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Seropositive rheumatoid arthritis associated with decreased diffusion capacity of the lung

G. SCHERNTHANER, O. SCHERAK, G. KOLARZ, AND F. KUMMER
From II. Medical Clinic, University of Vienna, Austria

Schernthaner, G., Scherak, O., Kolarz, G., and Kummer, F. (1976). *Annals of the Rheumatic Diseases*, **35**, 258–262. **Seropositive rheumatoid arthritis associated with decreased diffusion capacity of the lung.** Sixty-two patients with classical or definite rheumatoid arthritis were subjected to lung function analysis. The various parameters—spirography, plethysmography, blood gas analysis, measurement of lung compliance, and diffusion capacity—were correlated with duration and stage of disease, and with rheumatoid factor titres.

A statistically significant correlation was found to exist between Rose-Waaler titre and specific diffusion capacity. Similar results between Rose-Waaler titre and lung compliance, however, were not statistically significant.

Involvement of the lungs in rheumatoid arthritis (RA) has been found in varying degrees depending on the method of investigation. Lung changes in RA have been reported by several authors. The prevalence depends on the method of investigation, namely, whether autopsy (Aronoff, Bywaters, and Fearnley, 1955; Talbott and Calkins, 1964), *x*-ray (Horler and Thompson, 1959; Georg, 1961; Sievers, Hurri, and Perttala, 1964; Brannan and others, 1964; Patterson, Harville, and Pierce, 1965; Pierce, 1968; Walker and Wright, 1969; Vignon, 1972; Hofner, Lobenwein-Weinegg, and Thumb, 1974), or lung function (Newcomer and others, 1964; Huang and Lyons, 1966; Loddenkemper, Bach, and Carton, 1970; Popper, Bogdonoff, and Hughes, 1972; Frank and others, 1973; Laitinen, Salorinne, and Poppius, 1973; Morere, Stain, and Nouvet, 1973; Davidson, Brooks, and Bacon, 1974; Börngen, 1975) was applied.

Rheumatoid factors have also been shown frequently in idiopathic interstitial fibrosis of the lung (Tomasi, Fudenberg, and Fiuby, 1962; Turner-Warwick and Doniach, 1965; Ward and Stalker, 1965), in which case morphological changes often appear to be very similar to those seen in rheumatoid lung disease. Hence, several authors have looked for a dependency of lung function changes on seropositive arthritis and found a higher frequency of overall lung function disturbance in seropositive RA (Frank and others, 1973; Morere and others, 1973). The question arose whether these changes were due to a general deterioration of the arthritic patient, or to the influence of the immunological process itself on certain well-defined lung function parameters.

Patients

Sixty-two patients (55 women, 7 men) with classical or definite RA were submitted to lung function analysis. Classification was made according to Steinbrocker, Traeger, and Batterman (1949). The following clinical-serological data were examined: determination of rheumatoid factors (Rose-Waaler titre), sedimentation rate (Westergren), electrophoresis, antinuclear antibodies, LE cells, peripheral blood count, chest *x*-ray, and electrocardiogram. Patients with heart disease or considerable anaemia (women $\leq$Hb 9g/dl; men $\leq$10g/dl) were excluded. 9 patients (14·5%) had smoked approximately 15 cigarettes daily during the past 20 years. No patient had any histological or clinical evidence of dust exposure.

In Table IA and B the 62 patients are classified according to clinical data (age, duration of disease, Steinbrocker-staging) and rheumatoid factor; these parameters were correlated with lung function data.

Lung function data

(1) Lung volumes (vital capacity, VC; functional residual capacity, FRC; total lung capacity, TLC; residual volume, RV).

(2) Ventilatory capacity (FEV_1, maximal breathing capacity, MBC).

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Correspondence to Dr. G. Kolarz, II. Medizinische Universitatsklinik, Garnisongasse 13, A-1097, Vienna, Austria.

Table IA *Stage of disease (Steinbrocker), Rose-Waaler titre, duration of disease, and patient's age*

	Stage of disease (Steinbrocker)					
	1	*2*	*3*	*4*	*Total no.*	*Age (years) (mean ± SD)*
Age (years)						
Mean	54·05	58·53	59·83	58·14		57·46
SD	18·48	13·31	12·25	8·00		14·43
n	20	17	18	7	62	
Rose-Waaler titre						
≧1 :64	7	10	13	2	32	59·06 ± 12·39
< 1 :64	13	7	5	5	30	54·63 ± 17·76
Duration of disease (years)						
0–3	13	3	1	–	17	51·64 ± 17·93
4–10	5	9	4	1	19	58·73 ± 13·55
> 10	2	5	13	6	26	60·23 ± 11·60

Table IB *Groups of patients with increasing Rose-Waaler titre, by age and stage of disease*

	Rose-Waaler titre			
	1:64	*1:64/1:128*	*1:256/1:512*	*>1:512*
Age (years)				
Mean	54·63	58·58	56·16	64·12
SD	17·70	13·66	12·95	8·90
n	30	12	12	8
Stage of disease (n)				
1	13	3	2	2
2	7	3	3	4
3	5	5	6	2
4	5	1	1	–

(3) Breathing mechanics (airway resistance, R_{aw}; static compliance, C; expressed as specific compliance, C/FRC).

(4) Diffusion capacity, D_{LCO}; expressed as specific D_{LCO} (D_{LCO}/FRC).

(5) Blood gas analysis (Po_2, base excess) from arterialized capillary blood.

Methods

Spirogram at the open circuit system with integration of the flow signal (Siemens/Erlangen); whole body plethysmography by a constant volume type (Siregnost FD 91, Siemens/Erlangen). Compliance was measured by the oesophageal method during a 'quasi-static' manoeuvre (vital capacity, very slow inspiratory and expiratory). Diffusion capacity was measured by the steady state procedure with end-tidal sampling of 'alveolar' CO-concentration (Alveodiffusionstest, Jaeger/Würzburg). Blood gases were analysed by the Radiometer-unit/Copenhagen.

VC and TLC were compared with the expected values of Baldwin, Cournand, and Richards (1948), FEV_1 was expressed in %VC, FRC and RV in %TLC, specific compliance was considered normal > 0·055; lower limit of normal for specific D_{LCO} was 4·5 units/l FRC.

Bronchial obstruction was assessed by airway resistance > 3·0 and/or FEV_1 < 60%VC, as well as by proportional increase of the area of the compliance loop during maximal ventilation.

Results

Mean values (with standard deviation) of lung function parameters of the 62 RA patients are given in Table II; these values are shown for seropositive and seronegative patients separately, indicating the percentage of patients with abnormal findings. Individual lung function parameters were compared with clinical data and a statistically significant correlation was found between rheumatoid factor and specific D_{LCO} only. There were no statistically significant correlations in other parameters. However, a pathological specific compliance was noticed more frequently in patients of Steinbrocker stages 3 and 4 than in those of 1 and 2. A linear relationship, however, did not exist between a decrease of specific compliance and stage of the disease. The group of patients with pathological specific D_{LCO} showed some increase with Steinbrocker stages, but this was not significant.

The results indicate some correlation between D_{LCO} and the presence of rheumatoid factor and its titre, respectively. Decreased D_{LCO} occurred more frequently in seropositive patients ($P < 0·05$), the mean values differing significantly between the two groups ($P < 0·025$). The higher the RF titre the larger the percentage of patients with impaired D_{LCO} ($P < 0·01$). While the relationship between mean D_{LCO} and the four titre groups was not significant, a clear trend can

Table II *Results of lung function study of 62 patients with RA, 30 seronegative, 32 seropositive*

	Total group ($n = 62$)	*Seronegative* ($n = 30$)	*Seropositive* ($n = 32$)
VC (% of nominal value) (ab < 90)			
Mean	99·29	98·91	99·65
SD	14·43	17·88	16·29
% abnormal	29	30	28
FRC (% of TLC) (ab > 62)			
Mean	60·85	59·83	61·82
SD	7.47	7·89	7·13
% abnormal	45	43·4	46·8
RV (% of TLC) (ab > 45)			
Mean	44·08	41·73	45·32
SD	9·50	12·37	8·84
% abnormal	42	46·6	37·5
FEV_1 (% of VC) (ab < 70)			
Mean	74·63	74·94	74·32
SD	8·27	9·17	7·46
% abnormal	21	20	21·8
R_{aw} (ab > 3·0)			
Mean	2·00	2·30	1·81
SD	1·30	1·56	0·97
% abnormal	17·7	20	15·6
C_{sp} (ab < 0·055)			
Mean	0·064	0·068	0·061
SD	0·019	0·022	0·016
% abnormal	38·4	27·6NS	48·4NS
D_{LCO} (ab < 4·5)			
Mean	5·00	5·60*	4·29*
SD	1·96	2·32	1·12
% abnormal	47·4	31†	64·2†
Po_2 (ab < 75, > 95)			
Mean	80·46	80·96	80·00
SD	6·99	7·46	6·61
% abnormal	21	20	21·8
Pco_2 (ab < 35, > 45)			
Mean	37·25	37·61	36·92
SD	4·28	4·70	3·89
% abnormal	25·8	30	21·8

* $P < 0·025$ (t-test).
† $P < 0·05$ (χ^2 test).
VC = vital capacity; FRC = functional residual capacity; RV = residual volume; FEV_1 = maximal breathing capacity; R_{aw} = airway resistance; C = specific compliance; D_{LCO} = specific diffusion capacity; ab = abnormal.

be seen (Figure). In addition, seropositive patients more frequently showed a decrease in lung compliance; however, these changes were less extensive than those of diffusion capacity.

Discussion

Table III shows the results of other authors who found lung function disturbance in patients with RA, expressed in percentage of total material. Our data do not differ from these. Morere and others (1973) observed a triad of impaired D_{LCO}, C, and Po_2 more frequently in seropositive than in seronegative patients. Less pulmonary dysfunction in seronegative RA was reported by Frank and others (1973); however, titre of rheumatoid factor (RF) did not correlate significantly with normal and pathological

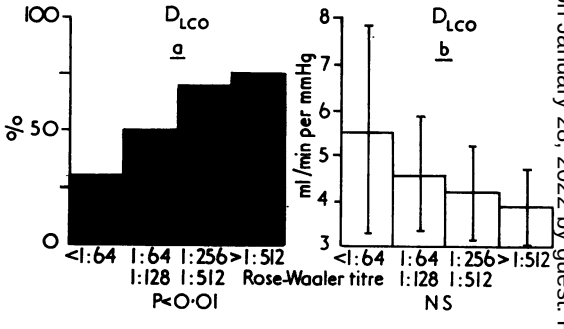

FIGURE *Correlation between D_{LCO} and Rose-Waaler titre. (a) Patients are divided into groups with increasing titre, showing percentage of patients with pathological D_{LCO} (4·5 ml/min per mmHg.) (b) Mean values of D_{LCO} (ml/min per mmHg) in each group*

Table III *Review of previous reports of lung function in RA*

Author	D_{LCO} (%)	*Specific compliance* (%)	*Vital capacity* (%)
Davidson and others (1974)	24	–	–
Frank and others (1973)	41·4	–	–
Huang and Lyons (1966)	57·1	–	27·2
Laitinen and others (1973)	30	20	20
Morere and others (1973)	55·4	40·5	–

D_{LCO}; furthermore, there was no correlation between the frequency of rheumatoid nodules and disturbance of lung function. Popper and others (1972), found no relation between pulmonary dysfunction and RF titre or the presence of rheumatoid nodules. In contrast, our results suggest a significant correlation between D_{LCO} and RF. Diffusion capacity can be altered by changes at the alveolar membrane, and for other reasons, e.g. by loss of pulmonary capillary volume. The latter can take place also by reduction of perfusion at the arteriolar level, as it occurs in thromboembolic disease and on the basis of inflammatory changes. An increased distending pressure and, therefore, decreased lung compliance has been found mostly in the presence of interstitial changes (congestion, fibrosis etc.). Morphologically, two different types of vascular changes have been reported (Fassbender, 1975) in RA: a nonspecific reaction of the endothelium seen in a variety of inflammatory diseases, being followed by exudation in the surrounding tissue (pneumonitis). This alteration is reversible in the early stage, but may lead to an irreversible fibrosis. Only in seropositive patients might an additional process consisting of necrosis of the arterial wall occur due to autoantibodies or immune-complex deposits. Secondarily, fibroblasts invade the necroses and cellular proliferation of the endothelium occurs. However, these changes have been reported in the vessels of the systemic circulation only; no author refers explicitly to analogous changes in the lesser circulation. A different mechanism has been discussed by Nagaya, Buckley, and Sieker (1969) who stressed the fact of immune-complex deposits in the alveolar wall of patients with progressive idiopathic interstitial fibrosis.

The decrease of lung compliance found frequently in RA is probably due to inflammatory changes of interstitial tissue, which can develop into interstitial fibrosis. Because interstitial, vascular, and alveolar changes can develop independently of each other and, therefore, may not occur to a similar extent in a given patient, compliance and D_{LCO} are not necessarily decreased in the same way.

Restriction of lung volumes can be due to pleurisy, increased thoracic rigidity (Huang and Lyons, 1966), and to rheumatoid myopathy. A slight to moderate inspiratory shift of midbreathing level (FRC in % TLC) and increase in residual volume (in % TLC) can be due either to the decrease in inspiratory reserve volume, or simply to age-dependent changes of the lung. However, the distribution of these alterations is nearly equal among seropositive and seronegative groups. Bronchial obstruction (as indicated by raised airway resistance and decreased FEV_1) was found in 17·7%. Smoking habits (9 patients, 14·5%) should not be neglected entirely when changes in D_{LCO} are being reported. However, the distribution of these patients was equal in the respective groups. Lung function changes in RA are certainly of multifactorial origin. Our results indicate an association with rheumatoid factors which may have a role in the pathophysiology of decreased diffusing capacity.

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