Thorax, 1980, **35**, 851–855

Membrane diffusing capacity and pulmonary capillary volume in rheumatoid disease

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ABSTRACT In some patients with rheumatoid disease gas transfer across the lungs is abnormal. We measured the membrane component of gas transfer (Dm) and pulmonary capillary volume (Vc) in 48 patients with rheumatoid arthritis and in 48 normal volunteers matched for age, sex, and smoking habits. Volunteers had normal chest radiographs and normal forced expiratory volume in one second and vital capacity. There were no significant differences between the rheumatoid and control groups for Dm. Mean Vc in rheumatoid male smokers (64·0 ml, SD 16·5) was significantly lower than in control male smokers (76·3 ml, SD 18·0 $p<0·05$). In rheumatoid female smokers mean Vc (43·4 ml, SD 13·3) was significantly lower than in rheumatoid female non-smokers (58·4 ml, SD 15·4 $p<0·01$). There was no significant difference between rheumatoid and control female non-smokers (mean Vc 58·4 ml and 60·7 ml respectively). Significant differences in Vc in terms of per cent predicted normal were found between patients receiving corticosteroids and those not receiving corticosteroids or penicillamine ($p<0·02$) and between patients with nodules and those without ($p<0·05$). Patients with persistently low transfer factor for five years had a significantly lower Vc ($p<0·02$). There was no consistent correlation between Dm and Vc and dynamic compliance or static recoil pressure. It appears that the abnormality of transfer factor in rheumatoid disease previously demonstrated is caused by reduction of Vc. It seems that involvement of pulmonary blood vessels occurs in patients with nodules and is suppressed by treatment with corticosteroids.

In their report of lung involvement in rheumatoid disease Ellman and Ball[1] described the pathology in two patients. In one there was interstitial pneumonitis, fibrosis between alveoli, and some endothelial proliferation with fibrinoid degeneration of blood vessels. In the other case there was interstitial pneumonitis and cuboidal epithelium was described in the alveoli. There was also intra-alveolar fibrosis but the blood vessels were normal. Subsequent reports[2-5] sometimes described prominent alveolar or bronchiolar inflammatory changes and in some cases there was marked arterial involvement. Some descriptions were of fibrosis with or without arterial changes. Subsequent studies of respiratory function in rheumatoid disease[6-8] showed that transfer factor (T_L) was low in many patients. We have extended these observations by determining the membrane factor (Dm) and pulmonary capillary volume (Vc), the components of transfer factor, in patients with rheumatoid disease.

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Methods

Forty-eight patients with classical or definite rheumatoid arthritis were attending hospital annually for respiratory function tests. They were not studied at the time of any acute respiratory tract infection or within seven days after receiving a general anaesthetic. They were matched for age, sex, and smoking habits with 48 normal volunteers. The normal subjects had no symptoms of respiratory disease, normal chest radiographs, and normal forced expiratory volume in one second and vital capacity. Transfer factor for carbon monoxide was measured by the single breath method using a Morgan Resparameter or Transfertest as described by Cotes.[9] Patients breathed pure oxygen for five minutes before each of the first two estimations when the inspired mixture was CO and helium in oxygen (high P_{O_2}). After 20 minutes two estimations were made in air (low P_{O_2}) of T_L with an inspired mixture of 0·28% carbon monoxide and 14% helium in air. For each test, patients expired to functional residual volume before inspiring to total

lung capacity. The breath-holding time was 10 seconds, the washout volume was 0·7 litres, and sample volume 0·7 litres. Back tension of carbon monoxide (BT CO) was measured by re-breathing into a three litre bag of oxygen for four minutes. Carbon dioxide was absorbed by soda lime.

$$\text{BT CO} = \frac{\text{rebreathing CO concentration} \times \text{expired } O_2 \text{ concentration}}{\text{rebreathing } O_2 \text{ concentration}} \quad \text{Equation 1}$$

Back tension of carbon monoxide was measured before the first and again before the second or after the fourth TL test. The appropriate value for each test was judged by extrapolation or interpolation and BT CO was subtracted from measured inspired and expired CO concentration. θ was calculated for each test using the formula

$$\frac{1}{\theta} = \frac{0{\cdot}0057\ P_{O_2} + 0{\cdot}33}{\text{Hb\%}} \quad \text{Equation 2}$$

(θ = ml carbon monoxide uptake/ml blood/mm Hg)

P_{O_2} = expired concentration O_2

$$\text{Hb\%} = \frac{\text{measured Hb g per dl}}{14{\cdot}8 \text{ g per dl}} \times 100$$

which assumes that λ, the ratio of oxygen uptake by red cell membrane to uptake by red cell interior, is ∞. Since

$$\frac{1}{TL} = \frac{1}{Dm} + \frac{1}{\theta Vc} \quad \text{Equation 3}$$

from the experiments at high and normal P_{O_2} two values of TL and θ are obtained, and Dm and Vc can then be calculated.[9-11] We did this by plotting $1/TL$ against $1/\theta$ and measuring slope ($1/Vc$) and intercept ($1/Dm$). Dynamic compliance (Cdyn) was measured as described in a previous paper.[12]

Results

Mean age, height, and TL on air are shown with mean Dm and Vc in table 1. Rheumatoid and control groups did not differ significantly in terms of age, height, or TL on air, nor was Dm found to be different between groups. Pulmonary capillary volume was significantly lower in male rheumatoid smokers compared with controls ($p = <0{\cdot}05$). There was no significant difference between rheumatoid and control females, but Vc was significantly lower in rheumatoid women who smoked compared with those who did not ($p = <0{\cdot}01$). However, there was no difference between control female smokers and non-smokers.

To compare various groups of rheumatoid patients Dm and Vc were expressed as per cent predicted (PN).[13 14] Mean values for various groups are given in table 2. There were no significant differences for Dm. Pulmonary capillary volume was significantly lower in patients not receiving corticosteroids ($p < 0{\cdot}02$) and in patients with nodules ($p = <0{\cdot}025$) but there was no significant correlation ($r = -0{\cdot}12$) with Rose Waaler titre. There was no significant relationship between Dm and Vc and the number of joints involved, nor between Dm and duration of arthritis ($r = -0{\cdot}24$), but there was a significant relationship ($p = <0{\cdot}01$) between Vc and duration of arthritis ($r = 0{\cdot}34$).

In those patients who had shown persistently low TL, Vc was significantly lower ($p = <0{\cdot}02$) than in those whose TL had been normal at most visits. In the patients who had two out of three positive findings of cough, breathlessness, and abnormal chest radiographs at each visit compared with those who did not, there was no significant difference in Dm or Vc. In 15 patients Dm was less than 70% predicted but only five of these patients had persistently low TL. In 26 patients Vc was less than 70% predicted; in 10 TL had been persistently low. In seven patients both Dm and Vc were lower than 70% predicted. Four of these had been known to have low TL, but only two had persistent symptoms and abnormal chest radiographs.

There was no consistent pattern of relationship between Dm and Vc and Cdyn. The correlation coefficients for Cdyn with Dm were $-0{\cdot}39$ for 17 male rheumatoid smokers, 0·44 for 11 female rheumatoid smokers, and 0·57 for 11 female rheumatoid non-smokers. For Cdyn with Vc, r for male smokers was 0·20, for female smokers $-0{\cdot}71$, for female non-smokers $-0{\cdot}33$. In 28 patients Dm and Vc

Table 1 *Mean TL air, Dm, and Vc in rheumatoid and control patients*

Group	Number	Mean age (yrs)	SD	Mean height (metres)	SD	Mean TL (air)	SD	Dm	SD	Vc (ml)	SD
Rheumatoid male smokers	18	51·5	10·55	1·73	0·08	23·82	4·58	42·34	13·95	63·99	16·49
Control male smokers	18	49·4	12·99	1·77	0·07	26·98	4·86	47·32	13·27	76·27	18·01
Rheumatoid female smokers	15	51·0	11·32	1·63	0·07	17·88	2·42	37·69	11·70	43·40	13·32
Control female smokers	15	53·3	11·05	1·65	0·07	18·64	3·80	34·07	11·04	55·32	22·06
Rheumatoid female non-smokers	15	55·1	12·57	1·60	0·07	19·47	2·95	31·32	8·82	58·35	15·35
Control female non-smokers	15	52·6	14·55	1·65	0·07	21·15	2·75	36·01	8·90	60·56	14·24

TL and Dm in ml/min/mmHg ÷ 2·98 = mmol/kPa.

Table 2 *Dm and Vc in terms of per cent predicted normal in various subgroups*

Group	*Number*	*Smokers*	*Mean Dm*	*SD*	*Mean Vc*	*SD*
Corticosteroid treatment	25	17	84·1	29·99	81·8	22·37
No corticosteroid or penicillamine	16	11	90·7	26·56	65·1	22·73
Corticosteroids and penicillamine	7	5	79·4	27·71	70·9	24·25
Patients with nodules	19	13	87·4	34·08	62·5	22·22
No nodules or sicca syndrome	27	21	83·7	23·10	80·9	25·27
Definite or possible sicca syndrome	7	5	84·1	24·55	66·9	17·89
DSCAT<1/256	14	13	87·4	31·10	65·7	26·26
DSCAT⩾1/256	34	23	84·9	26·66	77·1	24·19
Duration of arthritis<10 yr	21	14	84·6	32·43	66·5	19·57
Duration of arthritis ⩾10 yr	27	19	82·6	28·69	79·4	27·72
<10 joints involved	32	22	87·1	27·58	75·9	28·26
⩾10 joints involved	16	11	87·1	27·36	67·8	15·56
Airways obstruction	15	12	81·5	19·94	79·1	29·17
No airways obstruction	33	21	87·5	30·71	73·1	21·33
Persistent symptoms and abnormal chest radiograph	13	9	82·3	23·16	78·7	24·72
No persistence of symptoms and abnormal chest radiograph	35	24	86·9	29·48	72·0	25·32
Persistently low TL	17	12	81·4	25·33	62·2	20·19
TL not persistently low	30	20	89·2	28·68	81·2	24·8

were expressed as % PN and static recoil pressure as % predicted[15]; r for Dm was 0·41, for Vc 0·16.

Discussion

Transfer factor (TL) measures the rate of passage of carbon monoxide across the alveoli into the capillary blood. It may be reduced when the ventilation of the lung is impaired, when the matching of ventilation/perfusion is very uneven, or when the amount of blood available in the capillaries for carbon monoxide uptake is reduced by anaemia or by obliteration of the vascular bed. Georges *et al*[16] suggest that where there is inhomogeneity of diffusing constants Vc may be better than Dm in estimation of pathological changes in the lungs. As the inflammatory and fibrotic change in rheumatoid disease have a patchy distribution this inhomogeneity may explain the finding in our study of reduction in Vc without significant fall in Dm.

In our patients the probability that the low Vc was related to rheumatoid disease was emphasised by the association of low Vc with the presence of nodules. There was however, no significant correlation with the number of joints involved or with Rose Waaler titre, whereas Kolarz[17] found that abnormality of KCO was related to Rose Waaler titre. Treatment with penicillamine reduces the Rose Waaler titre, but exclusion of patients taking penicillamine did not produce any significant relationship between titre and Dm or Vc.

It was also noteworthy that treatment with corticosteroids seemed to prevent the change in Vc. If corticosteroid treatment had caused hypertension or left ventricular failure this would have produced a higher Vc, but there was no clinical evidence that this occurred. It seems more likely that corticosteroids suppress the inflammatory changes which have been described[1-4] in pulmonary blood vessels of rheumatoid patients.

De Horatius and Williams[18] showed deposition of antigammaglobulin in alveolar walls and arterioles after injection of rheumatoid factor. Postmortem studies[19] have demonstrated IgM in pulmonary arterioles and alveolar walls adjacent to cavitating rheumatoid nodules, and IgM in patients with "interstitial pneumonia." Such immunological reactions in pulmonary arterioles might be suppressed by treatment with corticosteroids. Gold and Jennings,[20] studying 20 patients with systemic lupus erythematosus, a condition in which immune complex deposition is associated with vasculitis, found five patients in whom Vc was low, and there were associated physiological abnormalities indicative of pulmonary vascular obstruction.

From Hamer's[21] study of sarcoidosis and from the study of systemic sclerosis[16] it appeared that low Vc was associated with more advanced disease. In our patients Vc was significantly higher in patients with arthritis of longer duration, but 21 of the 27 patients whose arthritis had been present for more than 10 years were being treated with corticosteroids. Of eight patients not receiving corticosteroids whose Vc was less than 60% predicted, six had suffered from arthritis for less than 10 years.

Significant reduction of Vc was found in smokers rather than non-smokers and the difference between rheumatoid female smokers and non-smokers was

the most significant in this study, although there was no difference between control female smokers and non-smokers. Some published results for Dm and Vc do not distinguish between smokers and non-smokers and there are more results for normal male than for normal female subjects. Frans *et al*[10] studied healthy men and found that Dm and Vc were both lower in smokers. It was not possible to recruit a sufficient number of rheumatoid male patients who had never smoked, but normal male non-smokers have been studied in our laboratory. Pulmonary capillary volume was not significantly different from healthy male smokers. There is a suggestion from our results that the combination of rheumatoid disease and smoking reduces pulmonary capillary volume.

The patients in our study had been seen on a number of occasions and in 17 TL had been persistently low. This was not explained by anaemia, which is common in rheumatoid disease. In these patients with persistently low TL Vc was significantly lower than in the other rheumatoid patients. In six of these 17 patients KCO was normal. It might be expected in these patients that the low transfer factor would be caused by low Dm associated with reduced alveolar volume. Membrane factor was low in three cases, in one of whom alveolar volume was low.

From equation 3, since Vc is the capillary volume and θ the rate of uptake of oxygen by the red cell, it follows that the variable Dm must include the other factors influencing TL—that is, both ventilation of the alveoli and the structure and area of the alveolar wall and capillary membrane. Uneven and reduced alveolar ventilation could be caused by airways obstruction. Although this (FEV_1 2 SD below mean predicted normal) was fairly common in our patients and is associated with smoking, we found no evidence that it was associated with abnormal Dm or Vc. Georges *et al*[16] found a highly significant correlation of effective compliance with Vc, but not with Dm. The sex and smoking habits of their patients were not given. It is probable that the majority of patients with systemic sclerosis were female, possibly non-smokers. The similarity of their results for DIPF and systemic sclerosis was very striking. In our patients correlation coefficients for Cdyn with Dm and Vc differed in direction for men and women, but were consistent for female smokers and non-smokers. The most significant relation between Vc and Cdyn was in female smokers, whereas in female non-smokers a relationship of lesser significance was found between Cdyn and Dm. For recoil pressure there was again better correlation with Dm. Staub *et al*[22] found that increasingly negative oesophageal pressure in normal subjects was associated with increased TL and increased Vc. This would probably not be found if there were pathological changes in the arteries.

Macklem and Becklake[23] found that in emphysema both recoil pressure and TL were reduced, in asthma recoil pressure and TL were normal, but in pulmonary fibrosis there was no correlation between the two measurements. In rheumatoid disease a greatly increased recoil pressure is attributable to fibrotic changes in the lungs. On the other hand, patients with joint involvement of the thoracic cage or muscles might produce smaller pressures and therefore lower Dm as a result of failure to achieve full ventilation of the alveoli. The mixture of these different problems would make it impossible to detect individual effects when studying the group as a whole.

Although in our patients there is a suggestion that in women there may be some relationship of Dm measurements to the mechanical properties of the lung, the notable abnormality is the reduction in Vc. This appears to be related to both smoking and rheumatoid disease and the change seems to be suppressed by treatment with corticosteroids.

We thank Dr Alan Hill for permission to study his patients, the Arthritis and Rheumatism Council for financial support, Mrs S Davies and Mrs C Brown for technical assistance, Dr R Greenwood for statistical advice, Mrs D Gulland for help with the bibliography, and Mrs P Boitoult and Mrs D Kingham for typing the manuscript.

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