A Longitudinal Study of Lung Function in Nonsmoking Patients With Rheumatoid Arthritis*

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Study objectives: Patients with rheumatoid arthritis (RA) have a high prevalence of pulmonary function test (PFT) abnormality, but the long-term significance of this is unknown. We performed a longitudinal study of pulmonary function in asymptomatic, nonsmoking patients with active RA requiring disease-modifying drugs. We looked for temporal change in lung function and characteristics that would predict subsequent development of PFT abnormality or respiratory symptoms.

Methods: In 1990, 52 patients (44 women; age range, 29 to 78 years; median, 56 years) underwent clinical assessment (drug history, RA severity, immunologic, and inflammatory markers) and PFTs (spirometry, body plethysmography, gas transfer). PFT results were expressed as standardized residuals (SRs). Thirty-eight patients were reassessed in 2000. A self-administered questionnaire was used to identify respiratory symptoms.

Results: The prevalence of pulmonary function abnormality was higher than expected compared with a reference population, but there was no significant increase in number over 10 years (8.7% in 1990 and 8.8% in 2000). When assessed by group means and compared with reference values, reduced diffusing capacity of the lung for carbon monoxide (DLCO) and increased ratio of residual volume (RV) to total lung capacity (TLC) [RV/TLC] were the only abnormalities to develop over the study period (mean DLCO in 2000, – 0.47 SR; 95% confidence interval [CI], – 0.91 to – 0.01; RV/TLC, 0.49 SR; 95% CI, 0.13 to 0.84). However, rates of change of pulmonary function variables were not significantly different from zero. Logistic regression did not identify any meaningful relationship between disease characteristics and PFT abnormality.

Conclusions: Asymptomatic patients with RA have a higher prevalence of PFT abnormality than expected, but these do not increase in number over time. We did not identify any patient or disease-specific characteristic that could predict the development of respiratory disease in patients with RA. Analysis using percentage of predicted values, rather than SRs, is misleading as it exaggerates the extent of abnormality present. Abnormal lung function is a common and probably benign finding in nonsmoking, asymptomatic patients with RA.

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Key words: longitudinal; nonsmoking; pulmonary function; rheumatoid arthritis

Abbreviations: ANF = antinuclear factor; CI = confidence interval; CRP = C-reactive protein; DLCO = diffusing capacity of the lung for carbon monoxide; DMARD = disease-modifying antirheumatoid drug; ESR = erythrocyte sedimentation rate; FEF_{25-75} = midexpiratory flow; HRCT = high-resolution CT; KCO = transfer coefficient for carbon monoxide; PFT = pulmonary function test; RA = rheumatoid arthritis; RF = rheumatoid factor; RV = residual volume; sGaw = specific airways conductance; SR = standardized residual; TLC = total lung capacity; VC = vital capacity

Rheumatoid arthritis (RA) is a common multisystem disorder of unknown etiology affecting approximately 1% of the population.¹ Cross-sectional surveys of lung function in RA are common and have demonstrated a high prevalence of abnormality characteristic of interstitial and both large and small airway disease.²–⁵ More recently, high-resolution CT

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(HRCT) has confirmed the high prevalence of parenchymal and airway disease, often in asymptomatic patients and sometimes in the absence of pulmonary function or radiographic abnormality.5,7 The outcome of such patients with subclinical pulmonary involvement is unknown.

Previous longitudinal studies of pulmonary function in patients with RA have not suggested a consistent pattern of change. Beyeler et al8 showed a decrease in FEV1, whereas Linstow et al9 described an increase in diffusing capacity of the lung for carbon monoxide (DLCO), and Chakravarty and Webley10 reported reversible pulmonary function changes, suggestive of interstitial disease, after introduction of gold. All these studies have included smokers, and Beyeler et al8 and Chakravarty and Webley10 attempted to assess the impact of drug therapy on pulmonary function.

The purpose of this study was to ascertain the prevalence of pulmonary function test (PFT) abnormalities in a population of nonsmoking patients with RA and no respiratory symptoms. We wished to determine how these changed over a 10-year period and identify factors that might predict the onset of symptoms or abnormality of lung function.

Materials and Methods

Recruitment

In 1990, we recruited patients from the RA second-line medication clinic at the Centre for Rheumatic Diseases at Glasgow Royal Infirmary. All patients had RA diagnosed by a consultant rheumatologist, according to American College of Rheumatology criteria,11 and were receiving one or more disease-modifying antirheumatoid drugs (DMARDs). Inclusion criteria were lifelong nonsmoking, no documented or recalled evidence of lung disease, and absence of respiratory symptoms on general inquiry at initial consultation. Informed consent was obtained from all patients, and the local Research Ethics Committee approved the study.

Clinical Evaluation

In 1990, we recorded rheumatoid factor (RF) and antinuclear factor (ANF) titers, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), articular disease status (Ritchie articular index), duration of morning stiffness, and history of DMARD use.12 ESR was measured by a Starsed assay (Mechatronics; R&R Hoorn, Holland). RF titer was determined by nephelometry, with a titer of > 22 IU/mL indicating seropositivity. ANF titer was determined by indirect immunofluorescence using rat liver substrate. CRP was determined by photometric analysis, with a titer of < 6 mmol/L indicating normality. All patients underwent comprehensive PFTs.

In 2000, the patients were invited to attend for repeat assessment. They underwent the same PFTs and also completed a modified form of a self-administered respiratory symptom questionnaire (American Thoracic Society Division of Lung Diseases 78-A adult symptom questionnaire).13 Questions concerning passive smoking exposure were added, and the language was altered in some places to British from American English. The expected prevalence of symptoms was obtained from the third National Health and Nutrition Examination Survey.14

Pulmonary Function

Spirometry, flow-volume loops, and lung volumes were measured using the Morgan Medical Autobox (Morgan Medical; Kent, UK) in 1990 and the V6200 Autobox (SensorMedics Corporation; Yorba Linda, CA) in 2000. The variables measured were vital capacity (VC), FEV1, mid-expiratory flow (FEF25-75), residual volume (RV), total lung capacity (TLC), specific airways resistance, and specific airways conductance (sGaw). DLCO was measured with the single-breath technique using the Transflow System (Model 540; Morgan Medical). These values were corrected for hemoglobin concentration. Tests were performed according to the British Thoracic Society/Association of Respiratory Technology and Physiology guidelines.13 The same investigator performed the tests in 1990 and 2000.

Results of at least three satisfactory maneuvers were analyzed, and the reported values were the highest value for FEV1 and VC and the mean of the three results for each of the remaining indexes. We used the regression equations for normal values derived from the European coal and mineworkers database,16 which use height, age, and sex as independent variables. Excluding one subject, the median difference (interquartile range) in height over the study period was -1 cm (-3 to 1 cm). This is commensurate with age-related change. One subject was severely affected by spinal deformity over the study period, losing 17 cm in height; in this case, arm span was used. Values were defined as abnormal if greater than two standardized residuals (SRs) from the predicted result.

Statistical Analysis

Group data are shown as mean ± SD unless otherwise specified. Pulmonary function data have been given as mean absolute values and SRs. The latter are calculated from the following:

\[ SR = \frac{\text{observed value} - \text{predicted value}}{RSD} \]

where RSD is the residual SD taken from the regression analysis. This is the residual SD taken from the regression analysis.

Results

We studied 52 patients (44 women; age range, 29 to 78 years; median, 56 years). Thirty-eight patients were seropositive, and all were receiving DMARD therapy with a median lifetime use of two agents (range, one to four agents). The DMARDs used and the number of patients prescribed them are as follows: IM gold (n = 25), sulfasalazine (n = 22), penicillamine (n = 11), hydroxychloroquine (n = 8), methotrexate (n = 4), and azathioprine (n = 3). Only three patients had been solely administered
hydroxychloroquine, indicating that we had a very small number of patients with mild rheumatoid disease. Patient characteristics at study entry are shown in Table 1.

By 2000, 9 patients of the original cohort had died and 43 patients were invited for reassessment. Two had died from respiratory disease (pulmonary fibrosis, lung cancer/tuberculosis), and the remaining seven patients died from extrapulmonary malignancy (n = 4), ischemic heart disease (n = 1), renal failure (n = 1), and general debility (n = 1). Figure 1 summarizes patient follow-up.

**Cross-Sectional Results**

Table 2 shows the group mean PFT results for all patients in 1990. Both FEV1/VC and FEF25–75 were significantly lower than predicted. VC was significantly higher than predicted, but this was not considered to be of physical significance. In 1990 for the subset of patients with repeat values only, FEF25–75 was significantly reduced (1.22 SR; range, –1.68 to –0.76; n = 13; p < 0.0001). Table 3 shows the follow-up PFT results. FEF25–75 has remained low, but now RV/TLC was significantly increased and DLCO reduced. Only 31 of our group had DLCO measurements performed in both 1990 and 2000. Mean measurements of sGaw for the 50 patients from 1990, the retested 38 patients in the subgroup, and the 2000 repeats were 1.62 ± 0.7 kPa/s, 1.72 ± 0.7 kPa/s, and 1.75 ± 0.6 kPa/s, respectively (normal value, >1.1 kPa/s).

**Longitudinal Results**

To enable comparison of longitudinal changes between the various pulmonary function parameters, we calculated the difference (in SRs) between measured and predicted values for each subject with repeat values. We then expressed these as a rate of change by dividing the change in difference between the two sets of PFTs by the time interval in years. None of the rates of change of SR was significant. The decline in DLCO was a trend only, with a p value of 0.1. Although we could demonstrate an abnormality when the longitudinal results were compared with a reference population, we could not demonstrate a difference between the results from the two time points. Mean SR values are displayed in Figure 3. The percentage of PFTs that lay outside the normal range in 1990 was higher than expected when compared with a reference population (8.7% vs 5%, p = 0.003). In 2000, the incidence of abnormality remained higher than expected (8.8% vs 5%, p = 0.003), with no significant change over the 10 years.

To examine the changes in type of PFT abnormality over time, we classified patients with abnormal PFTs as having an obstructive, restrictive, or mixed pattern (Table 4). There were no significant differences in the patterns of abnormality or total numbers of patients with abnormality between 1990 and 2000 (p > 0.2). Twenty-seven percent of our population in 1990 and 2000 had PFT abnormalities that together could be classified as suggesting a disease pattern.

**Symptom Results**

Forty patients in 2000 completed the respiratory symptom questionnaire either when reassessed (n = 34) or by telephone (n = 6). Thirty-five percent of this cohort had acquired respiratory symptoms. Breathlessness was most common (25%), followed by cough (16%), sputum production (12.5%), and wheeze (7.5%). The expected prevalence figures of

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**Table 1—Baseline Characteristics in 1990**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56 (29–78)</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>14 (0.25–40)</td>
</tr>
<tr>
<td>Lifetime DMARD use, No. of agents</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Morning stiffness, min</td>
<td>30 (0–720)</td>
</tr>
<tr>
<td>Ritchie articular index</td>
<td>2 (0–30)</td>
</tr>
<tr>
<td>Pain score</td>
<td>32 (0–73)</td>
</tr>
<tr>
<td>RF (38 positive)</td>
<td>1/256 (1/16–1/0.24)</td>
</tr>
<tr>
<td>ANA (30 positive)</td>
<td>1/256 (1/32–1/2,048)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>40 (4–137)</td>
</tr>
<tr>
<td>CRP, mmol/L</td>
<td>16 (5–235)</td>
</tr>
</tbody>
</table>
these symptoms in lifelong age-matched nonsmokers are 20.4%, 6.1%, 5%, and 7.7%, respectively. The presence of symptoms in 2000 was not associated with abnormal lung function in either 1990 or 2000 when assessed by binary logistic regression.

**Regression Analysis**

Binary logistic regression was used to try to predict membership of the following patient groups: (1) those with PFT abnormalities in 1990, (2) those with PFT abnormalities in 2000, (3) those who acquired respiratory symptoms, (4) those who did not attend for repeat tests, and (5) those who died. The variables used either singly or in combination in the prediction model were sex, age, passive smoking exposure, ESR, CRP, disease duration, pain score, articular index, RF, ANF, DMARD use, and PFT exposure, TLC, L 4\(2\) 4.82 (3.02 to 6.63) 0.49 (0.13 to 0.54) 0.008

**Table 3—Results in 2000 for Subset Who Returned for Repeat Assessment**

<table>
<thead>
<tr>
<th>Tests</th>
<th>No.</th>
<th>Mean (95% CI)</th>
<th>SRs Mean (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV(_1), L</td>
<td>41</td>
<td>2.18 (0.91 to 3.46)</td>
<td>0.017 (−0.36 to 0.39)</td>
<td>0.93</td>
</tr>
<tr>
<td>FEV(_1)/VC, %</td>
<td>41</td>
<td>76.4 (60.6 to 92.2)</td>
<td>−0.17 (−0.54 to 0.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>VC, L</td>
<td>41</td>
<td>2.92 (1.38 to 4.45)</td>
<td>0.47 (0.11 to 0.84)</td>
<td>NPS</td>
</tr>
<tr>
<td>RV, L</td>
<td>40</td>
<td>1.95 (1.10 to 2.80)</td>
<td>0.155 (−0.24 to 0.55)</td>
<td>0.43</td>
</tr>
<tr>
<td>TLC, L</td>
<td>40</td>
<td>4.82 (3.02 to 6.63)</td>
<td>−0.001 (−0.42 to 0.42)</td>
<td>1.0</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>40</td>
<td>46.1 (30.1 to 62.1)</td>
<td>0.49 (0.13 to 0.84)</td>
<td>0.008</td>
</tr>
<tr>
<td>FEF(_25-75), L/s</td>
<td>13</td>
<td>2.33 (0.26 to 4.39)</td>
<td>−1.06 (−1.48 to −0.65)</td>
<td>0.0001</td>
</tr>
<tr>
<td>DLco, mmol/mm Hg/min†</td>
<td>31</td>
<td>17.9 (9.72 to 29.5)</td>
<td>−0.47 (−0.91 to −0.01)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

*See Table 2 for expansion of abbreviation.
†Values adjusted for hemoglobin.
Of the two, the use of SRs is more methodologically sound.35 There are a number of drawbacks to an analysis based on percentage of predicted values. They overestimate the significance of lung function variation in smaller and older subjects, which makes the combination of group results of uncertain validity and can lead to the description of significant abnormality where none exists. Lung volumes have a natural decline with age, but the spread of values remains unaltered; therefore, percentage of predicted values would show an erroneous change over time, whereas SRs avoid this problem. This is because the denominator is becoming smaller while the absolute difference between the actual and the
predicted value is unchanged. The reporting of SRs also allows direct comparison of the degree of abnormality between PFT variables that have different units and SDs.

To demonstrate the effect of using percentage of predicted values rather than SRs, the group mean values from Table 2 are shown again in Table 5, but this time using percentage of predicted. A one-sample analysis for significance assuming a mean value of 100% has been performed. As can be seen, many more of the PFT variables appear abnormal, which is erroneous.

There are fewer studies8-10,33,34 that have looked at longitudinal change in pulmonary function in patients with RA. Again, these are of heterogeneous design with conflicting results. The study9 with the longest follow-up assessed pulmonary function over an 8-year period in 63 patients with RA. At entry, all the patients had reduced DLCO. They found that DLCO and transfer coefficient for carbon monoxide (KCO) improved but VC decreased. This unexpected gas transfer finding could represent regression toward the mean given the way in which the expected gas transfer finding could represent regres-

Table 4—Incidence of Patterns of Abnormality

<table>
<thead>
<tr>
<th>Patterns*</th>
<th>1990</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive</td>
<td>7/41</td>
<td>5/41</td>
</tr>
<tr>
<td>Restrictive</td>
<td>2/41</td>
<td>3/41</td>
</tr>
<tr>
<td>Mixed</td>
<td>2/41</td>
<td>3/41</td>
</tr>
<tr>
<td>Any abnormality</td>
<td>11/41</td>
<td>11/41</td>
</tr>
</tbody>
</table>

*Obstructive = low FEV/VC or low sGaw or low FEF25-75 or high RV/TLC; restrictive = low VC or low TLC or low DLCO; any abnormality = obstructive or restrictive or mixed.

The cross-sectional results in Table 2 extend the findings of earlier studies. A nonsmoking RA population with no respiratory symptoms shows minor PFT abnormalities when compared with reference values, namely a reduced FEV1/FVC ratio as mentioned earlier. Although FEF25-75 was also decreased, we hesitate to attach any significance to this, as results were only available for a small subset of our patients.

Table 5—Results for All Study Patients in 1990

<table>
<thead>
<tr>
<th>Tests</th>
<th>No.</th>
<th>Percentage Predicted Mean (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>52</td>
<td>95 (90–101)</td>
<td>0.08</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>52</td>
<td>101 (97–105)</td>
<td>0.5</td>
</tr>
<tr>
<td>VC</td>
<td>52</td>
<td>94 (90–99)</td>
<td>0.01</td>
</tr>
<tr>
<td>RV</td>
<td>52</td>
<td>128 (119–136)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TLC</td>
<td>52</td>
<td>106 (101–111)</td>
<td>0.02</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>52</td>
<td>104 (100–110)</td>
<td>0.08</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>35</td>
<td>79 (70–90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DLCO*</td>
<td>45</td>
<td>117 (110–125)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Values adjusted for hemoglobin.
errors. As regards disease duration, this finding perhaps suggests that if PFT abnormalities are going to develop, then this will occur early in the course of the disease. Although one of our subjects with initially abnormal results died from progressive lung disease in the intervening period, in general abnormal initial PFT results did not predict a bad outcome. We are not able to explain the negative association found between sulfasalazine use and poor outcome, as the group treated with this agent were no different from the other subjects with respect to RA characteristics.

A significant proportion (35%) of our patients acquired respiratory symptoms by the end of the 10-year period, which was in excess of that expected for healthy, lifelong nonsmokers, and is in keeping with the higher prevalence of PFT abnormality in the study cohort. This figure is likely to be inflated as initial symptom evaluation was by informal questioning, whereas at reassessment we used a more sensitive tool. However, neither symptoms nor passive smoking exposure were associated with the development of pulmonary function abnormality or with a poor outcome.

CONCLUSIONS

We have demonstrated that, within a population of patients with RA selected as lifelong nonsmokers with no respiratory symptoms, the prevalence of pulmonary function abnormality is higher than expected when compared with a reference population, but did not increase over 10 years. Assessed by group means and SRs, both DLCO and RV/TLC became significantly abnormal in 2000 when compared with reference values. However, rates of change of pulmonary function variables were not significantly different from zero, and no particular trend emerged when patients were classified as having an obstructive, restrictive, or mixed picture. Neither disease characteristics nor development of respiratory symptoms were associated with abnormal lung function. Analysis using percentage of predicted values, rather than SRs, is misleading, as it exaggerates the extent of abnormality present. Abnormal lung function is a common and probably benign finding in nonsmoking, asymptomatic patients with RA.

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