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Airways obstruction in rheumatoid arthritis

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SUMMARY Owing to the report of an association between rheumatoid arthritis (RA) and obliterative bronchiolitis we have determined the prevalence of airflow obstruction in unselected patients with RA and normal chest radiographs. Spirometry was performed on 100 patients with rheumatoid arthritis and 84 control subjects matched for age, sex, and smoking habits. Patients with rheumatoid arthritis had significantly lower values for FEV_1, FVC, FEV_1/FVC, and MMEFR when compared with the controls: 39 patients had abnormal spirometry, and at least 32 showed airways obstruction. The prevalence of airflow obstruction is remarkably high, and we suggest that airway disease may be the commonest form of lung involvement in rheumatoid arthritis.

Rheumatoid arthritis (RA) is associated with a number of different lung disorders. These include pleural effusions, Caplan's syndrome, pulmonary rheumatoid nodules, fibrosing alveolitis, bronchiectasis, and a increased incidence of chest infections (Walker, 1967). Surprisingly little attention has been paid to the airways in RA. Reports of lung function tests have been few and have either concentrated on patients with interstitial lung disease (Newcomer *et al.*, 1964; Patterson *et al.*, 1965; Walker and Wright, 1969) or ignored evidence of obstruction, excluding such patients (Worwell *et al.*, 1975) or attributing the abnormalities to smoking. Collins *et al.* (1976) reported airflow obstruction in 26 of 43 patients with RA but 24 of the 26 were smokers.

We have reported 6 patients with obliterative bronchiolitis (Geddes *et al.*, 1977a) and suggested an association between RA and airway disease. In order to assess the prevalence of airflow obstruction in RA we have, therefore analysed the spirograms from 100 consecutive patients with RA obtained in a prospective study.

Patients and methods

One hundred consecutive patients with RA (American Rheumatism Association classical or definite) attending the Westminster Hospital Rheumatology Clinic were tested. No attempt was made to select the patients on the grounds of respiratory symptoms, smoking history, or severity of joint disease, though any patient with significant chest *x*-ray abnormality was excluded. Eighty-four healthy control subjects with normal chest *x*-rays were also tested. These were referred for routine chest *x*-ray for insurance purposes or before taking up employment. They were matched with the rheumatoid patients for age, sex, and smoking habits as shown in Table 1. The mean age of patients with RA was 53·4 years (range 23–78) and for controls 51·0 years (range 21–72). Patients and controls were matched for number of cigarettes smoked per day and age. It was not possible to calculate the number of pack years, as full details of smoking history were not available for the control group.

Spirometry was performed with an Ohio Electomed Model 780 dry piston spirometer, which generates electrical signals of volume and flow. These signals were fed into the hospital IBM 1800 computer, which calculated the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and maximum mid-expiratory flow rate (MMEFR). At the same time a spirogram was drawn

Table 1 *Characteristics of patients and control subjects*

		Male			*Female*		
		No.	*Mean age*	*Mean cigs./day*	*No.*	*Mean age*	*Mean cigs./day*
RA	Smokers	19	53·6	16·8	34	52·0	14·7
	Nonsmokers	6	52·0	–	41	54·4	–
	Total	25	53·2	–	75	53·4	–
Control	Smokers	18	51·6	15·9	28	51·2	14·5
	Nonsmokers	6	50·0	–	32	50·6	–
	Total	24	51·2	–	60	50·9	–

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on a paper recorder in the laboratory. Each patient produced at least 3 spirograms, and the 1 which produced the highest values with a smooth curve was selected for analysis. Predicted values were derived for each patient by using the data of Cotes (1975) for FEV_1 and FVC and of Morris *et al.* (1971) for MMEFR.

Results

Table 2 shows the means and standard errors of the measurements in the patients and controls for both the smokers and the nonsmokers.

The control population showed good agreement with predicted values for all measurements except MMEFR. The mean MMEFR among our controls was 82% of the predicted value. However, 54% of our controls were smokers, while the predicted values of Morris *et al.* (1971) were obtained in nonsmokers, and this may partly explain the difference. The mean value of each measurement among the controls was lower in smokers than nonsmokers, but the difference is not significant ($P>0{\cdot}05$).

Patients with RA had significantly lower mean values of FEV_1, FVC, FEV_1/FVC, and MMEFR than controls, and this difference was greatest for MMEFR. When the patients with RA were divided into smokers and nonsmokers and compared with their matched controls, much the same abnormalities were found. FEV_1 and MMEFR were both significantly reduced for smokers and nonsmokers with RA. The low mean FEV_1/FVC ratio, however, reached significance only among the smokers. Among patients with RA smokers had a lower FEV_1/FVC ($P<0{\cdot}01$) and MMEFR ($P<0{\cdot}001$) than nonsmokers.

The numbers of subjects with abnormal values for each spirometric measurement is shown in Table 3. We have defined as abnormal any measurement lower than the 95% one-tailed confidence limits of the controls (mean minus SD $\times$ 1·65). This gives the lower limit of normal as 71% of predicted for FEV_1 and the FVC, 84% of predicted for FEV_1/FVC, and 40% of predicted for MMEFR. This allows a much wider range of normal than is usual in most lung function laboratories. Nevertheless, 24% of the patients with RA had a low FEV_1/FVC and 38% had a low MMEFR. Since a number of individuals had more than 1 abnormal measurement, the abnormalities are summarised by patients in Table 4. The most sensitive test was the MMEFR, which was lower in patients with RA than controls for all decades except 20–29 years. The mean MMEFR (% predicted) for each decade fell with age in the patients with RA but was constant in the controls. The *t* test for independent means was used for statistical analysis. The data were normally distributed as judged by the Kolmogorov-Smirnov D statistic.

Table 3 *Number of subjects having abnormal values for each test (for definition of abnormal see text)*

		FEV_1	*FVC*	*FEV_1/FVC*	*MMEFR*
Smokers	RA	18	8	14	24
	Controls	2	0	2	2
Nonsmokers	RA	10	7	10	14
	Controls	0	0	1	0
Total	RA	28	15	24	38
	Controls	2	0	3	2

Table 4 *Abnormalities in patients with RA classified by defect*

	Smokers	*Nonsmokers*	*Total*
1. Low MMEFR only	7	1	8
2. Low MMEFR and FEV_1/FVC	14	10	24
Total 1 and 2	21	11	32
3. Low MMEFR and FVC	3	3	6
Total low MMEFR	24	14	38
4. Low FVC and normal MMEFR		1	

Discussion

Among the patients with RA and normal chest *x*-rays in this study at least one-third showed evidence of airflow obstruction. This prevalence is remarkably

Table 2 *Spirometric values for patients with RA and controls. Figures are mean ± standard error of the mean*

	No.	*FEV_1 (l)*	*FVC (l)*	*FEV_1/FVC (%)*	*MMEFR (l/sec)*
Smokers RA	53	2·05±0·11	2·91±0·15	71·6±1·3	1·59±0·14
Control	46	2·51±0·10	3·25±0·13	78·8±1·3	2·37±0·12
P<		0·01	NS	0·001	0·001
Nonsmokers RA	47	2·11±0·12	2·61±0·12	77·7±1·3	2·03±0·15
Control	38	2·61±0·12	3·35±0·17	78·6±1·2	2·61±0·13
P<		0·01	0·01	NS	0·01
Total RA	100	2·09±0·08	2·77±0·10	74·5±1·0	1·80±0·10
Control	84	2·56±0·08	3·30±0·10	78·7±0·9	2·48±0·09
P<		0·001	0·001	0·02	0·001

high and it is surprising that it has not been commented on in other reports. Previous studies of lung function in RA have tended to concentrate on evidence of pulmonary interstitial disease and to ignore the airways. Newcomer *et al.* (1964) tested 13 patients with RA and chest *x*-ray abnormalities and found restrictive defects.

However, 4 of their patients had definite airways obstruction and 10 had high residual volumes. They attributed these changes to age or smoking. Walker and Wright (1969) reported lung function tests in patients selected for evidence of fibrosing alveolitis, nevertheless 2 of their 9 patients had unequivocal airways obstruction. Similarly, Patterson *et al.* (1965) selected patients with fibrosing alveolitis for study. Frank *et al.* (1973) reported lung function tests on 41 unselected patients with RA and showed that 41·4% had abnormalities of gas transfer. A number (not specified) of their patients also had airways obstruction but this was attributed entirely to smoking. Average values for MMEFR are reported and appear to be lower than predicted, but full details are not given. Davidson *et al.* (1974) reported on lung function tests done in 42 patients with RA, with normal chest *x*-rays, and found low FEV_1/FVC ratios indicating airways obstruction in 10 patients. Their findings are very similar to ours except that the MMEFR was not reported. However, since the purpose of the study was to assess the prevalence of a low gas transfer in RA, the obstructive defect is not discussed.

Schernthaner *et al.* (1976) reported on 62 patients and found a correlation between diffusion capacity and rheumatoid factor. Their results also show that 42% of their patients had high residual volumes, 21% had low FEV_1/FVC ratios, and 18% had a high airways resistance.

All of these results suggest that airflow obstruction is common in RA. Only 1 study has, to our knowledge, specifically investigated airway function. In this study Collins *et al.* (1976) reported that 26 of the 43 patients with RA had MMFERs less than 80% predicted. They also showed that the mean MMEFR among smokers with RA was lower than that among matched smokers with degenerative joint disease, and this suggests that airflow obstruction may occur in RA more than can be explained by smoking alone. However, 24 of their 26 patients with low MMEFRs were smokers, and so the importance of RA alone in the development of airway obstruction is not possible to assess. The problem common to all these studies is the lack of control series, without which the prevalence of a functional abnormality in RA cannot be assessed accurately.

We found highly significant differences between patients with RA and matched controls for all the spirometric values we measured. The results in our controls agree well with the predicted values, and this suggests that they are truly representative of the normal population. Our control population have low MMEFRs compared with predicted, but this does not affect our results, since we are using these controls to determine the normal range. If anything, we have underestimated the prevalence of abnormality in RA by doing this. Most laboratories consider a value of 80% predicted to be abnormal, and this would considerably increase the number of abnormal patients in our series. The fact that we have selected patients with normal *x*-rays is similarly likely to underestimate the prevalence of abnormalities. Thirty-two patients had definite evidence of obstruction on the basis of a low FEV_1/FVC ratio or a low MMEFR with a normal FVC (Table 4). A further six patients have a low FVC. A low vital capacity can be caused by small airways disease alone (Green, 1977), and on this basis the results of these 6 patients may be interpreted as showing small airways obstruction without the need to postulate any fibrosis. If this interpretation is correct, the prevalence of airflow obstruction in our rheumatoid patients is 38%.

The role of muscular weakness in causing these spirometric abnormalities must be considered. Weakness results in a reduction of vital capacity. The FEV_1 is less affected, since most of the forced expiratory manoeuvre is effort-independent; muscular weakness therefore causes a rise in the FEV_1/FVC ratio. The MMEFR is effort-independent and will not be affected by muscular weakness.

Two possible explanations for this high prevalence of airways obstruction are worth considering. An association between RA and α1 antitrypsin phenotypes has been reported (Cox *et al.*, 1976), and this could in theory predispose some patients with RA to emphysema. However, in a separate study (Geddes *et al.*, 1977b) we have looked at the incidence of α1 antitrypsin phenotypes in our patients with RA who also took part in this study, and found no significant association. A more attractive explanation is that the obstruction is due to frequent respiratory tract infections. The role of recurrent infections independent of smoking in causing airflow obstruction is controversial. The fact that we have matched our patients for smoking habits and found evidence of airflow obstruction in the nonsmokers is strong evidence that neither smoking itself nor an increased susceptibility to its effects is the sole cause of airflow obstruction. Walker (1967) has shown that patients with RA are more prone to respiratory tract infections than patients with osteoarthrosis, and bronchiectasis is also more common. We have

reported 5 patients with RA in whom bronchiolitis caused progressive airway obliteration and respiratory failure (Geddes *et al.*, 1977a) and have since seen others. Murphy *et al.* (1976) reported a similar patient with RA and severe airways disease, although they attributed this to inhalation of fumes; we could not obtain such a history in any of our patients. It appears, therefore, that patients with RA may have an increased susceptibility to airway infections or a reduced ability to control and eradicate these infections. Such a tendency may be evident as bronchiectasis or progressive airway obliteration, but the present study suggests that a defect is present in many patients without overt pulmonary disease.

Walker (1967) noted that the diagnosis of bronchiectasis in his patients often preceded the development of RA. There has been much speculation about the initiating role of infective agents in the pathogenesis of RA. It may be that respiratory pathogens should be considered further in this light.

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