

# High resolution computed tomography of the lung in lifelong non-smoking patients with rheumatoid arthritis

W U Hassan, N P Keaney, C D Holland, C A Kelly

## Abstract

**Objectives**—To define pulmonary involvement on high resolution computed tomography (HRCT) of the thorax in lifelong non-smoking rheumatoid arthritis patients and to relate the results to pulmonary function, bronchial reactivity, and a variety of clinical and serological factors.

**Methods**—Twenty lifelong non-smoking RA patients (mean age 59 years (range 44–72; 18 females) were studied. Detailed medical and drug histories were taken. Protease inhibitor phenotype (Pi) and HLA-DR4 status were assessed. Schirmer's tear tests were performed to detect keratoconjunctivitis sicca (KCS). Spirometry, flow volume loops, and gas transfer factor measurement were recorded. The degree of bronchial reactivity (PC<sub>20</sub> FEV<sub>1</sub>) was measured by a methacholine inhalation test. Chest and hand radiographs and HRCT of the lung were performed in all patients.

**Results**—Thirteen patients were HLA-DR4 positive. Eighteen had the Pi MM and two the Pi MS phenotype. Eight patients had evidence of KCS on Schirmer's tear testing. Ten patients achieved PC<sub>20</sub> FEV<sub>1</sub> in the methacholine inhalation test. All the patients had normal chest radiographs and all showed evidence of erosive arthropathy on hand radiographs. Five patients (25%) showed basal bronchiectasis and one mild interstitial lung disease on HRCT. All five patients with bronchiectasis had the Pi MM phenotype, four had HLA-DR4, four had KCS and three achieved PC<sub>20</sub> FEV<sub>1</sub>; these values were not significantly different ( $p > 0.05$ ) from those in patients without bronchiectasis.

**Conclusion**—Using the highly sensitive technique of HRCT, we found evidence to suggest that the incidence of bronchiectasis in lifelong non-smoking RA patients may be much higher than previously reported.

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Rheumatoid arthritis (RA) is associated with a variety of pulmonary complications such as pleural effusion, pulmonary nodules, pulmonary fibrosis, and bronchiectasis.<sup>1</sup> Previous workers reporting an association of bronchiectasis and RA diagnosed the bronchiectasis on

the basis of a chronic productive cough, persistent coarse crackles on chest auscultation, and an abnormal chest radiograph. It is generally accepted that the chest radiograph may be normal in patients with bronchiectasis. In the past, an invasive procedure such as bronchography was required to establish a firm diagnosis of bronchiectasis. However, high resolution computed tomography (HRCT) is a non-invasive procedure which is nowadays regarded as the most useful investigation for diagnosing the condition.<sup>2</sup>

We have performed HRCT in 20 lifelong non-smoking asymptomatic RA patients to define pulmonary involvement and to relate the results to pulmonary function, bronchial reactivity, and a variety of clinical and serological factors.

## Patients and methods

We have previously shown a significantly high prevalence of airflow obstruction and bronchial reactivity to inhaled methacholine in 100 patients with RA, compared with 50 controls.<sup>3</sup> Of these 100 patients, 36 were lifelong non-smokers. From this population, 20 lifelong non-smoking RA patients, all with no respiratory symptoms at the time of the study and normal chest radiographs, were recruited to the present study.

Detailed medical and drug histories were obtained and patients were asked questions based on the Medical Research Council Questionnaire for the Respiratory System,<sup>3</sup> by a single observer (WH). Skin prick tests to house dust mite, grass pollens, *Aspergillus fumigatus*, mixed feathers and any other antigen for which the subject gave a history suggestive of sensitisation were performed on the anterior aspect of the forearm and compared with reactions to a control solution (Bencard). A weal of 2 mm or more and greater than that of the control was considered positive. Schirmer's tear test was performed in both eyes in all the patients and the response was considered abnormal if there was less than 10 mm wetting over five minutes bilaterally. Haemoglobin, erythrocyte sedimentation rate (ESR), autoantibodies, HLA-DR4 status, and Pi phenotypes were checked and radiographs of hand and chest performed. Bronchial reactivity to inhaled methacholine was assessed in all the patients as described before.<sup>3</sup> The following pulmonary function tests were performed: forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC),

Department of Rheumatology, Leicester Royal Infirmary, Leicester LE1 5WW, United Kingdom  
W U Hassan

Royal Infirmary, Sunderland SR2 7JE, United Kingdom  
N P Keaney  
C D Holland

Queen Elizabeth Hospital, Gateshead NE9 6SX, United Kingdom  
C A Kelly

Correspondence to: Dr W Hassan.

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FEV<sub>1</sub>/FVC, forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25-75</sub>), forced expiratory flow at 25% (FEF<sub>25</sub>), 50% (FEF<sub>50</sub>) and 75% (FEF<sub>75</sub>) of the vital capacity, residual volume (RV), total lung capacity (TLC), and gas transfer factor measurement (TLCO). Lung volumes were measured by the helium rebreathing method and the transfer factor by the single breath technique.<sup>3</sup> Observed values were compared with those predicted for age, gender, and height for each individual.

HRCT of the thorax was performed on a Schimadzu SCT 3000TX scanner. A series of slices were taken through the chest, each 2 mm in width and 20 mm apart. Technical factors were 120 KV and 300 mA. Dosimetry calculations estimated that the effective radiation was 0.4 mSv, which is equivalent to eight conventional chest radiographs. The HRCT was reported by a radiologist in the absence of clinical information. The term bronchiectasis, as used in this study, means dilation of the bronchial tree with thickened walls. The computed tomography diagnosis of bronchiectasis was established according to the criteria of Naidich *et al.*<sup>4</sup>

Results for FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, FEF<sub>25-75</sub>, FEF<sub>25</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>, RV, TLC, and TLCO are expressed as percentage of predicted for each individual adjusted for age, gender, and height. Differences between patients with and without bronchiectasis were assessed by the Mann-Whitney U test. Contingency tables were analysed for statistical significance by using Fisher's exact tests.  $p < 0.05$  was considered statistically significant. All analyses were performed using Minitab statistical package (Minitab software, Cleocom, Birmingham, UK).

## Results

The mean age was 59 years (range 44–72); 18 of the patients were female. The mean duration of RA was nine years (range 1–30). Eight patients were receiving salazopyrin, four penicillamine, and three intramuscular gold. All patients were taking NSAIDs and none of them was taking steroids at the time of study. Four patients had a history of intermittent wheeze, two of pleurisy, and one had had pneumonia after the onset of RA. Three patients were atopic on skin prick testing to house dust mite only. Schirmer's tear test was abnormal in eight patients. All the patients were rheumatoid factor positive. Mean haemoglobin concentration was 124 g/l (95% confidence interval (CI) 119 to 129), mean ESR 31 (95% CI 21 to 41), and mean  $\alpha$ -1 antitrypsin concentration was 2.50 g/l (95% CI 2.20 to 2.87) (normal range 1.1–2.1 g/l). Thirteen patients were HLA-DR4 positive, 18 had the Pi MM and two the Pi MS phenotype. Ten patients achieved PC<sub>20</sub> FEV<sub>1</sub> to inhaled methacholine. Three of these patients achieving PC<sub>20</sub> FEV<sub>1</sub> had a history of wheeze (one of these three also had had pneumonia), one had had pleurisy and one was atopic. All the patients had a normal chest radiograph and all had erosive arthropathy.

## Clinical features of patients with and without bronchiectasis

	Bronchiectasis (n = 5)	No bronchiectasis (n = 15)
Age (years)	60 (53–72)	65 (44–72)
Duration (years)	15 (5–27)	5 (1–30)
HLA-DR4	4	9
AAT (g/l)	2.9 (1.8–3.4)	2.5 (1.7–4.3)
Pi phenotypes (MM:MS)	5:0	13:2
KCS	4	1
PC <sub>20</sub> FEV <sub>1</sub> achieved	3	7
Methacholine dose (mg/ml)	22 (0.5–32)	20.3 (2–32)

Results are expressed as median (range) where relevant. Contingency tables are analysed by Fisher's exact test. AAT =  $\alpha$ -1 antitrypsin; KCS = keratoconjunctivitis sicca. No significant differences between groups.

HRCT demonstrated basal bronchiectasis in five patients (25%) (duration of RA five, eight, 18, 20, and 27 years) while in one patient the lungs had the basal ground glass appearance consistent with mild interstitial lung disease. In the bronchiectasis group, two patients had a history of pleurisy, one had pneumonia, and none had a history of wheeze; none was atopic on skin prick testing. There was no evidence of adjacent scarring on HRCT in patients who had had pleurisy or pneumonia. In the bronchiectasis group, one patient was taking salazopyrin, one penicillamine, and one gold. There was no significant difference between patients with and without bronchiectasis in age, gender, and duration of RA (table). All the five patients with bronchiectasis had the Pi MM phenotype; four of the five had a positive Schirmer's test. Four patients with bronchiectasis had HLA-DR4. Three patients with bronchiectasis achieved a PC<sub>20</sub> FEV<sub>1</sub> and there was no significant difference in the dose of inhaled methacholine required to achieve a PC<sub>20</sub> FEV<sub>1</sub> in patients with or without bronchiectasis (table). There was no significant difference in FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, FEF<sub>25-75</sub>, FEF<sub>25</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>, RV, TLC, and TLCO between patients with and without bronchiectasis ( $p > 0.05$ ; data not shown).

## Discussion

Although this was an uncontrolled study using a highly sensitive technique (HRCT) to detect pulmonary abnormalities, we were surprised to find that 25% of our patients had bronchiectasis. A previous study also reported a 25% incidence of bronchiectasis in their RA patients on HRCT,<sup>5</sup> but most of those patients were smokers and had respiratory symptoms. Another study examined 18 consecutive RA patients with HRCT and reported a variety of pulmonary abnormalities such as interstitial fibrosis (eight patients) and bronchiectasis (two patients).<sup>6</sup> Although the majority of these patients were lifelong non-smokers, 50% of them had abnormal chest radiographs. The fact that we studied only patients with a normal chest radiograph could explain the decreased frequency of interstitial lung disease observed in our patients.

It is generally believed that bronchiectasis precedes RA by many years, and that chronic suppuration in the lung leads to antigenic stimulation in susceptible individuals, causing RA; whether bronchiectasis preceded the onset

of RA in our patients is difficult to establish, but none of them had any regular respiratory symptoms before the onset of RA. Another possibility is that RA or its treatment leads to an increased frequency of respiratory tract infections causing bronchiectasis. We did not observe any significant difference in the respiratory symptoms or treatment with disease modifying drugs in our patients with and without bronchiectasis. Although there was no significant difference between the duration of their RA in patients with and without bronchiectasis, in general, patients with bronchiectasis had had RA for a longer period of time than those without.

Protease inhibitor (Pi) is the predominant serum antiprotease and protects vulnerable tissue from proteolytic enzymes released by inflammatory cells. Its absence or deficiency can lead to increased tissue destruction. It is not known if the effect of mild protease inhibitor deficiency is further potentiated in RA because of pre-existing inflammation in the joints and lungs. One previous study has reported rapidly progressive airflow obstruction in three patients with Pi MS phenotypes,<sup>7</sup> all of whom were current smokers. However, in common with two other studies,<sup>8,9</sup> we have not found any association between bronchiectasis and Pi phenotypes in our patients.

HLA-DR4 is reported to be associated with pulmonary abnormalities in RA,<sup>10,11</sup> but none of these studies assessed their patients for evidence of bronchiectasis. One previous study has assessed a large number of RA patients with and without extra-articular features and reported an association of HLA with bronchiectasis in patients with RA.<sup>12</sup> Although we did not find any significant association of HLA-DR4 and bronchiectasis in our patients, this could reflect the relatively small number of patients showing bronchiectasis in our study.

Patients with primary and secondary Sjögren's syndrome are more prone to the development of respiratory symptoms, airflow obstruction and bronchial hyperreactivity.<sup>3,13,14</sup> Four out of five of our patients with bronchiectasis had KCS. One previous study<sup>9</sup> also revealed an increased frequency of

bronchiectasis in patients with secondary Sjögren's syndrome. Surprisingly, patients with primary Sjögren's syndrome have not been found to have an increased frequency of bronchiectasis. One may speculate that the interaction between RA, treatment with immunosuppressive drugs, and Sjögren's syndrome, increases predisposition to the development of bronchiectasis.

In summary, using a highly sensitive technique such as HRCT, we found evidence in lifelong non-smoking RA patients to suggest that the incidence of bronchiectasis may be much higher than previously reported.

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