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Lung function in rheumatoid arthritis

A clinic survey

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The occurrence of fibrosing alveolitis in patients with rheumatoid arthritis (RA) is uncommon, but is generally held to indicate specific involvement of the lung parenchyma by the rheumatoid disease process (Scadding, 1969). Large surveys (Thompson, 1965; Patterson, Harville, and Pierce, 1965; Walker and Wright, 1969) have shown that radiologically apparent fibrosing alveolitis is found in 1 to 2% of patients with RA, and lung function tests in the affected patients have usually shown a low transfer factor with a restrictive pattern of ventilatory function.

The possibility that parenchymal involvement of the lung in RA may be present without radiological change is suggested by the higher incidence of 'interstitial pneumonia' (6%) in a large autopsy study (Cruickshank, 1957). This is further supported by analogy with lung involvement in systemic sclerosis (Catterall and Rowell, 1963) and asbestosis (Williams and Hugh-Jones, 1960) in which a diminished gas transfer may precede radiological change. More recently, Loddenkemper, Bach, and Carton (1970) and Frank, Weg, Harkleroad, and Fitch (1973) have described patients with RA who had marked impairment of gas transfer with normal chest *x*-rays; lung biopsy in some of these showed nonspecific alveolar infiltration and fibrosis.

Although there have been many reports of lung function in patients with RA and established fibrosing alveolitis, there is little information on unselected patients with RA (Bates, Macklem, and Christie, 1971). In two studies, Huang and Lyons (1966) reported eleven and Gray and Gray (1967) fourteen patients, and showed a reduction in vital capacity and/or transfer factor in some of them, but little information about smoking habits or occupational dust exposure was given. The purpose of this study was to assess lung function, especially gas transfer, in patients with RA who had no radiological evidence of respiratory disease. Lung function tests were therefore performed on patients with established RA attending a rheumatology clinic, excluding as far as possible other factors known to influence gas transfer.

Patients and methods

PATIENT SELECTION

42 patients (25 female, 17 male) took part in the survey. All were under 65 and were selected on the following criteria.

(*1*) Classical or definite seropositive rheumatoid arthritis (American Rheumatism Association criteria) of at least 3 years' duration. Rheumatoid factor was measured by the standard sheep cell agglutination test.
(*2*) No dyspnoea within the limits imposed by the arthritis.
(*3*) No clinical or radiological evidence of lung disease (all *x*-rays were reviewed by a single observer).
(*4*) No clinical or ECG evidence of cardiac disease.
(*5*) No gross anaemia (Hb not less than 11 g/100 ml, females; not less than 12 g/100 ml, males).
(*6*) Not on treatment with corticosteroids.

CLINICAL ASSESSMENT

The extent of joint involvement was assessed in each patient using the grading of hand *x*-rays and the functional index, as described by Steinbrocker, Traeger, and Batterman (1949). Occupational exposure to dust was assessed together with past and present respiratory symptoms using the M.R.C. Questionnaire on Respiratory Symptoms (1966). If an occupational history was suggested by this, more extensive questioning was undertaken by Professor P. J. Lawther.

METHODS

Respiratory function tests were carried out using standard techniques. Total lung capacity (TLC) and the subdivisions of lung volume (residual volume RV) were measured using a closed circuit spirometer, and transfer factor (TF) using a single breath technique; duplicate measurements of TF were made on each subject and the means used in the analysis. When making measurements of ventilatory function, 5 technically satisfactory readings were obtained for each subject and in all subsequent analyses the mean of all observations of forced expiratory volume in 1 sec ($FEV_{1.0}$), forced vital capacity (FVC), and peak expiratory flow (PF) have been used.

The predicted values for each subject were derived from the regression equations compiled by Cotes (1968) to take account of the variations in age and height for each sex. As suggested by Bates and others (1971), measurements were

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taken to be abnormal when less than 80% of the predicted value. Statistical analysis was by Student's 't' test and, where appropriate, analysis of variance.

Results

CLINICAL DATA

The clinical features of the patients are summarized in Table I, and it can be seen that there are no substantial differences between male and female patients studied. Respiratory symptoms and smoking habits are shown in Table II. Six patients had pet birds, but avian antigen precipitins were negative and none had abnormal lung function. No other significant occupational dust exposure was found.

RESPIRATORY FUNCTION TESTS

The results of respiratory function tests are summarized in Table III and Fig. 1. The striking abnormality is evident from Fig. 1 where it can be seen that ten

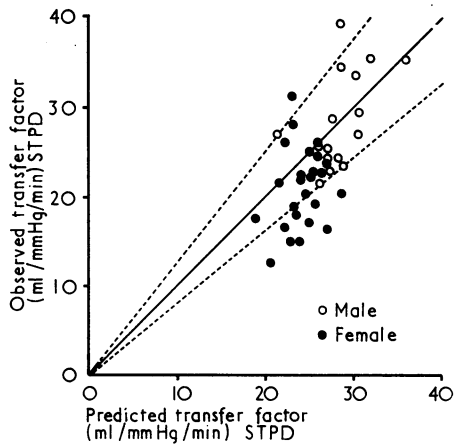

FIG. 1 *Transfer factor in the patients studied, plotting observed against predicted values. Broken lines indicate the normal range (±20% of the predicted value)*

Table I *Clinical data on the patients studied indicating, where appropriate, mean ± SD. Female patients are subdivided on the basis of low gas transfer (group B)*

	No. of patients	*Age (yrs)*	*Duration RA (yrs)*	*Rheumatoid factor (reciprocal titre)*	*Hb (g/100 ml)*	*ESR (mm/hr)*	*Nodules present*	*Functional index (grade)*		*Hand x-ray (grade)*	
								1–2	*3–4*	*1–2*	*3–4*
Male	17	52·8 ±8·1	10·8 ±7·0	539 ±799	13·4 ±1·2	51·2 ±23·8	8	12	5	5	12
Female A	15	46·6 ±11·7	8·6 ±6·6	121 ±72	12·3 ±1·6	39·8 ±25·9	5	11	4	7	8
B	10	46·2 ±13·6	10·2 ±5·4	228 ±233	12·1 ±1·2	59·5 ±32·6	5	7	3	3	7

Table II *Respiratory symptoms and smoking habits in patients studied. Female patients subdivided as in Table I*

	No. of patients	*Past respiratory illness*	*Chronic productive cough*	*Smoking habits (cigarettes)*		
				None	*<20/day*	*>20/day*
Male	17	9	5	5	9	3
Female A	15	4	7	8	5	2
B	10	4	7	2	3	5

Table III *Lung function tests indicating mean ± SD with predicted mean ± SD. Female patients are subdivided on the basis of low TF (group B)*

	TLC (l.)	*RV (l.)*	*RV/TLC (%)*	*FEV_1 (l.)*	*FVC (l.)*	*FEV_1/FVC (%)*	*PF (l./min)*	*TF (ml/mmHg/min STPD)*
Male	6·28 ± 0·93	1·77 ± 0·84	27·30 ± 10·47	3·02 ± 0·78	4·39 ± 0·82	68·52 ± 9·15	459·5 ± 79·0	28·20 ± 5·27
% predicted	94·8 ± 12·7	82·0 ± 39·5	77·3 ± 27·7	92·0 ± 17·3	101·6 ± 15·2	94·6 ± 11·7	83·3 ± 13·5	99·2 ± 16·3
Female								
A	4·74 ± 0·90	1·58 ± 0·55	32·20 ± 8·54	2·26 ± 0·53	3·06 ± 0·46	74·70 ± 11·90	327·1 ± 67·3	23·98 ± 3·16
% predicted	95·0 ± 14·6	87·6 ± 29·2	94·7 ± 23·6	93·3 ± 17·0	101·4 ± 11·2	93·6 ± 14·6	80·8 ± 17·2	97·0 ± 14·1
B	4·37 ± 0·94	1·65 ± 0·68	36·91 ± 9·08	2·04 ± 0·44	2·71 ± 0·50	75·7 ± 7·4	315·0 ± 42·5	16·88 ± 2·42
% predicted	89·7 ± 17·2	95·7 ± 41·2	108·9 ± 28·3	84·5 ± 18·4	92·2 ± 16·4	94·5 ± 11·5	78·9 ± 9·2	68·9 ± 6·2

patients, all female, have a low TF (less than 80% predicted). In order to see whether the clinical features or other lung function tests in the patients differed from the remainder, they are shown on Tables I, II, and III as a separate subgroup (group B) from the other female patients (group A). It can be seen from these tables that the affected patients have no real distinguishing features and other lung function tests did not differ significantly from those of the rest of the patients.

In the remaining patients ventilatory function was impaired in three female (2 smokers) and seven male patients (6 smokers) as defined by a low FEV/FVC per cent., and twelve had a low PF (7 females, 5 males). In none of these was there any increase in TLC or subdivisions of lung volumes to suggest emphysema, and comparison of the TF in patients with and without airways obstruction showed no significant difference.

CLINICAL FACTORS IN RELATION TO LUNG FUNCTION

In order to study lung function in the group as a whole the patients were subdivided on the basis of clinical criteria and the TF examined in each group, using per cent. predicted values to eliminate the variability due to age, height, and sex.

(a) Rheumatoid arthritis

There was no significant relationship between the TF and the duration of RA, the presence of subcutaneous nodules, functional index, severity of radiological involvement on hand *x*-ray, haemoglobin, ESR, or titre of rheumatoid factor.

(b) Respiratory history

There was no significant difference in TF between patients with and without past respiratory illness. There was, however, a significant relation between smoking and TF as indicated in Figs 2 and 3, with significant difference not only between nonsmokers, light and heavy smokers ($\chi^2 = 7{\cdot}36$; $P < 0{\cdot}05$), but also smokers with and without a chronic cough ($\chi^2 = 5{\cdot}21$; $P < 0{\cdot}05$). No significant relationship was found between smoking and the other respiratory function tests.

Discussion

The purpose of this study was to identify, in a routine clinic, rheumatoid patients with impaired gas transfer but normal chest *x*-rays, as described by Loddenkemper and others (1970). Gas transfer may, however, be influenced by factors other than parenchymal disease of the lung itself, and for this reason patients with anaemia (Rankin, McNeill, and Forster, 1961) and heart disease (Hamer, 1965) were necessarily excluded from the study. As a result, the group

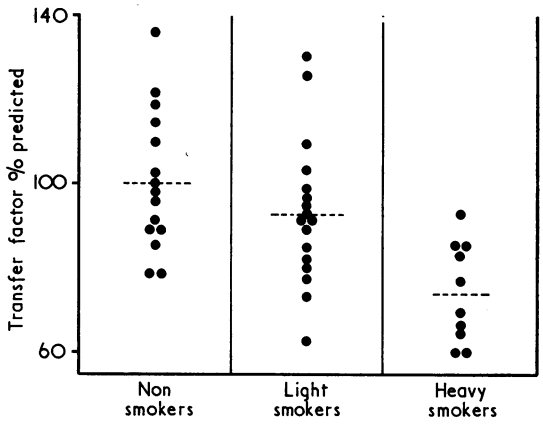

FIG. 2 *The influence of smoking habits on transfer factor; the difference between heavy smokers and the other two groups is significant* ($P < 0{\cdot}05$)

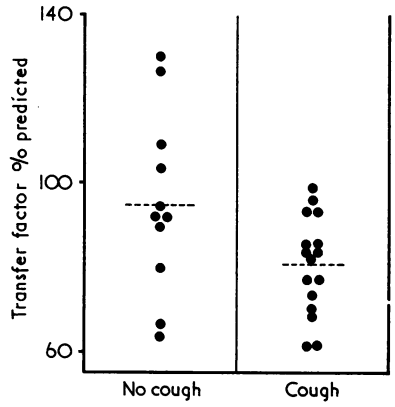

FIG. 3 *The influence of smoking on transfer factor; the difference between smokers with and without a chronic cough is significant* ($P < 0{\cdot}05$)

finally studied was far from unselected, particularly as anaemia is such a common feature of active RA. Nevertheless, of the 42 patients studied, ten were found to have a TF of less than 80% predicted (the arbitrary lower limit recommended by Bates and others, 1971). Even using the stricter limit of two standard deviations below the predicted value as suggested by Sobol and Weinheimer (1966), six patients had impaired gas transfer without any apparent cause. Since this study was completed, Frank and others (1973) have reported an even higher incidence (47%) of abnormal gas transfer in 41 patients with RA, but in some of these the chest *x*-rays were abnormal.

What evidence is there that this abnormality represents specific rheumatoid involvement of the lungs? The clinical features and pulmonary function tests of patients with fibrosing alveolitis and RA reported in

the literature have been reviewed by Walker and Wright (1968). Though the results of ventilatory function are somewhat variable, gas transfer is almost always impaired, but in these and the cases of Loddenkemper and others (1970) the value for TF was considerably lower than in the present study, generally less than 12 ml/mmHg/min. It is possible that this may merely reflect a difference in the extent of parenchymal lung damage in the different groups, rather than any difference in the underlying pathology. The clinical features of established cases do, however, differ from those of the affected patients in this study. Thus, fibrosing alveolitis is generally commoner in males with late onset RA, while all our patients were female and spanned all age ranges. A higher incidence of subcutaneous nodules, and high ESR and titre of rheumatoid factor have also been described, but in these and other clinical features the abnormal group showed no significant difference from the remainder of the patients.

The only other factor to emerge from the present data is the general relationship between gas transfer and smoking habits. Thus, all but two of the patients with low TF were smokers, and all those with the most marked impairment of gas transfer (less than 70% predicted) were heavy smokers; and this is similar to the results of Frank and others (1973) who found that the tobacco consumption in their abnormal group was significantly higher than in the normal patients. Walker and Wright (1968) drew attention to the lack of information on smoking habits in reported cases of fibrosing alveolitis and RA and it is of considerable interest that heavy smoking was much commoner in the cases they studied than the rheumatoid population as a whole. This raises the possibility that, by analogy with the undue susceptibility to pulmonary infections in RA (Walker, 1967), these patients may also respond abnormally to other noxious stimuli such as cigarette smoking. However, it is clear from Figs 2 and 3 that the relationship between smoking habits and TF applies to the group as a whole, and this is generally recognized from other studies of smoking in normal subjects which show an impairment of gas transfer of the same order as in the present study (Rankin, Gee, and Chosy, 1965; Woolf and Suero, 1971). It is also of interest that though ventilatory function is less consistently affected by smoking, the finding of difference in TF between smokers with and without chronic cough in this study is similar to other data relating ventilatory function and smoking habits (Read and Selby, 1961). It seems likely, therefore, that whether or not specific rheumatoid involvement of the lungs is present, smoking habits may account for some of the impairment of gas transfer which has been observed in this study, and this may well be relevant to the interpretation of other studies where no details of smoking habits are given.

The evidence from the present study suggests that abnormal lung function may occur fairly commonly in asymptomatic patients with RA and normal chest *x*-rays. Ten patients without any clinically distinguishing features have a TF falling below the normal range; this may represent parenchymal involvement of the lung or simply reflect the high incidence of smoking in this group. In order to confirm this lung biopsy would be necessary, but this was not felt to be justifiable in asymptomatic patients, particularly as the results of treatment are poor (Stack and Grant, 1965). The significance of these findings can therefore only be determined by careful follow-up with further lung function studies.

Summary

Respiratory function tests were undertaken in 42 patients (25 female, 17 male) with rheumatoid arthritis in order to see whether parenchymal involvement of the lung could be detected in patients with a normal chest *x*-ray. Significant airways obstruction was present in ten patients (3 female, 7 male), but impaired gas transfer, as measured by the carbon monoxide method, was present in ten female patients without any other abnormality. This latter group had no history of occupational exposure to dust, and did not differ in respiratory symptoms or clinical features from the remainder of the patients, apart from the fact that most were heavy smokers. A significant correlation between gas transfer and smoking habits was found in the group of patients as a whole, and it is concluded that while abnormal gas transfer may indicate rheumatoid involvement of the lung, smoking habits must be taken into account in the interpretation of the results.

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