Annals of Nuclear Medicine Vol. 19, No. 6, 455–460, 2005

Detection of alveolar epithelial injury by Tc-99m DTPA radioaerosol inhalation lung scan in rheumatoid arthritis patients

Berna Okudan,* Mehmet Şahin,** Feride Meltem Özbek,* Ali Ümit Keskin*** and Erkan Cüre**

*Nuclear Medicine Department and **Internal Medicine/Immunology Department, Suleyman Demirel University, School of Medicine, Isparta, Turkey
***Biomedical Engineering Department, Yeditepe University, Istanbul, Turkey

Rheumatoid arthritis (RA) is a systemic autoimmune disorder primarily involving the joints. Lung alterations in RA may be primary or secondary to pharmacological treatments and may involve the alveoli, interstitium, airways and/or pleura. Technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) aerosol inhalation scintigraphy is a sensitive and noninvasive test commonly employed to assess pulmonary epithelial membrane permeability. The purpose of the this study was a) to investigate the changes of pulmonary alveolar epithelial permeability in patients with RA, b) to determine the relationship between the clearance rate of Tc-99m DTPA and pulmonary function test (PFT) results, and c) to determine the relationship between the clearance rete of Tc-99m DTPA and clinical parameters of disease. Twenty-five patients with RA but without lung alterations were included in the study. The patients were 22 females, and 3 males; mean age 53.6 ± 8.7 years. Technetium-99m DTPA aerosol inhalation scintigraphy was performed on the study and healthy control groups. Clearance half times ($T_{1/2}$) were calculated by placing a mono-exponential fit on the curves. Penetration index (PI) was calculated on the first-minute image. There were no significant differences in the mean $T_{1/2}$ or mean PI values between the RA patients and control subjects. No correlation was found between the mean $T_{1/2}$ values of Tc-99m DTPA clearance and activity of RA, clinical values, or the spirometric measurements except FEV_1/FVC and functional status in RA patients ($p = 0.02$, $p = 0.01$, respectively). However, a weak correlation was found between duration of disease and $T_{1/2}$ values of Tc-99m DTPA clearance ($p = 0.006$). PI values tended to correlate with $FEF_{25–75}$, although, this was not statistically significant ($p = 0.057$). This study shows that no changes occur in alveolar-capillary permeability in RA patients without lung alterations.

Key words: Tc-99m DTPA aerosol inhalation scintigraphy, clearance, rheumatoid arthritis, alveolar epithelial injury, pulmonary permeability

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder primarily involving the joints. Extra-articular manifestations of RA often include lung involvement with heterogeneous clinical presentation and radiological findings.[1] Autopsy studies reveal that the percentage of RA patients with pathological changes in the lung is significantly higher than that of RA patients with noted clinical symptoms of a lung disease. Lung alterations in RA may be primary or secondary to pharmacological treatments and may involve the alveoli, interstitium, airways and/or pleura.[2] These alterations may significantly impair lung function and some of them are potentially life threatening. Thus, clinical examination and lung function testing should be performed in all patients with RA at the time of diagnosis and during follow-up. Those patients with clinical alterations and/or impaired lung function should undergo a complete diagnostic study.[1–3]

Technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) aerosol inhalation scintigraphy is a

Received December 20, 2004, revision accepted May 27, 2005.

For reprint contact: Berna Okudan, M.D., İstek Lojmanları 19 Mayıs Mah. Hilmipaşa Cad., Uzay Sokak No: 10/7 Kozyatagı-Kadıköy, İstanbul, TURKIYE.

E-mail: okudanb@yahoo.com

simple, sensitive and noninvasive test commonly employed to assess pulmonary epithelial membrane permeability.[4,5] Alterations in lung clearance of Tc-99m DTPA aerosol have been shown in persons who smoke and in those with various lung disorders, as well as in house painters and following blunt chest trauma.[6–8] However, to our knowledge, alterations of pulmonary epithelial membrane permeability have not been described in patients with RA in the literature. 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 purpose of the this study was a) to investigate the changes of pulmonary alveolar epithelial permeability in patients with RA, b) to determine the relationship between the clearance rate of Tc-99m DTPA and pulmonary function test (PFT) results, and c) to determine the relationship between the clearance rete of Tc-99m DTPA and clinical parameters of disease.

MATERIALS AND METHODS

From 2001 to 2004, we selected 80 consecutive patients with RA from a rheumatology department to be included in a prospective study aimed at evaluating alveolo-capillary permeability in RA. Patients who fulfilled the 1987 American College of Rheumatology classification criteria for rheumatoid arthritis were selected for this study.[9] Of these 80 patients, those who had concurrent presence of lung changes precluding an accurate evaluation of airways (including a previous history of chronic obstructive lung disease or lung fibrosis secondary to RA) or the inability to undergo PFT at the same session were excluded from the study. Patients were administered a modified American Thoracic Society Respiratory Questionnaire relating to cough, dyspnea, sputum production, wheeze, past medical problems, and risk factors for respiratory disease such as smoking, medications, occupation, and recreational history.[10] Cigarette consumption was evaluated in pack years (one cigarette pack year = 20/day for 1 yr). Never smokers had smoked less than 20 packs during their lifetime. In this respect, the patients were definite nonsmokers and life-long nonsmokers. In total, remaining 25 patients with RA were included in the study. The patients consisted of 22 females, 3 males; mean age 53.6 ± 8.7 years. Data were obtained regarding ages, duration of disease, smoking history, clinical symptoms and medication of the patients. None of the patients had previously been exposed to silica and none had a chest infection in the previous 3 months. In all 25 patients, standard chest radiographs and high-resolution computerized tomography (HRCT) were evaluated. The HRCT was performed with 1 mm thick sections at 10 mm intervals with prone slices to exclude dependent changes. All patients had normal chest radiographs and HRCT results. The spirometric PFT were performed by Sensorimedics Vitalograph Spirometry. PFT included the

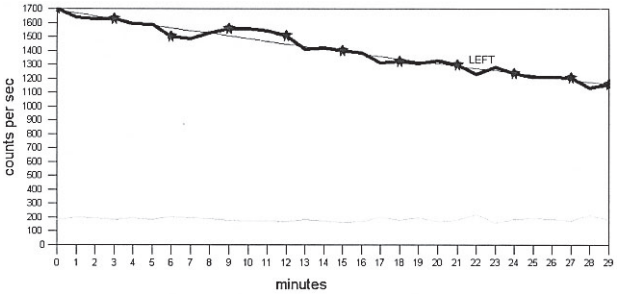

Fig. 1 The time-activity curves of Tc-99m DTPA aerosol scintigraphy from the left lung field from RA patients.

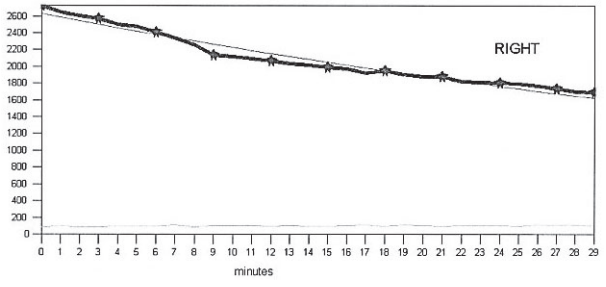

Fig. 2 The time-activity curves of Tc-99m DTPA aerosol scintigraphy from the right lung field from RA patients.

following parameters: Forced expiratory volume in first second [FEV_1], $\%FEV_1$, forced vital capacity [FVC], %FVC, $\%FEV_1/FVC$, mean forced expiratory flow rate during the middle of FVC [$\%FEF_{25–75}$], peak expiratory flow [%PEF]. Results for pulmonary function tests are expressed as a percentage of those predicted for each individual adjusted for age, gender and height. Rheumatological evaluation included the assessment of morning stiffness, number of swollen joints, Stein-brocker functional capacity (range: I to IV, where IV represents maximal disability), Ritchie articular index (RAI) (range: 0 to 78, where 78 represents maximal pressure-induced pain in all joints), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration and rheumatoid factor.[9] The patients were classified as having active disease, as has been previously validated by the presence of three or more of the following; (1) rheumatoid factor positive; (2) ESR ≥30 or CRP ≥20; (3) >2 joint erosions; (4) Ritchie index >12.[11] Of these 25 patients, thirteen patients had active phase and the remaining had inactive disease regarding laboratory measurements. The patients were treated with Methotrexate, Salazopyrine, Cloroquine/Hydroxycloroquine or Leflunomid (Table 1). As a normal control group, 25 healthy nonsmokers were included in the study (18 females, 7 males; mean age, 53.1 ± 8.6 years) and without a previous history of lung disease were studied. Spirometric pulmonary function tests (PFT), and radioaerosol lung scintigraphy were performed for all RA patients and control group on the same day. The study

Table 1 Clinical characteristics of rheumatoid arthritis (RA) patients

Clinical class	
I	9
II	13
III	3
IV	1
Ritchie articular index	4.80 ± 4.17
ESR (mm/h)	36.52 ± 25.87
CRP (mg/*l*)	16.31 ± 20.93
Rheumatoid factor (IU/m*l*)	126.87 ± 145.91
Duration of disease (months)	88.48 ± 52.59
Corticosteroids (n)	22
Methotrexate	13
Salazopyrine	15
Cloroquine/Hydroxycloroquine	7
Leflunomid	8

Table 2 Pulmonary function test (PFT) and Tc-99m inhalation scintigraphy results of patients and controls. Percentage of predicted values (%), one second forced expiratory volume [FEV_1], %FEV_1, forced vital capacity [FVC], %FVC, %FEV_1/FVC, mean forced expiratory flow rate during the middle of FVC [%$FEF_{25–75}$], peak expiratory flow [%PEF]

	RA patients (n = 25)	Controls (n = 25)	P value
Age (years)	53.6 ± 8.7	53.1 ± 8.5	0.72
Gender (M/F)	3/22	7/18	0.16
FVC (%)	86.0 ± 6.3	93.8 ± 16.3	0.18
FEV_1 (%)	89.6 ± 16.1	93.8 ± 18.6	0.24
FEV_1/FVC	86.0 ± 6.3	86.2 ± 8.3	0.60
$FEF_{25–75}$ (%)	102.5 ± 23.9	106.0 ± 36.7	0.90
PEF (%)	368.8 ± 78.2	423.0 ± 83.7	0.05
$T_{1/2}$ (%/min)	59.6 ± 14.83	51.9 ± 17.5	0.21
PI	0.82 ± 0.08	0.82 ± 0.06	0.28

protocol was approved by the Ethics Committee of the hospital. Informed consent was obtained from all individuals prior to participation in the study.

Tc-99m DTPA (Nordion, Belgium) was prepared from a freeze-dried kit according to the manufacturer's instructions. The quality control of Tc-99m DTPA was performed using instant thin-layer chromatography. The Ventiscan Biodex III aerosol delivery system, which produces submicronic particles [mean mass aerodynamic diameter (MMAD), 0.5 μm; geometric standard deviation (GSAD = 1.8)] was used at an O_2 flow rate of 10–12 l/min^{-1}. Four to five milliliters of 1,110 MBq (30 mCi) Tc-99m DTPA were placed into the nebulizer reservoir. Patients inhaled the radioaerosol in the supine position for 4 min at normal tidal breathing and then were disconnected from the system. Approximately 10% of total activity was administered to the patients during the 4 min inhalation. Immediately after the inhalation, scintigraphic data were recorded dynamically (1 frame/min) in posterior projection on a 128 × 128 matrix for a 30 min period using a dual-head gamma camera (Siemens E-CAM), using a low energy high-resolution collimator interfaced to a Siemens Computer System. During the image period, the supine position was preferred to decrease patient motion.

Regions of interest (ROIs) were drawn around the periphery of the right and left lung and on the major airways on the first-minute image. To obtain a pure alveolar ROI and to exclude the entire bronchial activity, the outer third of each lung was used as a peripheral lung region. The inner two-thirds of the lungs were defined as the central lung region. The brightness of the image was increased to visualize body background and the lung periphery. The same peripheral and central ROIs were used as both first and last lung images for each patient to reproduce the ROI drawing at the interval of 1 month. Time-activity curves were generated and corrected for Tc-99m decay. $T_{1/2}$ was calculated by placing a mono-exponential fit on the curves. $T_{1/2}$ of whole lung was calculated as a mean of the $T_{1/2}$ of left lung and right lung. Penetration index (PI) was also calculated by dividing the peripheral total counts by the sum of the peripheral and central total counts on the first minute image, in order to quantify the distribution of the inhaled radioaerosol. Also, scintigraphic data were evaluated regarding distribution of radiotracer in the lungs as diffuse, homogeneous, symmetric or localized distribution. We compared the values of the lung clearance Tc-99m DTPA with the results of PEFR, PI and the laboratory tests.

Statistical analysis: The Mann-Whitney U test was used to compare radioaerosol clearance, PI values and spirometric measurement for data. Spearman test and multiple regression analysis were used for correlations. All analyses were performed using the statistical package SPSS 9.5 for Windows, and a p value less than 0.05 was considered statistically significant.

RESULTS

Detailed clinical data and the results of PFT in the patients with RA were shown in Tables 1 and 2. There was no significant difference in the mean $T_{1/2}$ values between the RA patients and control subjects. In addition, we did not find any significant difference in the mean PI values between RA patients and controls. The mean $T_{1/2}$ values of Tc-99m DTPA clearance did not correlate with activity of RA, clinical values, or the spirometric measurements, except FEV_1/FVC ($r = 0.39$, $p = 0.02$) and functional status in RA patients ($r = 0.18$, $p = 0.01$) (Figs. 3, 4). When the results of PFT between RA patients and the controls were compared, there was no significant difference between the two groups. However, a mild correlation was found between duration of disease and $T_{1/2}$ values of Tc-99m DTPA clearance ($r = –0.37$, $p = 0.006$) (Fig. 5). When the parameters such as age, gender, duration of disease

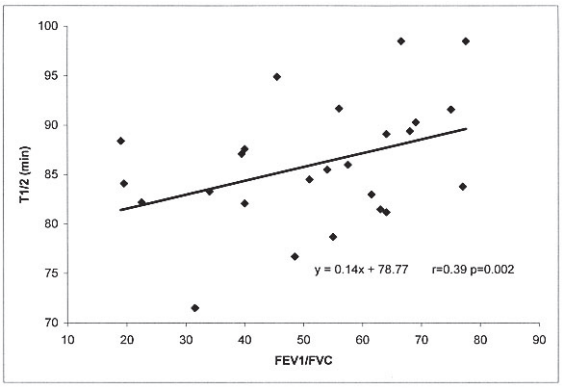

Fig. 3 The relationship between $T_{1/2}$ and FEV_1/FVC. Here, the correlation coefficient (r) is 0.39.

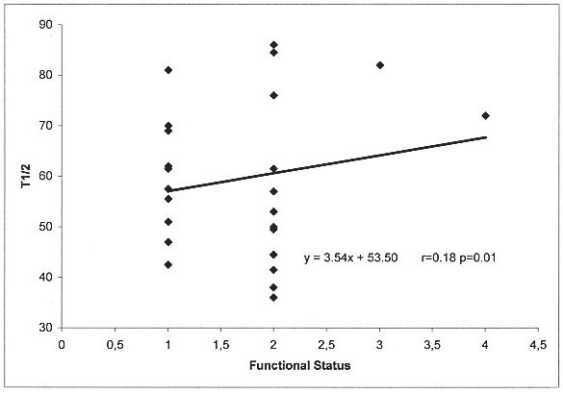

Fig. 4 The relationship between $T_{1/2}$ and functional status of disease. Here, r = 0.18.

and clinical parameters were taken into consideration, PI values tended to correlate with $FEF_{25–75}$, although, this was not statistically significant (p = 0.057) by multiple regression analysis. There was no difference between mean PI and mean $T_{1/2}$ values of Tc-99m DTPA clearance groups regarding activity status of illness.

DISCUSSION

The descriptions of lung involvement, in RA patients, have been reported earlier.[12,13] Most studies report that involvement of the respiratory tract detected by clinical examination or conventional radiology occurs in approximately 20% of RA patients.[14] Moreover, with high resolution CT scanning, lung alterations percentage of RA patients increased to 30–50%.[15] This percentage is dramatically increased up to 70% in post-mortem studies.[16]

As for many other features of this disease, the pathological mechanisms leading to lung damage are poorly understood. Similarly, the influence of genetic and environmental factors on the development and clinical course

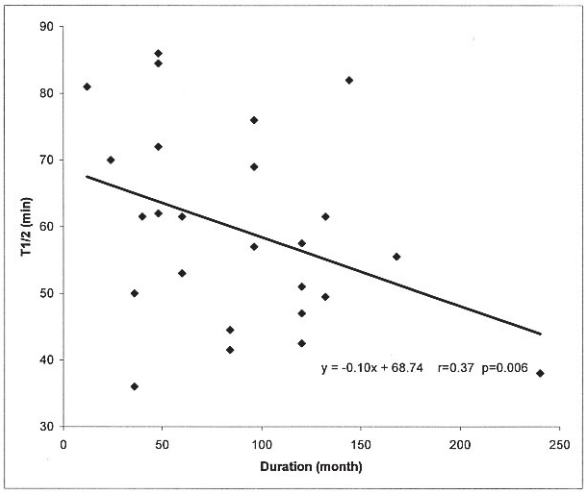

Fig. 5 The relationship between $T_{1/2}$ and duration of disease. Here, r = –0.37.

of the rheumatoid lung is not yet defined.[17] Besides, lung involvement in RA leads to morbidity and the potential occurrence of life-threatening comprications, making it mandatory to evaluate the presence of lung alterations in all patients.[18]

Integrity of the three compartments consisting of the alveolar space, capillary space, and interstitium is necessary to maintain normal gas exchange. Small aerosols can move across the three compartments by means of transcellular and intercellular route compartments.[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.[5,8]

In this study, we tried to determine the changes of pulmonary alveolar epithelial permeability in patients with RA by using Tc-99m DTPA aerosol lung scintigraphy earlier than with other conventional tests. The study was conducted with the idea that if fibrosis or active interstitial inflammation of the lung is involved in the pathophysiology then Tc-99m DTPA aerosol lung scintigraphy could be used to determine the changes of pulmonary alveolar epithelial permeability. We found a difference between RA patients and controls, but it was statistically insignificant, in the pulmonary epithelial permeability demonstrable by Tc-99m DTPA aerosol lung scintigraphy. However, we established a significant correlation between $T_{1/2}$ and FEV_1/FVC. We think that it depends on the obstructive pathology in early stages in RA. This results is correlated with previous studies. Collins et al.[20] indicated that an obstructive pattern was observed in RA. Several studies have reported alterations of respiratory function in RA patients. The functional involvement of the lung in these patients is rather heterogeneous.[21] Linstow et al.[22] reported a reduction of vital and diffusion capacities in their studies, indicating a

restrictive disease; however, other studies have shown a significant incidence of obstructive lung disease.[15,20–22] These functional alterations may not be associated with radiographic changes and in most cases patients are completely asymptomatic. Since obstruction appears to be localized mainly to the small airways, it has been suggested that these functional changes may represent an early phase preceding the development of clinical and/or radiographic evidence of constrictive or follicular bronchiolitis.[23,24] PI values tended to correlate with $FEF_{25–75}$, although, this was not statistically significant ($p = 0.057$). $FEF_{25–75}$ is a well-recognized test for small airway involvement, and single-breath nitrogen washout has been shown to be a highly sensitive test for small airway disease in smokers, preceding spirometric deterioration.[25] The slope of phase III is significantly correlated with the inflammation score for the small airway in smokers.[26] Also, we did not observe a statistically significant difference between $T_{1/2}$ and PI in RA patients and controls. These results might stem from the study group. We selected specifically asymptomatic patients without any abnormality in radiological examination. Furthermore, in RA patients, there were no differences in PFT results from controls. We think that this may depend on slow progression of fibrosis in RA. Usually the course is favorable as compared to that of idiopathic lung fibrosis.[27] The steroid-based treatment of fibrosis in RA patients is the cause of an active inflammatory process.[23,28,29] Besides, bronchoalveolar lavage cytology, as in other autoimmune diseases, shows an increased number of neutrophils, activated macrophages and T cells which may indicate the involvement of the lung in RA patients with negative chest radiograms.[27,30]

CONCLUSION

In this study, we showed that pulmonary epithelial permeability is not altered in RA patients without lung involvement, as determined by Tc-99m DTPA aerosol lung scintigraphy. Also, PI of Tc-99m DTPA is found to be similar in the RA patients and controls. The clearance rate of Tc-99m DTPA shows a relationship with the functional status of the disease. Further studies should be done on patients with symptoms and lung involvement.

ACKNOWLEDGMENT

The authors would like to thank to İsmail Soytemiz (Nordion/Turkey) for his kind support.

REFERENCES

1. Ruddy S, Harris ED, Sledge C. Kelley's Textbook of Rheumatology. In: Harris ED (ed). *Rheumatoid Arthritis. Sixth edition*, Saunders Comp., 2001: 921–1001.
2. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001; 27: 269–281.
3. Triggiani M, Granata F, Giannattasio G, Borrelli I, de Paulis A, Marone G. Lung involvement in rheumatoid arthritis. *Sarcoidosis Vasc Diffuse Lung Dis* 2003; 20: 171–179.
4. Coates G, O'Brodovich H. Pulmonary alveolar capillary permeability and fluid exchange. In: Loken MK (ed). *Pulmonary nuclear medicine*. Los Altos, CA; Appleton and Lange, Inc., 1987: 304–326.
5. Suskind H. Technetium-99m-DTPA aerosol to measure alveolar-capillary membrane permeability. *J Nucl Med* 1994; 35: 207–209.
6. Jones JG, Minty BD, Lawler P, Hulands G, Crawley JC, Veall N. Increased alveolar epithelial permeability in cigarette smokers. *Lancet* 1980; 12: 66–68.
7. Kaya M, Salan A, Tabakoglu E, Aydogdu N, Berkarda S. The bronchoalveolar epithelial permeability in house painters as determined by Tc-99m DTPA aerosol scintigraphy. *Ann Nucl Med* 2003; 17: 305–308.
8. Okudan B, Han S, Baldemir M, Yildiz M. Detection of alveolar epithelial injury by ^{99m}Tc-DTPA radioaerosol inhalation lung scan following blunt chest trauma. *Ann Nucl Med* 2004; 18: 310–315.
9. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Associations 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315–324.
10. Comstock GW, Tockman MS, Helsing KJ, Hennesy KM. Standardized respiratory questionnaires: comparison of the old with the new. *Am Rev Respir Dis* 1979; 119: 45–53.
11. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993; 36: 729–740.
12. Ellman P, Ball RE. A rheumatoid disease with joint and pulmonary manifestations. *Brit Med J* 1948; 2: 816–820.
13. Aronoff A, Bywaters EG, Fearnley GR. Lung lesions in rheumatoid arthritis. *Brit Med J* 1955; 23: 228–232.
14. Cervantes-Perez P, Toro-Perez AH, Rodriguez-Jurado P. Pulmonary involvement in rheumatoid arthritis. *JAMA* 1980; 243: 1715–1719.
15. Cortet B, Flipo RM, Remy-Jardin M, et al. Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Ann Rheum Dis* 1995; 54: 815–819.
16. Harmon KR, Leatherman JW. Respiratory manifestations of connective tissue disease. *Semin Respir Infect* 1988; 3: 258–273.
17. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. *Clin Chest Med* 1998; 19: 667–685.
18. Linstow M, Ulrik CS, Kriegbaum NJ, Backer V, Oxholm P. An 8-year follow-up study of pulmonary function in patients with rheumatoid arthritis. *Rheumatol Int* 1994; 14: 115–158.
19. Dolovich MB, Jordana M, Newhouse MT. Methodologic considerations in mucociliary clearance and lung epithelial absorption measurements. *Eur J Nucl Med* 1987; 13: S45–52.
20. Collins RL, Turner RA, Johnson AM, Whitley NO, McLean RL. Obstructive pulmonary disease in rheumatoid arthritis. *Arthritis Rheum* 1976; 19: 623–628.
21. Banks J, Banks C, Cheong B, et al. An epidemiological and clinical investigation of pulmonary function and respiratory

symptoms in patients with rheumatoid arthritis. *Q J Med* 1992; 85: 795–806.
22. Linstow M, Ulrik CS, Kriegbaum NJ, Backer V, Oxholm P. An 8-year follow-up study of pulmonary function in patients with rheumatoid arthritis. *Rheumatoid Int* 1994; 3: 115–118.
23. Geddes DM, Webley M, Emerson PA. Airways obstruction in rheumatoid arthritis. *Ann Rheum Dis* 1979; 38: 222–225.
24. Hassan WU, Keaney NP, Holland CD, Kelly CA. Bronchial reactivity and airflow obstruction in rheumatoid arthritis. *Ann Rheum Dis* 1994; 53: 511–514.
25. Cosio M, Ghezzo H, Hogg JC. The relations between structural changes in small airways and pulmonary function tests. *N Engl J Med* 1978; 298: 1277–1281.
26. Berend N, Wright JL, Thurlbeck WM, Marlin GE, Woolcock AJ. Small airways disease: reproducibility of measurements and correlation with lung function. *Chest* 1981; 79: 263–268.
27. Rajasekaran BA, Shovlin D, Lord P, Kelly CA. Interstitial lung disease in patients with rheumatoid arthritis: a comparison with cryptogenic fibrosing alveolitis. *Rheumatology (Oxford)* 2001; 40: 1022–1025.
28. Scherak O, Popp W, Kolarz G, Wottawa A, Ritschka L, Braun O. Bronchoalveolar lavage and lung biopsy in rheumatoid arthritis. *In vivo* effects of disease modifying antirheumatic drugs. *J Rheumatol* 1993; 20: 944–949.
29. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. *Arthritis Rheum* 1996; 39: 713–722.
30. Kolarz G, Scherak O, Popp W, et al. Bronchoalveolar lavage in rheumatoid arthritis. *Br J Rheumatol* 1993; 32: 556.