Pulmonary function tests and high resolution computed tomography of the lungs in patients with rheumatoid arthritis

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Abstract

Objective—To compare the results of pulmonary function tests (PFTs) and high resolution computed tomography (HRCT) of the lungs in rheumatoid arthritis (RA) patients.

Methods—Sixty eight patients (54 women, 14 men) fulfilling the revised criteria for RA were consecutively included in a transversal prospective study. Their mean age was 58.8 years (range: 35–82) and the mean duration of the disease was 12 years (range: 5–16). Rheumatoid factor was positive in 52 patients (76.5%). Fifty two patients (76.5%) were lifelong non-smokers. Detailed medical and drug histories were obtained. PFTs comprised spirometry and gas transfer measurements. Results for PFTs were expressed as percentage of predicted values for each individual adjusted for age, sex, and height. HRCT was undertaken with a Siemens Somatom Plus.

Results—A significant decrease of FEV1/FVC, FEF25%, FEF50%, FEF75%, FEF25–75%, and TLCO was observed (p<0.05) and 13.2% of the patients had a small airways involvement defined by a decrease of FEF25–75% below 1.64 SD. The most frequent HRCT findings were: bronchiectasis (30.5%), pulmonary nodules (28%), and air trapping (25%). The patients with small airways involvement had a high frequency of recurrent bronchitis (75% v 34%, p=0.05) and bronchiectasis (71% v 23%, p=0.019). The patients with bronchiectasis were characterised by low values of FEV1, FVC, FEF25–75%, and TLCO (p<0.01), a high prevalence of small airways involvement (29% v 5%, p=0.019), and a low prevalence of HLA DQA1 *0501 allele (14% v 33%, p<0.05).

Conclusion—This study suggests a significant association between small airways involvement on PFTs and bronchiectasis on HRCT in unselected RA patients.

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Rheumatoid arthritis (RA) is a common systemic disease with a prevalence ranging from 0.5% to 2%. Pulmonary involvement is a well known extra-articular manifestation of RA and might be the second cause of death after infection.[1] Although interstitial lung disease is a well known manifestation of RA, small airways involvement may be the commonest form of RA lung involvement.[2–4] Apart from pulmonary function tests (PFTs), other non-invasive tools such as high resolution computed tomography of the lungs (HRCT) have been shown to be of interest in the assessment of rheumatoid lung disease.[5–8] Using HRCT, bronchiectasis seems to be one of the most frequent lung manifestations particularly in patients complaining of respiratory symptoms[8] and its frequency ranges from 20% to 30% according to the authors.[7] [8] However few studies have assessed both the use of HRCT and PFTs in RA patients.[6] [7]

This prospective study aimed to compare HRCT and PFTs in unselected RA patients in the assessment of pulmonary involvement.

Methods

PATIENTS

This prospective study was conducted in one department of rheumatology from October 1994 to January 1996 and included 68 unselected outpatients with RA as defined by the ARA classification.[9] None of the patients had previously been exposed to silica to avoid confusion between rheumatoid and pneumoconiotic lung lesions. The systematic evaluation of their lung changes was approved by the hospital ethics committee and all patients gave written informed consent to participate.

Detailed medical smoking (one pack year = 20 cigarettes daily for one year) and drug histories were obtained. Rheumatological evaluation included the assessment of the following parameters: morning stiffness duration, number of swollen joints, Ritchie articular index ,[10] Steinbrocker classification,[11] health assessment questionnaire,[12] erythrocyte sedimentation rate, C reactive protein concentration, HLA DRB1, DQ A and B genotypes. DRB1 genotype was determined by polymerase chain reaction–restriction fragment length polymorphism method (PCR–RFLP) as proposed by Danzé *et al.*[13] DQ A and B were typed by PCR followed by probing with sequence specific oligonucleotides. The presence of Sjögren's syndrome was diagnosed according to the European criteria.[14] Radiographs of hand were performed to calculate the Larsen's score.[15] Pulmonary evaluation comprised questions about the presence of any respiratory symptom such as dyspnoea, cough or sputum production and a thorough physical examination.

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PULMONARY FUNCTION TESTS

PFTs were performed on the Medical Graphics PF/DX and on the body plethysmography system 1085 (Medical Graphics). PFTs included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow at 25% of the vital capacity (FEF25%), forced expiratory flow at 50% of the vital capacity (FEF50%), forced expiratory flow from 25% and 75% of vital capacity (FEF25–75%), residual volume (RV), total lung capacity (TLC), gas transfer factor measurement (TLCO), and gas transfer factor measurement (TLCO)/alveolar volume (V_A). Observed values were compared with those predicted for age, sex, and height.[16] The results were expressed as percentage. According to the results of PFTs and on the basis of a decrease of PFT values below 1.64 residual SD,[16] three groups were defined: group 1: large airways obstruction defined by a low FEV1/FVC ratio, group 2: small airways involvement defined by a low FEF25–75% ratio in the absence of reduced FEV1/FVC ratio and in the absence of restrictive syndrome, and group 3: restrictive disorder defined by a decrease of TLC, FVC, and FEV1 with a normal FEV1/FVC ratio. This threshold (−1.64 SD) is, when data are normally distributed, at the lower 90% confidence limit.

HIGH RESOLUTION COMPUTED TOMOGRAPHY OF THE LUNGS

HRCT of the thorax was performed with a SIEMENS Somatom Plus (Erlangen, Germany). Serial slices were taken through the chest, each 1 mm in width and 10 mm apart. Technical factors were 137 KV and 255 mA. Images were reconstructed using a high spatial frequency algorithm for parenchymal analysis. HRCT studies were performed at the suspended end inspiratory volume with one second scan time; patients were scanned in the supine position. In cases of articular limitation especially involving the shoulders, HRCT was performed with the patient's arms positioned alongside the body without any side effects on the image quality. The HRCT examinations were interpreted by two experienced radiologists in the absence of clinical information and decision was obtained by concensus. Multiple radiological criteria for the diagnosis of lung involvement were assessed. The screened abnormalities were: nodules; ground glass attenuation (visibility of the bronchi and the vessels); honeycombing defined as areas of cystic spaces with thickened walls; bron-

chiectasis defined as bronchial dilatation, often with thickening of the wall according to the criteria of Naidich *et al*,[17 18] air trapping defined by a decreased attenuation of pulmonary parenchyma, especially manifest as less than normal increase in attenuation during expiration; and pleural effusion.

STATISTICAL ANALYSIS

The results of FEV1, FVC, FEV1/FVC, FEF25%, FEF50%, FEF75%, FEF25–75%, TLCO, TLCO/V_A are expressed as the percentage of the predicted value for each individual adjusted for age, sex, and height. Group data are expressed as mean (SD), median, and range if necessary (activity and disability parameters). Statistical comparisons were made using Student's *t* test for unpaired data or Mann-Whitney U test as appropriate. Comparisons between patients with and without bronchiectasis concerning PFT results was made using raw data apart for TLCO/V_A (percentage of the predicted value). One way analysis of variance was made to study the influence of treatment on PFTs. Contingency tables were analysed for statistical significance using the χ^2 test and Fisher's exact tests as appropriate. A probability value of ≤ 0.05 was considered to be statistically significant.

Results

RA FINDINGS AND PULMONARY SYMPTOMS

There were 68 patients (54 women, 79.4%). Their mean (SD) age was 58.8 (10.6) years. The mean (SD) duration of the the disease was 12 (9.2) years. Table 1 summarises the activity and disability parameters. Subcutaneous rheumatoid nodules were noted in 24 cases (35.3%), and 14 patients (20.6%) were suffering from Sjögren's syndrome. There was no evidence of other extra-articular manifestations and particularly vasculitis. Fifty three patients were receiving corticosteroids with a mean duration of four years and 46 (64.7%) were taking non-steroidal anti-inflammatory drugs (NSAIDs). Thirteen patients (19.1%) were not receiving any second line drug. Eighteen patients (32.7%) were taking methotrexate, 12 (21.8%) intra-muscular gold, 11 sulphasalazine (20%), six hydroxychloroquine (10.9%), six tiopronin (sulphydryl compound, 10.9%), and two cyclosporin A (3.7%). Rheumatoid factor was positive in 52 patients (76.5%). Shared epitope positive (DRB1* 0101,0102,0401,0404,0405,0408,1001) DR4 alleles were observed in 30 patients (44%).

Fifty two patients (76.5%) had never smoked and 16 (23.5%) were current or ex-smokers. The mean cigarette consumption was 25.7 (22.3) pack years. Twenty five patients (36.8%) were complaining of recurrent bronchitis (mean: twice a year), nine patients (13.2%) had a history of wheeze, five (7.4%) had pneumonia confirmed radiologically, three (4.4%) had pleurisy, and seven (10.3%) had had pulmonary tuberculosis. Forty seven patients (69.1%) were complaining of respiratory symptoms: dyspnoea (n=40, 58.8%), cough (n=21, 30.8%), and sputum production (n=18, 26.5%). Late inspiratory

Table 1 Activity and disability parameters

Activity and disability parameters	Mean (SD)	Median (range)
Morning stiffness duration (min)	78 (87.8)	45 (0–300)
Number of swollen joints	1.9 (2.4)	1 (0–10)
Ritchie articular index	7.9 (6.4)	7 (0–27)
Steinbrocker classification	2.4 (0.7)	3 (1–4)
HAQ	1.67 (0.74)	1.75 (0–2.88)
Erythrocyte sedimentation rate	48 (29.6)	44 (2–130)
C reactive protein (mg/l)	43 (45.3)	29 (0–253)
Larsen's score (wrist)	2.5 (1.4)	3 (0–5)
Larsen's score (metacarpophalangeal joint)	2.5 (1.7)	2 (0–5)
Larsen's score (interphalangeal joint)	1.5 (1.6)	1 (0–5)

HAQ=health assessment questionnaire.

crackles were observed in 11 cases (16.1%), coarse crackles in one case (1.5%), sibilants in one case (1.5%), and pleural rub in two cases (2.9%). We did not find finger clubbing.

PFT FINDINGS
Table 2 summarises the results of PFTs. Compared with values predicted for age, sex, and height we found a significant decrease of FEV1/FVC, FEF25%, FEF50%, FEF75%, FEF25–75%, and TLCO (p<0.05). The results of PFTs were not different in the 52 non-smokers and in the 16 current or ex-smokers (table 3). The sole significant difference in PFTs on different treatments concerned FEV1/FVC, which was decreased in patients receiving tiopronin compared with those receiving intra-muscular gold: 70.8 (19.6) versus 81.8 (6.6) (p=0.04).

Large airways obstruction was noted in six cases (9%), small airways involvement in eight of 59 cases (14%), and restrictive disorder in eight cases (12%). Small airways involvement was not evaluated in nine cases: past history of radiation therapy for breast carcinoma (n=3), pulmonary fibrosis (n=2), sequelea of pulmonary tuberculosis (n=3), major pleural effusion (n=1).

CT FINDINGS
Table 4 summarises the results of HRCT. Air trapping was not assessed in four cases because of technical difficulties. In four patients ground glass attenuation was not assessed because of a past history of radiation therapy for breast carcinoma in three cases and major pleural effusion in one case. Bronchiectasis was not evaluated in nine cases because of a past history of radiation therapy for breast carcinoma in three cases, a pulmonary fibrosis in two cases, sequelea of pulmonary tuberculosis in three cases, and major pleural effusion in one case.

HRCT was abnormal in 55 patients (80.9%). The most frequent abnormalities depicted on HRCT were bronchiectasis, which were found in 18 patients (30.5%), pulmonary nodules (28%), and air trapping (25%).

Table 2 Results of PFT (data are expressed as mean (SD))

PFT measurements	Percentage of the predicted values
FEV1	93.1 (23.9)
FVC	98.9 (20.9)
FEV1/FVC	82.5 (31.9)**
FEF25%	65 (36)**
FEF50%	75.7 (36.2)**
FEF75%	82.6 (31.9)**
FEF25–75%	72.9 (35.4)**
RV	113.3 (37)*
TLC	101.5 (21.7)
TLCO	88.8 (30)**
TLCO/V$_A$	103.6 (20.6)

FEV1=forced expiratory volume in one second; FVC=forced vital capacity; FEV1/FVC; FEF25%=forced expiratory flow at 25% of the vital capacity; FEF50%=forced expiratory flow at 50% of the vital capacity; FEF75%=forced expiratory flow at 75% of vital capacity; FEF25–75%=forced expiratory flow from 25% and 75% of vital capacity; RV=residual volume; TLC=total lung capacity; TLCO=gas transfer factor measurement and TLCO/A. *p<0.05, **p<0.01 (comparison of the results observed with those predicted for age, sex, and height).

Table 3 PFT values (mean (SD)) according to smoking status

PFT measurements	Non-smokers (n=52)	Current or ex-smokers (n=16)
FEV1	95.5 (24.6)	85.1 (20.4)
FVC	100.5 (21.7)	93.4 (18.1)
FEV1/FVC	78.9 (10.2)	74.8 (10.9)
FEF25%	68.75 (36.9)	52.7 (33.5)
FEF50%	78.7 (36.9)	65.6 (33.4)
FEF75%	86.17 (31.3)	70.6 (32.1)
FEF25–75%	75.8 (35.7)	63.5 (33.8)
RV	115 (37.1)	107.2 (30)
TLC	100.3 (19.5)	105.8 (27.8)
TLCO	89.1 (29.8)	87.8 (31.6)
TLCO/V$_A$	105.6 (20.7)	97.4 (19.4)

There was no significant difference between the two groups studied. Abbreviations as shown in table 2.

Table 4 HRCT findings

HRCT findings	Number of cases (%)
Abnormal pattern	55/68 (80.9)
Bronchiectasis	18/59 (30.5)
Nodules	19/68 (28)
Air trapping	16/64 (25)
Ground glass attenuation	11/64 (17.1)
Honeycombing	2/68 (2.9)
Pleural effusion	1/68 (1.5)

RESULTS ACCORDING TO PFT FINDINGS
Patients with airflow obstruction (low FEV1/FVC)
Four of six patients of this group had a past history of wheeze and three were current or ex-smokers. This group did not differ from other patients in terms of activity and disability parameters or concerning the results of HRCT.

Patients with small airways involvement (low FEF25–75%)
Seventy five per cent of these patients were non-smokers and seven of eight (87%) were complaining of dyspnoea. The frequency of pulmonary symptoms was not significantly different in this group compared with other patients except for the history of recurrent bronchitis, which was more frequently observed in this group (75% versus 34%, p=0.05). Activity and disability parameters were not significantly different in these patients compared with the others. The frequency of secondary Sjögren's syndrome was not significantly different in patients with and without small airways involvement. Bronchiectasis was more frequently depicted in this group than in other patients: 71% versus 23%, p=0.019; one patient was excluded for bronchiectasis evaluation because of a past history of radiation therapy for breast cancer. Finally a non-significant increase of HLA DR2 and DR7 was found in this group compared with other patients: 25% versus 9% and 13% versus 7% respectively.

Patients with restrictive syndrome
Four of eight (50%) of these patients were smokers. Pulmonary symptoms and particularly dyspnoea were not more frequently observed in this group. On HRCT a non-significant increase of honeycombing (two of eight, 25% versus none of 60, 0%) and ground glass attenuation (37.5% versus 13.3%) were found.

RESULTS ACCORDING TO HRCT FINDINGS
Bronchiectasis
The patients with bronchiectasis by HRCT were characterised compared with the others by a high frequency of non-smokers (93.8% versus 70.8%, p=NS), a high frequency of dyspnoea (88.2% versus 56.1%, p=0.03), a significant decrease of FVC (2.37 (0.6) versus 3.26 (1), p=0.003), FEV1 (1.77 (0.6) versus 2.56 (0.8), p=0.0016), FEF25–75% (1.66 (1.3) versus 2.52 (1.1), p=0.009), TLC (4.9 (1.1) versus 5.5 (1.2), p=0.02), TLCO (5.5 (1.5) versus 7.7 (2.1), p=0.0003), and TLCO/V_A (94.6 (18.4) versus 107.8 (21), p=0.03). The patients with bronchiectasis were characterised by a high frequency of small airways involvement by PFTs (29.4% versus 5%, p=0.019) and a high frequency of air trapping (41.2% versus 19.5%, p=NS). The frequency of Sjögren's syndrome was not significantly different in patients with and without bronchiectasis (33% versus 22%). Activity and disability parameters were not significantly different in patients with and without bronchiectasis. HLA DR genotype was not different according to the absence or the presence of bronchiectasis. The prevalence of DQA1*0501 allele was significantly lower in patients with bronchiectasis compared with the others (14% versus 33%, p=0.03). According to the the presence or the absence of the shared epitope (HLADRB1*0101, *0102, *0401, *0404, *0405, *0408, and *01001) we have compared the patients with and without bronchiectasis. No statistical difference was observed according to the presence or the absence of bronchiectasis.

Air trapping
PFT values were not statistically different in this group compared with those observed in other patients. Air trapping was not associated with the presence of large airways obstruction or small airways involvement.

Ground glass attenuation
Ground glass attenuation was more frequently depicted in smokers than in non-smokers (50% versus 21%, p=NS) and in patients suffering from recurrent bronchitis (60% versus 36%, p=NS). With PFTs these patients demonstrated a significant decrease FVC (p=0.003) with normal values of TLCO/V_A.

Discussion
Our study suggests a high prevalence of small airways involvement in a population of unselected RA patients. Small airways obstruction is characterised in our study by a significant decrease of FEF25%, FEF50%, FEF75%, and FEF25–75% compared with the values predicted for age, sex, and height. Small airways obstruction is a well recognised manifestation of rheumatoid lung involvement[2–4]; however the high prevalence of smokers in the previous published studies suggests that smoking might be the main cause of small airways involvement in RA.[3] Conversely 76.5% of our patients were lifelong non-smokers suggesting that RA might explain the results of PFTs. Although PFT values were generally lower in current or ex-smokers than in non-smokers, there was no significant difference between these two groups. This finding might be explained by the high standard deviation of the values of PFTs in the group of current and ex-smokers. Indeed the values of standard deviations are comparable in smokers and in non-smokers whereas their number are lower. Moreover it is possible that the low number of smokers and particularly current smokers (n=7) did not permit the significant threshold to be achieved. The prevalence of small airways involvement defined on the basis of FEF25–75% values below 1.64 SD (14%) is lower than the one reported by Geddes et al[2] perhaps because of the low prevalence of smokers in our study and the choice of the threshold for PFTs. However this threshold (−1.64 SD) was chosen because it is at the lower 90% confidence limit. The patients with small airways involvement had a high prevalence of recurrrent bronchitis suggesting that respiratory tract infections might play a part in the pathogenesis of rheumatoid lung disease.[19] Conversely our study does not support the hypothesis that secondary Sjögren's syndrome might play a part in the pathogenesis of small airways involvement, the frequency of secondary Sjögren's syndrome being similar in patients with and without small airways involvement confirmed by PFTs. In contrast Radoux et al[20] have found a strong association between small airways involvement and secondary Sjögren's syndrome in RA patients. However we have not used the same criteria for the the diagnosis of Sjögren's syndrome as Radoux et al[20] and this might explain this discrepancy. We have found a significant decrease of TLCO with a normal TLCO/V_A ratio suggesting the absence of major interstitial involvement in our population in agreement with the results of Linstow et al.[21] In the group of patients with large airways obstruction the abnormalities seem to be related to wheeze and smoking rather than RA as the frequencies of wheeze and smoking were high (66.6% and 50% respectively). Restrictive syndrome was observed in eight of 68 patients (12%) and might be related to parenchymal tissue inflammation. However only two patients of this group had an evidence of lung fibrosis using HRCT and TLCO/V_A was in the normal range in this group (101.8%). Finally second line drugs and particularly methotrexate does not influence the results of PFTs. The patients receiving tiopronin (sulphydryl compound), however, had a low FEV1/FVC ratio compared with those receiving intramuscular gold. Obliterative bronchiolitis has been rarely reported in patients treated by tiopronin[22] and none of the patients receiving tiopronin in our study had clinical evidence of obliterative bronchiolitis.

By HRCT the most frequent abnormality was bronchiectasis, which was found in 30.5%. These results are in agreement with those published by Hassan et al and Cortet et al.[7 8] Air trapping that is related to airways obstruction

was observed in 25% and might be an interesting pattern in the assessment of rheumatoid lung disease.

The patients with small airways involvement confirmed by PFTs had a high prevalence of bronchiectasis compared with the others (71% *v* 23%). Among patients with bronchiectasis confirmed by HRCT we have found a high prevalence of small airways involvement (29.4% *v* 5%) and a significant decrease of FEF25–25%. To our knowledge this the first study reporting an association between small airways involvement on PFT and bronchiectasis on HRCT. Indeed Hassan *et al*[7] in a study including 20 lifelong non-smoking patients with RA have found bronchiectasis in 25%—that is, with a similar frequency to our own—but failed to demonstrate a high prevalence of small airways involvement in patients with bronchiectasis. This discrepancy could be because of the small number of patients in Hassan's study. Moreover data concerning the influence of bronchiectasies on PFT results were not shown in this study. Hassan *et al*[7] have found a high frequency of sicca syndrome (80%) in patients with bronchiectasis whereas we have not found an association between bronchiectasis and secondary Sjögren's syndrome. Sicca syndrome could be related to varied causes, however, and not only to Sjögren's syndrome. In addition our patients with bronchiectasis had low $TLCO/V_A$ values and these results are in agreement with those of Shadick *et al*[23] who have found a significant decrease of $TLCO/V_A$ in RA patients with bronchiectasis.

This study suggests the absence of association between bronchiectasis and HLA DR genotype in agreement with the results of Hillarby *et al.*[24] Our data indicate a lower frequency of HLA DQA1*0501 genotype in patients with bronchiectasis whereas Hillarby *et al*[24] have found a higher frequency of HLA DQA1*0501, DQB1*0201, and HLA DQB1*0601 genotypes in patients with RA and bronchiectasis compared with patients with RA without bronchiectasis. In comparison, the frequency of HLA DQA1*501 determined in 233 healthy unrelated people from the north of France was 28%[25] and comparable with the one observed in our RA patients without bronchiectasis (33%). The discrepancies between the study of Hillarby and our own do not seem to be the consequence of genetic differences between French and English populations because Hillarby *et al*[24] have found a similar frequency of HLA DQA1*501 in their control population (27%) than in our own. The main explanation might be that Hillarby *et al*[24] have diagnosed bronchiectasis using clinical and radiological findings whereas in our study the diagnosis of bronchiectasis was based only on HRCT.

Finally we failed to find any association between ground glass attenuation on HRCT and low carbon monoxide diffusion capacity.

In summary this study suggests a strong association between small airways involvement confirmed by PFTs and bronchiectasis using HRCT. Small airways involvement might be related to an increased frequency of respiratory tract infections. Moreover bronchiectasis is not associated with poor activity or disability parameters. Finally our results do not support the hypothesis of a possible contribution of secondary Sjögren's syndrome in the pathogenesis of small airways involvement and bronchiectasis in RA.

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