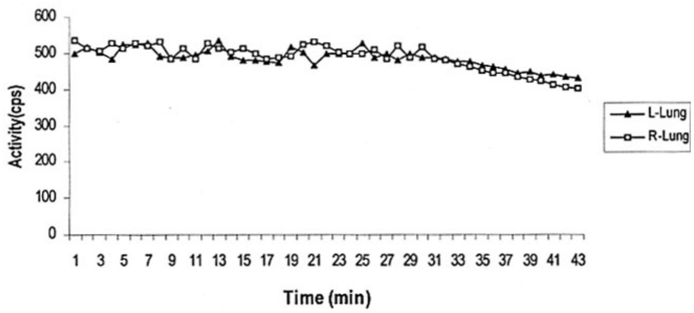

Fig. 1 The time-activity curves of Tc-99m DTPA aerosol scintigraphy from right (R) and left lung (L) field from a PSP patient are illustrated.

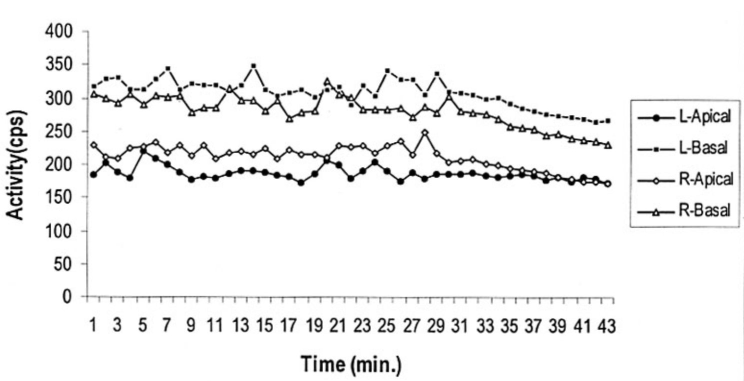

Fig. 2 The time-activity curves of Tc-99m DTPA aerosol scintigraphy from apical and basal parts of right (R) and left lung (L) field from the same PSP patient are illustrated.

Table 1 The recurrence rate (RR), side of affected lung, and percentage of pneumothorax in affected lung (PP), pulmonary function tests (PFT)

No	Age/sex	RR	Side	PP%	FVC	FVC%	FEV_1	FEV_1%	FEV_1/FVC	FEF_{25-75}	PEF%	DL_{CO}	DL_{CO}%
1.	20/M	1	Left	100	6.85	123	6.28	135	92	7.13	96	41.8	111
2.	36/M	1	Right	100	4.88	108	4.06	107	83	4.28	105	22.2	71
3.	24/M	1	Right	30	4.51	85	4.47	100	99	6.14	68	24.4	67
4.	29/M	1	Right	30	5.12	89	4.59	97	90	5.3	54	28.2	73
5.	41/M	2	Right	100	4.32	96	3.76	101	87	4.55	81	34.1	110
6.	38/M	1	Right	20	4.15	82	4.14	100	100	5.72	68	40.3	118
7.	45/M	2	Right	60	5.6	113	4.3	107	77	3.9	70	23.4	70
8.	21/M	1	Right	15	5.57	96	5.12	106	92	5.77	65	30.7	78
9.	60/M	3	Right	20	2.74	70	2.63	85	96	3.87	64	18.5	70
10.	30/M	1	Left	100	7.67	138	6.16	135	80	6.24	91	44.5	119
11.	25/M	1	Right	100	3.92	75	3.89	88	99	6.21	70	36.9	103
12.	18/F	1	Right	20	4.31	87	3.66	87	85	4.86	70	27.6	80
13.	35/F	2	Right	30	4.06	92	3.19	85	79	3.39	82	28.1	91

control of Tc-99m DTPA was performed using instant thin-layer chromatography. The Ventiscan Biodex III aerosol delivery system, which produces submicronic particles (the mean particle size = 0.5 μm) containing 1.295–1.48 GBq (35–40 mCi) Tc-99m DTPA in 2–4 m*l* saline, was used. Patients in the sitting position inhaled the radioaerosol for 5 min at normal tidal breathing and then were disconnected from the system. Immediately after the inhalation, scintigraphic data were recorded dynamically at 2-second intervals for the first minute, and 1-minute intervals for the remaining 14 minutes (1 frame/min) in posterior projection on a 64 × 64 matrix using a single-headed rotating gamma camera (Siemens Orbiter). The camera was set with a 20% window around the peak energy of Tc-99m and shielded by a low-energy all-purpose collimator. Clearance of Tc-99m DTPA from the lung was then monitored over a 15-min period, and the computer for subsequent analysis stored lung images. Upon completion of the data acquisition, regions of interest (ROIs) were drawn around both the periphery of the right and left lung, and apical and basal parts of each lung. The time-activity curves derived from ROIs over the right and left lung (Fig. 1), and the apical and basal parts of each lung (Fig. 2). In this way, the mean rate of clearance of radioactivity for the right and left lung, and apical and basal parts of each lung was calculated as percent per minute. The clearance rate was expressed in terms of the percentage decrease in Tc-99m DTPA activity per minute (%/min) due to pulmonary alveolar epithelial permeability.

Statistical analysis

The statistical analyses were performed using the SPSS/PC (version 10.0) software package. Values are expressed as means (SD) and statistical significance level of 0.05 was used. Mann-Whitney U test was used for comparison of $T_{1/2}$ values between PSP patients and the control subjects. Wilcoxon test was used for the comparison of $T_{1/2}$ values between apical and basal parts of each lung. The $T_{1/2}$ values of Tc-99m DTPA clearance were correlated with the results of PFT, the recurrence rate of PSP, and the percentage of pneumothorax in affected lung by the Spearman rank correlation test.

Table 2 The clearance rate of Tc-99m DTPA aerosol lung scintigraphy: comparison between PSP patients and control subjects

	Clearance rate $T_{1/2}$ (%/min)	
	PSP patients (n = 13)	Controls (n = 13)
Right		
Total lung	59.7 ± 19.5	67.67 ± 13.02
Apical lung	78.1 ± 37.9	76.75 ± 18.7
Basal lung	67.4 ± 35.5	62.01 ± 16.6
Left		
Total lung	64.8 ± 40.1	73.63 ± 16.5
Apical lung	125.4 ± 164.3	121.3 ± 138.9
Basal lung	103.3 ± 131.8	64.5 ± 14.9

For all Mann-Whitney U tests, $p > 0.05$

RESULTS

Detailed clinical data and the results of PFT in patients with PSP were shown in Table 1. There was no significant difference in the mean $T_{1/2}$ values for total, apical, and basal lung between PSP patients and the control subjects. These results were shown in Table 2. In addition, we did not find any significant difference in the mean $T_{1/2}$ values between the apical and basal parts of each lung in PSP patients. No correlation was found between the mean $T_{1/2}$ values of Tc-99m DTPA clearance and the recurrence rate of PSP, the percentage of pneumothorax in affected lung, or the spirometric measurements in PSP patients. When the results of PFT between PSP patients and the controls were compared, there was a significant difference in FEV_1 ($p = 0.022$), FEV_1/FVC ($p = 0.023$), $DL_{CO}\%$ ($p = 0.018$), respectively.

DISCUSSION

PSP occurs predominantly at rest in tall, thin individuals with an average age of 15 to 30 years.[7] Males are usually more commonly afflicted than females as in our study. These patients are mildly symptomatic due to their otherwise normal lungs and pulmonary reserve. Frequent thoracoscopic evaluation of PSP reinforces the observation that this disorder is regularly associated with apical subpleural blebs or bullae. The presence of apical blebs or bullae has previously been described in this group of patients,[8] and likely constitutes the basis for recurrence in most patients. Mostly, PSP is attributed to rupture of a subpleural bleb or bulla. The etiology of bulla and bleb formation is obscure. The high incidence of adhesions suggests that an inflammatory reaction has preceded the event of PSP. These adhesions were found significantly more frequently in patients with blebs or bullae than in patients with a macroscopically normal lung.[9] This observation supports the hypothesis that an inflammatory process is involved in the etiology of blebs and bullae. In the study of Lichter and Gwynne,[10] chronic inflammation was found in most of the resected specimens of their patients with a pneumothorax.

The cause of air leakage in patients with PSP is unknown although several internal (local ischemia, impaired ventilation, increased transpulmonary pressure) and external (smoking, inactivity, atmospheric pressure drops) factors have been postulated.[11–16] Bens et al.[12] found blebs and bullae in 81% of nonsmokers with PSP. Boutin[17] has postulated that blebs and bullae are the result of a degenerative process of the lung and grow with age. In addition, it has been hypothesized that oxidative stress might have a role in the pathogenesis of PSP.[3]

Integrity of the three compartments consisting of the alveolar space, capillary space, and interstitium is necessary to main normal gas exchange. Small aerosols can move across the three compartments by means of transcellular and intercellular route compartments.[18,19] Tc-99m DTPA aerosol lung clearance half time can express an index of alveolar epithelial permeability change, and it is a highly sensitive tool with a wide spectrum for detecting lung injuries, even those of a mild degree.[20–22]

In the current study, we sought to determine the changes of pulmonary alveolar epithelial permeability in patients with PSP by using Tc-99m DTPA aerosol lung scintigraphy. The study was conducted with the idea that if an inflammatory or a degenerative process of the lung is involved in the etiology of blebs and bullae in PSP,[9,10,17] then Tc-99m DTPA aerosol lung scintigraphy could be used to determine the changes of pulmonary alveolar epithelial permeability. However, we did not find any significant difference in the pulmonary epithelial permeability between PSP patients and the controls demonstrable by Tc-99m DTPA aerosol lung scintigraphy. Furthermore, in PSP patients, we found no difference in the clearance rate of Tc-99m DTPA between the apical and basal parts of the lungs. It was also reflected that there were no gravity gradient effects for the clearance rate of Tc-99m DTPA aerosols.[23] In addition, we thought that the differences in FEV_1, FEV_1/FVC, and $DL_{CO}\%$ values in patients with PSP resulted from the 4 patients who ceased smoking. We know that lung epithelial permeability typically increases in smokers, but returns to normal values over a 4-week period after smoking has ceased.[24] In our study, although the clearance rate of Tc-99m DTPA was normal, FEV_1, FEV_1/FVC, and $DL_{CO}\%$ values did not return to normal in these patients. Abnormal values of FEV_1, FEV_1/FVC, and $DL_{CO}\%$ indicate obstructive involvement. We think that ex-smokers in our study might have pulmonary emphysema, although they had normal chest X-ray findings. Sanders et al. showed that CT could depict mild pulmonary emphysema even in cases in which chest X-ray shows only normal findings.[25]

The clearance rate of Tc-99m DTPA in our study was not related to the spirometric measurements. This finding is consistent with the results of previous studies.[26] In addition, we found no relation between the clearance rate of Tc-99m DTPA and the recurrence rate of PSP, or the percentage of pneumothorax in affected lung.

In conclusion, we showed in this study that pulmonary epithelial permeability is not altered in PSP patients as determined by Tc-99m DTPA aerosol lung scintigraphy. The clearance rate of Tc-99m DTPA is similar in the apical and basal parts of each lung in PSP patients. The clearance rate of Tc-99m DTPA does not show any relation with the recurrence rate of PSP, or the percentage of pneumothorax in affected lung in PSP patients.

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