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Frequency dependence of dynamic compliance in patients with rheumatoid arthritis

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ABSTRACT An investigation of lung function was carried out in 99 randomly selected patients with classic or definite rheumatoid arthritis and in 60 control subjects matched for age, sex, and smoking habits. Mean FEV_1 and mean VC were both significantly lower in the rheumatoid patients due to significant differences for women but mean FEV/VC ratio was 73·0% in the rheumatoid group and 72·1% in the control.

Steady-state transfer factor was significantly greater in the normal men than in the comparable rheumatoid group, but there was no difference for women. After excluding patients with FEV_1 less than 80% predicted normal and patients with low compliance, 72 rheumatoid patients and 45 controls provided series of tracings that could be assessed for a fall in Cdyn of 20% between 20 cycles and 60 cycles a minute. Dynamic compliance was not significantly different in any group at any rate of respiration. Fourteen of 72 rheumatoid patients and three of 45 controls showed frequency dependence (FDC). After the age of 50 the prevalence in the rheumatoid group was 11/38 and in the control group 2/27. This difference was significant ($P<0·05$). FDC was not consistently related to other abnormalities of lung function or to the duration, severity, or treatment of the rheumatoid arthritis. In various categories of smoking habits, dust exposure, or allergic tendency, the prevalence was always greater in the rheumatoid group. This provides evidence of patchy involvement of small airways, or alveoli and connective tissue, by the rheumatoid process.

Pleural and pulmonary involvement occur in rheumatoid arthritis and may be the presenting feature (Ellman and Ball, 1948; Cruickshank, 1959; Horler and Thompson, 1959). Early reports were chiefly concerned with radiological and histological abnormalities but during recent years studies of lung function have also been reported. The histological abnormalities affect bronchioles, alveoli, interstitial tissue, and blood vessels, and it is not clear that any particular pattern of involvement is most common. Studies of lung function have shown that there may be a restrictive pattern of ventilation, low lung compliance, low transfer factor and changes in blood gases (Morère *et al*, 1972; Frank *et al*, 1973; Whorwell *et al*, 1975). The low transfer factor might be consequent to abnormal alveolar structure, to loss of capillary volume, or to distortion of respiratory bronchioles leading to uneven alveolar ventilation. Newcomer *et al* (1964) showed that some patients with rheumatoid arthritis had a reduced maximal mid-expiratory flow rate (MMEFR), and this finding was confirmed by Collins *et al* (1974) who studied 38 patients. The physiological demonstration of possible bronchiolar disease was followed by description of the clinical picture of bronchiolitis by Geddes *et al* (1977) in six patients. Uneven ventilation may be shown by a fall in dynamic compliance (Cdyn) when measured at increasing respiratory rates. This frequency dependence of compliance has been studied in smokers in an attempt to show early disease of small airways before an obstructive pattern of ventilation becomes evident on spirometry (Woolcock *et al*, 1969). In coalworkers' pneumoconiosis where histological abnormalities may be seen at the bronchiolar level, frequency dependence has been shown (Seaton *et al*, 1972) and it might be expected that this abnormality would also be seen in patients whose bronchioles are affected by the inflammatory changes of rheumatoid disease.

This study was designed to investigate Cdyn at various respiratory rates in patients with rheu-

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matoid arthritis and in matched normal volunteers.

Methods

Patients with classic or definite rheumatoid arthritis between the ages of 16 and 70 were asked to volunteer for the study after the investigations had been explained to them. The selection was random including both outpatients and inpatients, but patients admitted for surgery were not studied during the week after operation. Patients were excluded if there was a history of some other pulmonary disease but were not excluded by symptoms of cough or breathlessness that could have been related to rheumatoid disease. Control (normal) volunteers were recruited from other medical and surgical patients, from the spouses of rheumatoid patients and patients with respiratory disease, and from hospital staff. It had been intended to study 100 control subjects who would be matched with rheumatoid patients for age, sex, and smoking habits. It was subsequently decided that 50 controls would be sufficient, and recruitment was continued until each control group contained at least half the number of patients in the matching rheumatoid group.

A completed questionnaire for all patients gave the following information: details of smoking habits and the number of years the subject had smoked; exposure to birds, farm dust, or other agents likely to provoke an extrinsic allergic alveolitis; family history or personal history of allergy; the presence of cough, breathlessness, finger clubbing, or crackles; radiological evidence of changes in the lung areas; the number of joints affected and duration of arthritis, and treatment with corticosteroids, gold, or penicillamine.

Lung volumes were measured with patients standing and compliance with the patients seated. FEV_1 and VC were measured with the McDermott dry spirometer and Resparameter. MMEFR was measured by the Resparameter, and the residual volume by helium dilution. Transfer factor (TL) was measured at rest and on exercise by the steady state method using an end-tidal sampler. Exercise was performed using legs or arms and a bicycle ergometer with a work load adjusted to give an oxygen uptake on exercise of about 1 litre a minute. Cdyn was measured at four speeds of about 20, 36, 60, and 85 breaths a minute. Two runs of ten breaths were recorded at each speed. A constant volume history was obtained by asking the patient to inspire to total lung capacity, expire as fully as possible, and then return to the mid-vital capacity range. A volume of 500 ml was marked on the dial of the spirometer so that the patient would breathe in the same range each time and the range achieved was recorded. If the patient fell short of the vital capacity by more than 200 ml the attempt was repeated after a rest. Runs where the tidal volume fell outside the range by more than 400 ml in either direction were not used in analysis. Volume was recorded using a McDermott spirometer fitted with a potentiometer. An oesophageal balloon 1 cm in diameter 10 cm in length filled with 0·5 ml of air was placed about 40 cm from the mouth. Differential pressure between the balloon and the mouth was recorded using a Hewlett-Packard 268B transducer. Flow was recorded by a Lilley pneumotachograph connected to a Hewlett-Packard 270 transducer. Recordings were made on a thermal recorder at paper speeds of 25 or 50 mm/s. Compliance was measured as the volume/pressure changes between points of no flow over a minimum of 5 cycles at each speed. The frequency response of the McDermott spirometer in series with the Lilley pneumotachograph and 270 transducer were tested by a square wave. This was generated by attaching 1500 g weights to the bottom of the bellows and letting it fall. The response was measured at paper speeds of 100 and 500 mm/s. For the two McDermott spirometers used, the 90% response time for 500 ml was 0·05 to 0·072 s, giving a frequency response between 4·63 and 6·67 Hz. For the pneumotachograph and transducer, at a flow rate of 100 l/min, 90% response time was 0·015 s, giving a frequency response of 22·2 Hz. The accuracy of the zero flow record and the absence of phase difference between oesophageal balloon and pneumotachograph were checked as recommended by Macklem (1974).

Static recoil pressure (Pst) was measured where possible. After a period of recorded quiet respiration patients were asked to take three deep breaths then to inhale to total lung capacity and to hold it for three seconds. Some patients also produced expiratory pressure volume curves by exhaling in small steps of 300 to 500 ml, relaxing for one to two seconds at these intervals while pressure and volume were continuously recorded.

Mean values for height, age, lung volume, TLSS and Cdyn were compared between groups using Students *t* test. Predicted normal values were taken from Cotes (1975).

Results

CHARACTERISTICS OF PATIENTS AND CONTROLS

One hundred and one patients with rheumatoid arthritis volunteered. Two were excluded from all investigations because they had severe airways obstruction, in one from bronchial asthma and in the other from emphysema. One woman included in the rheumatoid series had suffered from bronchial asthma during childhood. Sixty control subjects were studied; two men and one woman had suffered from asthma during childhood. Table 1 shows the distribution in terms of age, sex, and smoking habits. Two women who had smoked less than five cigarettes daily 20 years previously were classified as non-smokers, but other ex-smokers were classified as smokers. There was a slight excess of heavy (greater than 20 a day) cigarette smokers in the control population. When divided into groups with past or present exposure to industrial fumes or dust or other organic dust or in terms of social class, inspection showed no apparent difference between the two populations for either sex.

SYMPTOMS

Table 2 shows the prevalence of symptoms. One female and three male patients and one male control had breathlessness walking on the flat. In all other subjects it was of lesser degree.

FEV_1 AND VC

Table 3 shows mean age, height, FEV_1, and VC. There was no difference between rheumatoid and control groups in mean age or height. FEV_1 and VC in terms of percentage predicted normal values (PN) were both significantly lower in the female rheumatoid patients ($p<0.05$) but the FEV_1/VC ratio was not significantly reduced. There was no significant difference between rheumatoid and control men for FEV_1, VC, FEV_1/VC, or MMEFR.

TRANSFER FACTOR

Mean values are shown in table 3. The only significant difference between rheumatoid and control groups was the exercise TL in men ($p<0.05$).

EXCLUSIONS FROM ANALYSIS FOR FREQUENCY DEPENDENCE OF COMPLIANCE

Some traces were very difficult to analyse because of oesophageal contractions; some patients were unable to breathe in time with the metronome or to breathe in the same tidal volume range at different speeds. These have been excluded. Eleven rheumatoid patients and four controls with FEV_1 less than 80% and six rheumatoid patients and one control with low compliance were also excluded. The six rheumatoid patients with a low Cdyn (less than 1 l/kPa) at all rates of respiration included one male and two female smokers and three non-smokers. There was no particular age distribution, and duration of arthritis ranged from less than two years to 39 years. Two patients had a low FEV_1, in one case associated with low VC, and in four patients TL was low at rest or on exercise. Three patients had basal crackles but

Table 1 *Distribution of age, sex, and smoking habits for rheumatoid patients and control subjects*

Age	*99 Rheumatoid patients*				*60 Control subjects*			
	Male		*Female*		*Male*		*Female*	
	S	*NS*	*S*	*NS*	*S*	*NS*	*S*	*NS*
< 25 yr	1	0	0	1	1	0	0	0
26–40 yr	3	1	7	8	3	0	4	5
41–55 yr	18	0	8	13	10	0	6	8
56–70 yr	13	1	13	12	7	0	8	8
Totals by sex	35	2	28	34	21	0	18	21
	37		62		21		39	

S=Smoker.
NS=Non-smoker.

Table 2 *Symptoms in rheumatoid patients and control subjects. Percentages in parentheses*

	Male smokers		*Female smokers*		*Female non-smokers*	
	Rheumatoid *n=35*	*Control* *n=21*	*Rheumatoid* *n=28*	*Control* *n=18*	*Rheumatoid* *n=34*	*Control* *n=21*
Breathlessness	12 (34)	10 (48)	8 (29)	6 (33)	11 (32)	6 (29)
Cough	12 (34)	11 (52)	12 (43)	3 (17)	8 (24)	3 (14)

chest radiography showed no evidence of fibrosing alveolitis. The volunteer with low compliance also had low TL.

DYNAMIC COMPLIANCE

Table 4 shows the number remaining for analysis in each group with mean values for Cdyn at four rates of respiration. There was no difference between rheumatoid and non-rheumatoid groups at any rate of respiration. Within each group there was no significant change in Cdyn at higher rates of respiration. There was no significant correlation between exercise TL and Cdyn, and table 4 shows that mean values for Cdyn for groups of rheumatoid patients with abnormal chest radiograph did not differ from the mean values.

FREQUENCY DEPENDENCE OF COMPLIANCE

Frequency dependence of compliance (FDC) was said to be present if Cdyn at a rate of 60/min was 20% and statistically significantly lower than at a rate of 20/min (Hill *et al*, 1972). Some patients excluded from the mean figures because their rates of respiration did not fall precisely within the stated limits achieved a series of readings at increasing rates of respiration. These were examined to see if they showed a 20% fall over a similar range. Table 5 shows the higher frequency of this phenomenon in the rheumatoid group and table 6 shows the characteristics of the individuals with this finding. When the frequency of FDC was examined by the χ^2 test using Yates's correction there was no significant difference between the rheumatoid and control groups as a whole. Over the age of 50, using Fisher's exact test, the frequency was significantly higher in the rheumatoid group $0{\cdot}05 > p > 0{\cdot}01$.

STATIC RECOIL PRESSURES

Satisfactory recoil pressures were obtained for 32 patients and 12 controls. Abnormally high pressures were found in two patients, both of whom showed a low TL. Six other patients with a low TL included two with low recoil pressures. In the 32 patients there were 10 who had lower than expected recoil pressures using the prediction formulae of Knudson *et al* (1977).

Discussion

Dynamic compliance was measured using a spirometer because there would be considerable problems in getting some disabled rheumatoid patients inside a body plethysmograph. Some of the patients attending the laboratory had legs in splints. Satisfactory measurements of static recoil pressure are difficult to make without an accurate measurement of lung volumes in relation to TLC,

Table 3 *Mean values for age, height, FEV_1 and VC, and* TL

		Age		*Height*		*FEV_1*		*VC*		*FEV/VC%*		TLss *rest*		TLss *exercise*	
		Mean	*SD*	*Mean*	*SD*	*%pred*	*SD*	*%pred*	*SD*			*Mean %pred*	*SD*	*Mean %pred*	*SD*
Female Rheumatoid	62	51·0	11·8	1·61	0·06	102·3	17·4	105·9	16·2	73·9	8·3	116·3	38·8	175·9	40·6
Female control	39	50·0	11·4	1·62	0·06	109·1	17·6	121·9	15·8	74·2	7·6	100·2	29·0	187·9	46·1
Male Rheumatoid	37	51·6	10·0	1·73	0·07	95·9	14·4	97·5	13·5	71·6	8·1	120·6	30·7	186·4	42·9
Male control	21	50·7	12·3	1·76	0·05	96·5	14·7	106·5	14·0	68·9	7·8	117·7	31·8	225·1	52·0

Table 4 *Mean values Cdyn at increasing rates of respiration in l/kPa*

Group	*No*	*15–25/M*		*30–40/M*		*55–65/M*		*78–90/M*	
		Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*
Male rheumatoid smokers	26	2·05	0·21	2·02	0·21	2·02	0·23	2·03	0·25
All male rheumatoid	28	2·08	0·20	2·04	0·19	2·01	0·21	2·00	0·23
Male non-rheumatoid smokers	15	2·46	0·30	2·48	0·29	2·43	0·23	2·66	0·30
Female rheumatoid smokers	23	1·68	0·09	1·63	0·12	1·56	0·12	1·34	0·15
Female non-rheumatoid smokers	16	1·50	0·08	1·37	0·08	1·50	0·11	1·40	0·11
Female rheumatoid non-smokers	20	1·58	0·13	1·55	0·06	1·55	0·12	1·55	0·15
Female non-rheumatoid non-smokers	15	1·92	0·27	1·79	0·17	1·64	0·22	1·88	0·31

No = Number suitable for analysis.
Conversion: SI to traditional units—1 l/kPa ≈ 0·098 l/cmH_2O.

Table 5 *Prevalence of frequency dependence*

	Rheumatoid	*Non-rheumatoid*
Male smokers	5/25	1/15
Male non-smokers	1/2	
All males	6/27	1/15
Female smokers	5/23	0/15
Female non-smokers	3/22	2/15
All females	8/45	2/30
Total	14/72	3/45
All aged over 50 years	11/38	2/27

and these can best be obtained using a variable volume plethysmograph. From our tracings it was often difficult to be sure if the patients had achieved TLC, and small errors in measurement of volume are related to very substantial differences in the pressure expected. The results for Cdyn were felt to be acceptable and more reliable than measurement of static compliance because on each occasion the patient started with a VC manoeuvre which was measured, and if this fell short by more than 200 ml that particular run was abandoned. Similarly, by watching the values on the dial of the spirometer it was ensured that measurements were recorded in the same tidal volume range for each rate of respiration, as Mills *et al* (1963) have shown that FDC might be produced by changing the levels of inspiration. This study showed no difference between the rheumatoid and the control group for mean Cdyn at any rate of respiration. Six patients had a low compliance which is a lower prevalence of abnormality than was found by Morère *et al* in 1972. Some of their patients, however, were studied in a semi-recumbent position that is likely to affect the findings (Knowles *et al*, 1959).

Smokers were expected to show a fall in compliance at increased respiratory rates (Ingram and O'Cain, 1971; Hüttemann *et al*, 1972), but this finding was not confirmed in the larger number of subjects in this study. There was a slight excess of heavier smokers in the control group and six male volunteers were excluded from analysis for FDC because their FEV_1 was less than 80% of predicted. Only one of the remaining 15 normal men showed FDC while it was present in one of the two randomly enlisted rheumatoid non-smoking men. The prevalence was similar in smoking and non-smoking rheumatoid women. Bobbaers *et al* (1971) found that six patients with mild chronic bronchitis showed FDC. Cough was recorded in 40 smokers in this study. Six were excluded from analysis because of a low FEV_1, and five others showed FDC. Previous work has shown that adults who have suffered from asthma in childhood showed FDC in later life (Woolcock *et al*, 1969; Hill *et al*, 1972), but four subjects in this series who had previously had asthma did not show this pattern of behaviour.

Most studies of Cdyn have involved patients under the age of 50. Frank *et al* (1973) in a study of patients aged between 50 and 85 suggested that Cdyn tended to fall with increased rates of breathing if flow resistance was increased, but this tendency was very small compared to changes seen in emphysema. Pierce and Ebert (1958) showed a

Table 6 *Features of patients and controls with frequency dependence of compliance*

Patient		*Age*	*Treatment*	*Rose Waaler titre*	*Duration of RA*	*Examinations*	*FEV/VC % pred*	*Exercise T_L % pred*	*Other information*
1	FRS	52	—	164/128	20 yr	Crackles X Ray	82/105	185	—
2	FRS	50	—	—	16/12	—	96/122	166	Mother has asthma
3	FRS	57	SP	512/1024	6/12	—	97/127	208	Son has eczema
4	FRS	33	S	< 8	3 yr	X Ray	92/100	157	—
5	FRS	58	S	64	26 yr	Crackles	80/96	156	Large hiatus hernia
6	FRNS	64	S	64	18/12	—	105/117	290	—
7	FRNS	68	S	256	22 yr	—	106/130	212	—
8	FRNS	69	S	32	>20 yr	X Ray	89/93	191	Son has asthma
9	RMS	64	?	1024/2048	8 yr	—	93/102	149	—
10	RMS	57	S	256	8 yr	X Ray	102/97·5	160	Welder and brother has asthma
11	RMS	40	—	−ve	2 yr	X Ray	124/117	166	—
12	RMS	58	S	−ve	13 yr	X Ray	105/110	315	Wood dust and birds
13	RMS	69	S	256	24 yr	—	105/104	243	—
14	RMNS	27	—	−ve	3½ yr	—	103/102	177	Engineering dust
15	NRFNS	50				—	135/137	162	Father has asthma
16	NRFNS	31				—	119/125	210	Contact dermatitis
17	NRMS	42				—	96/104	210	Mother ? asthma

S=Corticosteroids; P=Penicillamine; FRS=Female rheumatoid smoker; FRNS=Female rheumatoid non-smoker; RMS=Rheumatoid male smoker; RMNS=Rheumatoid male non-smoker; NRFNS=Non-rheumatoid female non-smoker; NRMS=Non-rheumatoid male smoker; X Ray=Abnormal diffuse shadowing on chest radiograph.

fall in Cdyn at increased respiratory rate in 11 male patients over the age of 65. Knudson *et al* (1977) studied patients in three age groups including 18 patients aged 65–75. They found that age had no effect on Cdyn at higher respiratory rates. In this study the prevalence of FDC over the age of 50 was significantly higher in rheumatoid patients. The only male control to show FDC was 42. Although these patients were older, their rheumatoid arthritis was not always of longer duration, varying from six months to 24 years. In this way they are similar to patients disabled with rheumatoid lung disease. It was not possible to attribute the fall in compliance at greater speeds to immobility of the chest wall as there was no tendency for patients showing this feature to have a larger number of joints affected by rheumatoid arthritis. Patients with only a few peripheral joints affected would be unlikely to have extensive involvement of the joints and the rib cage. In more than half of the cases it was possible to find some other factor, such as exposure to dust or an allergic tendency, that might have contributed to this finding, but in each of these categories the incidence of FDC in the rheumatoid group was twice that in the control group.

Histologically, changes are seen in respiratory bronchioles in rheumatoid arthritis (Edge and Rickards, 1957; Ognibene, 1960; Stack *et al*, 1965). If inhalation of irritant or antigenic materials led to changes in respiratory bronchioles these changes might be more pronounced in patients with rheumatoid arthritis, where the respiratory bronchioles were already affected by the inflammatory changes associated with rheumatoid disease. Perhaps modification of response to inhaled materials might occur in some way analogous to the modification of coalworkers' pneumoconiosis (Caplan, 1953).

The fall in compliance measured at higher rates of respiration is attributed to differing time constants throughout the lung, thereby being an index of patchy rather than generalised disease. The time constants are a product of resistance and compliance. When used to investigate effects of smoking before clinically evident obstructive airways disease is developed, FDC would be attributed chiefly to change in resistance of small airways. In rheumatoid disease FDC could be due either to bronchiolar involvement causing changes in resistance or to uneven involvement of alveoli and connective tissues by the inflammatory or fibrotic changes of fibrosing alveolitis, leading to scattered areas of altered compliance. Schofield *et al* (1976) found that airways closure occurred at normal values in nine subjects with established fibrosing alveolitis and concluded that in them there was no airways narrowing. In this study the six patients with a low compliance, including one with a reduced FEV_1/VC, did not show a fall in compliance with increasing rates of respiration (they were excluded from the analysis of incidence of FDC), which could be interpreted as evidence for an evenly distributed disease process, and four of these six patients had abnormal TL at rest or on exercise. The non-rheumatoid young patient with a low compliance showed FDC but the reason for the abnormal result was not evident. If the low compliance figures in the rheumatoid patients indicate generalised lung involvement the fact that the rheumatoid patients with FDC had normal compliance, although six had an abnormal chest radiograph, would support the proposition that they had patchy lung involvement. If FDC occurred in some cases without other abnormal findings it might perhaps detect early lung disease where treatment might be of some benefit. Any biopsy technique might miss scattered lesions. The other possibility is that FDC is not due primarily to rheumatoid inflammation, but that the rheumatoid disease modifies the effect of inhaled fumes or dusts causing small airways disease in a way analogous to the modification of coal workers' disease in rheumatoid arthritis.

The practical approach at present would be careful follow-up of patients showing FDC to discover whether they develop changes in transfer factor, a low compliance, or abnormal clinical or radiological features to suggest the presence of fibrosing alveolitis. The severe bronchiolitis described in rheumatoid disease has been a rapidly progressive or fatal disorder; possibly other patients have a milder form of the disease, and such patients might be detected among the group with frequency dependence. To shed light on these possibilities, a five-year follow-up study is being carried out at Stoke Mandeville Hospital.

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