Bronchial reactivity and airflow obstruction in rheumatoid arthritis

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Abstract

Objective—To investigate the prevalence of airways obstruction and bronchial reactivity to inhaled methacholine in rheumatoid arthritis patients and un-selected controls. The control population consisted of patients attending the rheumatology department for minor degenerative joint problems.

Methods—One hundred patients with rheumatoid arthritis (RA) [72 (72%) women, 28 (28%) men; mean (SD) age 58 (10) years] and fifty controls [30 (60%) women, 20 (40%) men; mean (SD) age 56 (9) years] were studied. Detailed medical, smoking and drug histories were taken; skin prick tests were performed to assess atopy and chest and hand radiographs were performed. Spirometry, flow volume loops and gas transfer factor measurement were performed to detect airflow obstruction and methacholine inhalation tests were carried out to assess bronchial reactivity.

Results—There was no significant difference between rheumatoid arthritis patients and the controls in age, sex, smoking status and atopy on skin prick testing (p < 0·05). A significantly higher number of patients with RA had a history of wheeze compared with the controls (18% v 4%, p < 0·05). FEV1, FVC, FEV1/FVC, FEF25–75%, FEF25%, FEF50% and FEF75% were all significantly lower in the rheumatoid arthritis group (p < 0·05). A significantly higher number of patients with RA compared with controls showed bronchial reactivity to inhaled methacholine [55 (55%) v 8 (16%), p < 0·05]. FEV1, FVC, FEV1/FVC, FEF25–75%, FEF25%, FEF50% and FEF75% were all significantly lower among the patients with RA achieving PD_{20} FEV1 to inhaled methacholine (p < 0·05).

Conclusion—In unselected rheumatoid arthritis patients both airflow obstruction and bronchial reactivity are significantly increased compared with controls.

(*Ann Rheum Dis* 1994; 53: 511–514)

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Accepted for publication 29 April 1994

Rheumatoid arthritis affects the respiratory system in various ways.[1] While interstitial lung disease is a well recognised complication of rheumatoid arthritis (RA), studies on small airways involvement have produced differing results.[2-10] Some of these studies, however, were uncontrolled,[7-8] some had very small numbers of patients,[6 7] while others either included a predominance of smokers[8] or defined nonsmokers by their smoking status at the time of assessment, without consideration of previous smoking.[3-4] In only one of these studies[9] was the smoking status of both ex-smokers and current smokers expressed as pack years. Several factors such as tobacco consumption, previous pulmonary infections, alpha-one anti-trypsin deficiency and drug treatment have been proposed as causes, although there is little doubt about the rare association between penicillamine and the development of bronchiolitis obliterans.[1]

Bronchoalveolar lavage studies in patients with RA have shown increased numbers of inflammatory cells compared with controls suggesting increased inflammation in the airways.[1] Surprisingly there has been no reported study on bronchial reactivity in patients with RA. In a prospective study we have assessed 100 patients with RA and 50 controls to estimate the prevalence of airflow obstruction and degree of bronchial reactivity.

Patients and methods

The research project was approved by the Sunderland Health Authority Ethics Committee and written consent was obtained from all the subjects. One hundred unselected, out-patients with rheumatoid arthritis as defined by the ARA classification[11] and 50 controls were included in the study. The control population was taken from patients attending the rheumatology department outpatients for minor degenerative joint problems. Each subject visited the hospital twice for study purposes.

On the first visit detailed medical, smoking (one pack year = 20 cigarettes daily for one year) and drug histories were obtained. Patients were asked questions based on the Medical Research Council Questionnaire for the respiratory system.[12] Skin prick tests for house dust mite, grass pollens, aspergillus fumigatus, mixed feathers and any other antigen for which the subject gave a history suggestive of sensitisation were carried out on the anterior aspect of the forearm and compared with the control solution (Bencard). A wheal of 2 mm or more and greater than that of the control was considered positive. In the rheumatoid arthritis patients haemoglobin, ESR, and auto-antibodies were checked and radiographs of hand and chest performed.

BRONCHIAL REACTIVITY

Bronchial reactivity was assessed by methacholine inhalation using a tidal breathing

method.[13] The Wright's nebuliser has a mean (SD) output of 0·14 (0·03) ml/min, when 5 ml of saline is nebulised at a flow rate of 8 litres per minute. Only those subjects with an FEV1 of more than 60% of predicted had the methacholine challenge test. First, normal saline was nebulised for two minutes followed by 90 seconds rest. If the base line FEV1 dropped by 20% or more the test was abandoned. The target value of FEV1 was calculated from the lowest post saline FEV1. Nebulised methacholine in saline was administered in a doubling concentration dose, starting at 0·5 mg/ml to a maximum of 32 mg/ml. After each dose, three FEV1 readings were taken after 90 seconds and the lowest value was recorded. The test was stopped when FEV1 dropped by at least 20% or when the maximum dose of methacholine was administered. The methacholine concentration provoking a 20% decrement in FEV1 (PD_{20} FEV1) was calculated from the log dose response curve.

PULMONARY FUNCTION TESTS

Within one month of the methacholine challenge, all patients with RA had detailed pulmonary function tests performed. These comprised forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow between 25% and 75% of vital capacity (FEF25–75%), forced expiratory flow at 25% (FEF25%), 50% (FEF50%) and 75% (FEF75%) of the vital capacity, residual volume (RV), total lung capacity (TLC) and gas transfer factor measurement (TLCO). Flow volume loops and TLCO measurements were performed using PK Morgan autolink apparatus (PK Morgan Ltd, Kent, UK). Lung volumes were measured by the single breath technique and TLCO by single breath technique. Observed values were compared with those predicted for age, sex and height as described by the working party of the European Community for Coal and Steel.[14] In the control population FEV1, FVC, FEV1/FVC, FEF25–75%, FEF25%, FEF50% and FEF75% were assessed by the same technique and on the same apparatus as used for the patients with RA.

STATISTICAL ANALYSIS

The results of FEV1, FVC, FEV1/FVC, FEF25–75%, FEF25%, FEF50%, FEF75%, RV, TLC and TLCO are expressed as the percentage of the predicted for each individual adjusted for age, sex and height. Group data are expressed as mean (SD). Two way analysis of variance was used to compare the effect of smoking on spirometry between the rheumatoid arthritis and the control group. One way analysis of variance was used to compare the effects of treatment on pulmonary function in the rheumatoid arthritis group. Contingency tables were analysed for statistical significance using the Chi square test and Fisher's exact tests as appropriate. All analyses were performed using Minitab statistical package (Minitab software, Cleocom, Birmingham, UK).

Results

In the rheumatoid arthritis group there were seventy two (72%) females and the mean (SD) age was 58 (10) years. The mean (SD) duration of rheumatoid arthritis was 10 (7) years. Thirty six (36%) patients had never smoked, forty (40%) were ex-smokers and twenty four (24%) were current smokers. The mean (SD) duration of smoking (pack years) in the ex-smokers group was 15 (10) and in the current smokers group 23 (12). Eighteen (18%) patients had a history of wheeze, twelve (12%) pleurisy, nine (9%) pneumonia and two (2%) had had pulmonary TB. Ten (10%) showed atopy on skin prick testing to house dust mite only. Thirty three (33%) patients were taking salazopyrin, seventeen (17%) intramuscular gold, eleven (11%) penicillamine and two (2%) methotrexate. Eighty one (81%) patients were taking NSAIDs. The mean (SD) haemoglobin was 124 (25) g/dl, mean (SD) ESR 33 (22) mm/hour with a median rheumatoid factor of 1:160. Three (3%) patients with RA were seronegative for rheumatoid factor and seven (7%) were ANF positive (>1:80). Fifty seven (57%) patients had an erosive arthropathy and three (3%) patients had an abnormal chest radiograph, two (2%) showing pulmonary fibrosis and one (1%) hyperinflation.

In the control group there were thirty (60%) female and the mean (SD) age was 56 (9) years. Nineteen (38%) patients had never smoked, eighteen (36%) were ex-smokers and thirteen (26%) were current smokers. The mean (SD) duration of smoking (pack years) in the ex-smokers group was 23 (13) and in the current smokers group 18 (8). Two (4%) patients had a history of wheeze, one (2%) pleurisy, two (4%) pneumonia and none had had pulmonary TB. Two (4%) showed atopy on skin prick testing to house dust mite only. Thirty four (68%) were taking NSAIDs intermittently.

There was no significant difference between the rheumatoid arthritis and the control group in mean (SD) age [58 (10) *v* 56 (9), p > 0·05] and sex [72 (72%) female and 28 (28%) male in the RA group *v* 30 (60%) female and 20 (40%) males, p > 0·05]. There was also no significant difference between the groups in the proportion of non-smokers, ex-smokers and current smokers (Chi square 0·228, DF-2, p > 0·05) or the mean (SD) number of pack years smoked [ex-smokers 15 (10) *v* 23 (13) and current smokers 23 (12) *v* 18 (8), p > 0·05]. A significantly higher proportions of patients with RA had a history of intermittent wheeze compared with the control group (18% *v* 4%, Chi square 16, DF 1, p < 0·005), but there was no significant difference between the two groups in the history of pleurisy (12% *v* 2%), pneumonia (9% *v* 4%), pulmonary TB (2% *v* 0), atopy on skin prick testing (10% *v* 4%) or between patients on NSAIDs (81% *v* 68%).

FEV1, FVC, FEV1/FVC, FEF25–75%, FEF25%, FEF50% and FEF75% were all significantly lower in the rheumatoid arthritis group compared with the control group (table 1). Smoking significantly effected all the

Table 1   To compare pulmonary function of the rheumatoid arthritis and the control group

	RA [n = 100]	Control [n = 50]	RA v Control		Smoking		Smoking × RA/control interaction	
			$F_{1,144}$	P	$F_{2,144}$	P	$F_{2,144}$	P
FEV1	98 (24)	109 (22)	7·71	0·006	7·70	0·001	0·45	ns
FVC	109 (24)	117 (19)	4·07	0·045	6·25	0·002	0·04	ns
FEV1/FVC	71 (10)	76 (8)	7·07	0·009	6·24	0·003	1·01	ns
FEF25–75%	63 (28)	83 (27)	17·03	0·000	5·54	0·005	0·74	ns
FEF-25%	87 (34)	103 (28)	9·23	0·003	2·42	0·090	0·22	ns
FEF-50%	80 (38)	95 (35)	7·36	0·007	5·09	0·007	1·62	ns
FEF-75%	57 (29)	79 (32)	19·60	0·000	5·31	0·006	0·11	ns

Group data expressed as mean (SD). Effect of smoking status (never smoked, ex-smokers, current smokers) on pulmonary function between the two groups and the interaction between smoking × RA/control is assessed by two-way analysis of variance. Forced expiratory volume in one second = (FEV1); Forced vital capacity = (FVC); FEV1/FVC; Forced expiratory flow between 25% and 75% of vital capacity = (FEF25–75%); Forced expiratory flow at 25% = (FEF25%), 50% = (FEF50%) and 75% = (FEF75%) of the vital capacity.

spirometric variables (except FEF25%) in both the rheumatoid arthritis and the control groups. However, there was no significant difference in the effect of smoking on pulmonary function

Table 2   To compare the effect of different treatments on pulmonary function in the rheumatoid arthritis group

	Treatment					$F_{4,95}$	P
	A [37]	B [33]	C [17]	D [11]	E [2]		
FEV1	92 (27)	106 (22)	97 (19)	102 (18)	66 (23)	2·46	ns
FVC	105 (22)	115 (17)	108 (22)	112 (17)	90 (4)	1·52	ns
FEV1/FVC	69 (11)	74 (10)	73 (6)	72 (5)	62 (18)	1·54	ns
FEF25–75%	59 (30)	71 (31)	61 (19)	64 (17)	29 (24)	1·64	ns
FEF-25%	78 (38)	97 (35)	86 (28)	92 (22)	59 (29)	1·80	ns
FEF-50%	69 (37)	93 (45)	75 (25)	81 (22)	39 (37)	1·02	ns
FEF-75%	53 (31)	62 (31)	58 (24)	56 (19)	26 (33)	2·24	ns

A: No second line agent, B: Salazopyrin, C: Intramuscular gold, D: Penicillamine, E: Methotrexate. Group data are expressed as mean (SD). One-way analysis of variance was used to compare pulmonary function between different groups.

Table 3   To compare clinical features and pulmonary function in patients with rheumatoid arthritis with PD_{20} and $PD_{<20}$ to methacholine

	PD_{20} (n = 55)	$PD_{<20}$ (n = 45)	95% CI for difference	P
Smoking status				
Never smoked	15 (42%)	21 (58%)		
Ex-smoker	23 (57%)	17 (43%)		(Chi square 5·118,
Current smoker	17 (71%)	7 (29%)		DF 2, p > 0·05)
Pack years				
Ex-smoker	16 (12)	14 (9)	−4·9, 8·9	ns
Current smoker	23 (13)	22 (12)	−11·8, 13·1	ns
Wheeze	13 (72%)	5 (28%)		ns
Pleurisy	6 (50%)	6 (50%)		ns
Pneumonia	7 (78%)	2 (22%)		ns
Atopy	4 (40%)	6 (60%)		ns
FEV1	87 (25)	107 (26)	−29·7, −9·1	0·0030
FVC	105 (21)	116 (19)	−18·4, −2·6	0·0090
FEV1/FVC	68 (6)	76 (9)	−12, −4·7	0·0001
FEF25–75%	54 (27)	75 (25)	−32·1, −11·3	0·0001
FEF25%	75 (34)	101 (28)	−38·2, −13·4	0·0001
FEF50%	67 (36)	95 (35)	−43·1, −14·7	0·0001
FEF75%	49 (26)	66 (30)	−28·9, −6·1	0·0035
RV	98 (21)	89 (20)	−0·6, 18·3	ns
TLC	102 (11)	96 (19)	−0·7, 12·1	ns
TLCO	73 (15)	80 (19)	−13·2, 0·6	ns

Group data expressed as mean (SD). RV, Residual volume; TLC, Total lung capacity; TLCO, transfer factor. Contingency tables are analysed by Chi square and Fisher's exact test as appropriate.

Table 4   To compare those patients in the rheumatoid arthritis and the control groups achieving PD_{20} FEV1

	RA	Control	95% CI for difference	P
Number of patients	55 (55%)	8 (16%)		Chi square 20·81, DF 1, p < 0·001
Smoking status				
Never smoked	15 (42%)	0 (0%)		
Ex-smoker	23 (57%)	5 (28%)		Chi square 2·95,
Current smoker	17 (71%)	3 (23%)		DF 2, p > 0·05
Pack years				
Ex-smoker	16 (12)	30 (10)	−26·3, −1·2	0·03
Current smoker	23 (13)	20 (14)	−34·4, 40·4	ns
FEV1	89 (9)	81 (20)	−10·1, 25·7	ns
FVC	105 (21)	106 (10)	−11·7, 8·4	ns
FEV1/FVC	68 (10)	63 (8)	−2·9, 12·5	ns
FEF25–75%	54 (27)	65 (44)	−49·7, 27	ns
FEF25%	75 (34)	70 (23)	−15·2, 26·8	ns
FEF50%	67 (36)	47 (33)	−9·1, 49	ns
FEF75%	49 (26)	57 (39)	−42·1, 26	ns

Group data expressed as mean (SD). Contingency tables are analysed by Chi square test.

between the rheumatoid arthritis and the control group (table 2). Within the rheumatoid arthritis group there was no significant difference in pulmonary function in patients on different treatments (table 3).

We divided our patients into two groups according to their bronchial reactivity. Those who achieved a 20% drop in their FEV1 up to a maximum of 32 mg/ml of methacholine were designated as PD_{20} and those who did not as $PD_{<20}$. In none of our patients did the baseline FEV1 fall by 20% following saline inhalation.

In the rheumatoid arthritis group fifty five (55%) patients achieved PD_{20}. There was no significant difference between the PD_{20} and $PD_{<20}$ group of rheumatoid arthritis patients in mean (SD) age [59 (11) v 57 (9), p > 0·05] and sex [41 (41%) F:14 (14%) M v 31 (31%) F:14 (14%) M, p > 0·05]. There was no significant difference between the two groups in the number of patients treated with NSAIDs (48% v 33%), salazopyrin (18% v 15%), gold (9% v 8%) and penicillamine (5% v 6%) or in mean (SD) Hb [123 (22) v 124 (29)], ESR [33 (21) v 34 (23)], median RF (1:160 v 1:180), ANF positive patients (5% v 2%) and erosions on hand radiographs (31% v 26%). Also there was no significant difference between the two groups in smoking status, history of wheeze, pleurisy, pneumonia or atopy on skin testing (table 3). FEV1, FVC, FEV1/FVC, FEF25–75%, FEF25%, FEF50% and FEF75% were all significantly lower in the PD_{20} group compared with the $PD_{<20}$ group, but there was no significant difference between the two groups in RV, TLC and TLCO (table 3).

A significantly higher proportion of patients with RA (55%) achieved PD_{20} compared with controls (16%) (p < 0·001) (table 4). There was no significant difference between the two groups in age [59 (11) v 61 (4), p > 0·05] and sex [41 (74%) F:14 (26%) M v 6 (75%) F:2 (25%) M, p > 0·05]. The number of pack years smoked were significantly higher in the control group. There was no significant difference between the two groups in pulmonary function (table 4).

Discussion

The pulmonary function tests in our study suggest that the incidence of airflow obstruction is significantly increased in patients with RA compared with controls. This is supported by the increased prevalence of

wheeze in patients with RA. Previous studies have explained similar findings on the basis of an increased prevalence of interstitial lung disease and smoking.[9] [10] However, these studies failed to demonstrate convincing evidence of interstitial lung disease and their assessments were based partly on the failure to demonstrate a significant reduction in the FEV1/FVC ratio in their patients. In our study only two (2%) patients had evidence of interstitial fibrosis on chest radiographs and residual lung capacity, total lung capacity and transfer factor measurement were normal in the rheumatoid arthritis group. Furthermore, the FEV1/FVC ratio was significantly reduced in rheumatoid arthritis patients. Our control population was taken from patients attending a rheumatology department for minor degenerative joint problems and although it did not represent a more 'general' group, there is no evidence to date to suggest an association of airflow obstruction or bronchial reactivity with minor degenerative joint problems.

The exact mechanism for the development of airways obstruction in rheumatoid arthritis is not yet known. One possibility is that the mucosal oedema secondary to pre-existing airways inflammation in rheumatoid arthritis[15] may lead to bronchial narrowing and hence cause airways obstruction. This aspect is being addressed in a further study in our unit. An increased incidence of respiratory tract infections such as viral bronchiolitis may play a role in the pathogenesis of airways obstruction, but in our study there was no significant increase in the history of pneumonia, pleurisy or pulmonary TB among patients with RA compared with controls. We also did not find any significant effect of disease modifying drugs on pulmonary function.

There has been no previously reported study on bronchial reactivity in rheumatoid arthritis. In unselected general population studies bronchial hyperreactivity is observed in 11–14% of the population.[16-18] In our study a significantly higher proportion (55%) of patients with RA showed increased bronchial reactivity compared with controls (16%) and there was no significant difference between the PD_{20} group of rheumatoid arthritis and the control group in smoking status or spirometry. However, within the rheumatoid arthritis group, patients with enhanced bronchial reactivity did have significantly lower values in all spirometric variables compared with the $PD_{<20}$ group, suggesting that pre-existing airflow obstruction may have contributed towards increased bronchial reactivity. There was no significant difference between the two groups in smoking status, however, the proportions of ex-smokers and current smokers were higher in the PD_{20}. History of wheeze, pleurisy, pneumonia or atopy on skin prick testing had no significant effect on bronchial hyperresponsiveness.

NSAIDs can cause exacerbation of pre-existing asthma and very rarely lead to the development of bronchospasm in people with no pre-existing lung pathology. In our study however, we did not find any significant effect of NSAIDs on bronchial reactivity. There was also no significant effect of disease modifying drugs, ANF or erosive arthropathy on bronchial reactivity. The cause of increased bronchial reactivity in patients with RA is unclear. Atopy is no more common in patients with RA than in a control population.[19] It is possible that inflammatory changes within the airways may sensitise the bronchial smooth muscle to inhaled methacholine, and mucosal oedema can lead to a lower baseline FEV1, but a study of the pathology of the airways themselves is needed to address this question.

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