Thorax 1983;**38**:778–784

Pattern of breathing during exercise in patients with interstitial lung disease

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ABSTRACT The responses to exercise were studied in 41 patients with pulmonary fibrosis, in whom vital capacity (VC) was reduced to 62% of predicted normal values. Maximum power output (PO_{max}) was 53% predicted; there was a significant relationship between PO_{max} and VC (r = 0·564). The maximum ventilation achieved during exercise was also related to VC (r = 0·614). Although arterial oxygen saturation (Sa_{O_2}) fell by more than 5% in 13 of 31 patients, there was no relationship between either Sa_{O_2} at PO_{max} or the exercise related fall in Sa_{O_2} and PO_{max}. Heart rate responses were higher than normal predicted values in seven patients, all of whom showed a low PO_{max} (36% predicted); this finding was due only in part to a fall in Sa_{O_2}. The ventilatory response to exercise was within normal limits for the patients as a whole; those subjects with the lowest PO_{max} showed relatively higher ventilatory responses to exercise but the difference was not significant. The pattern and timing of breathing was studied in 32 patients and compared with control subjects matched by sex, age, and size. Tidal volume (VT) was low in the patients; maximum VT was related to VC (r = 0·761), but at low values of VC VT_{max} was higher than in healthy subjects with comparable VC. The total breathing cycle time (Ttot) fell with progressive exercise in patients and controls; Ttot for a given ventilation was shorter in the patients. Inspiratory time (Ti) was shorter in patients than controls, as was Ti/Ttot. In most patients with diffuse pulmonary fibrosis exercise is limited by a reduced ventilatory capacity, despite the adoption of a short Ti and high inspiratory flow rate, both of which serve to optimise tidal volume and breathing frequency and presumably reduce both the force developed by inspiratory muscles and the sensation of breathlessness.

Measurement of the ventilatory responses to exercise provides useful information about the functional reserve capacity of the lungs and the control of breathing in healthy people and patients with pulmonary disease.[1] Patients with interstitial pulmonary disease (alveolitis and fibrosis) characteristically are dyspnoeic during exercise, and have a limited pulmonary reserve owing to mechanical and gas exchange abnormalities. There have, however, been few systematic studies of the exercise responses in these conditions.[2] To meet the ventilatory demands of exercise the intensity, duration, and frequency of force development in the respiratory muscles must alter to oppose the increased impedance. This report presents the results of standardised exercise studies carried out in 41 patients with various interstitial lung diseases. Our major aim was to define abnormalities of the pattern and timing of breathing; for this reason we measured the mean time spent in inspiration (Ti, the duration of inspiratory flow), the total duration of the respiratory cycle (Ttot), and the relationship of Ti to Ttot (the proportion of each breath duration which is spent in force development—the inspiratory "duty cycle"[3,4]).

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Accepted 21 June 1983

Methods

From 1972 to 1981 41 patients under investigation for interstitial lung disease took part in exercise studies as part of the pulmonary function assessment. Patients were accepted as having interstitial lung disease provided that they fulfilled the following criteria: (1) a diagnosis confirmed by lung biopsy

or a clinical course consistent with interstitial lung disease; (2) chest radiographs characteristic of interstitial lung disease; (3) vital capacity less than 80% of the predicted value; (4) absence of clinical or spirometric evidence of airflow obstruction, ischaemic heart disease, or other conditions affecting exercise capacity.

The 41 patients (24 males, 17 females) had an age range of 13–75 years (mean 46 (SD 13) years). Mean (SD) spirometric indices were: vital capacity 2·33 (SD 0·71) litres (62% (15%) predicted) and FEV_1/VC ratio 83% (10%). Predicted values were taken from Morris *et al*.[5] Diagnoses included cryptogenic fibrosing alveolitis (17 patients); pulmonary sarcoidosis (11); collagen vascular disorders (5); hypersensitivity pneumonitis (4); and eosinophilic granuloma (4).

Standard methods of exercise testing and spirometric measurement were used throughout the survey period and calibration of equipment and quality control was a regular routine.[6] Spirometric indices and exercise test results were taken from the laboratory report sheets except for inspiratory and total breath duration, which were measured from the original exercise test recordings. These were unavailable in nine patients. Thus complete data were obtained for only 32 patients; but the mean age, size, and spirometric variables in this group (table 1) were virtually identical to those of the total group of 41 patients.

To provide comparisons for the exercise responses, healthy subjects were selected from over 100 who had taken part in a study in our laboratory, each patient being matched with a healthy subject of the same sex, age (± 5 years), and height (± 5 cm) (table 1).

Spirometric measurements were made with a 13·5 litre Collins water sealed spirometer or dry spirometer (Vitalograph). The best of three measurements was taken as the forced expiratory volume in one second (FEV_1) and vital capacity (VC). Exercise tests were performed on an electrically braked cycle ergometer (Elema 380), care being taken to ensure that the height of the saddle and the position of the respiratory mouthpiece were comfortable. The exercise protocol followed was the "stage I" progressive incremental procedure routinely used in our laboratories for clinical exercise testing.[6] After satisfactory resting measurements had been recorded an initial work load of 100 or 150 kpm/min (16·4 or 24·5 w) was used. The power output was subsequently increased in increments of 50 or 100 kpm/min (8·2 or 16·4 w) at the end of each minute, exercise being performed continuously. Subjects were asked to continue exercising for as long as possible. Throughout the test the subject breathed through a mouthpiece connected to a Lloyd valve having a combined dead space of 50 ml. Inspired ventilation ($\dot{V}I$) was measured with a dry gas meter (Parkinson Cowan CD4) fitted with a potentiometer. Measurements of $\dot{V}I$, tidal volume (VT), respiratory rate, Ti, and total breath duration (Ttot) were made for 20 second averaged periods at each work load. In a separate study measurements of Ti made with a pneumotachograph and the dry gas meter showed a small delay in the gas meter response leading to a 5–10% underestimation of Ti/Ttot, which was not influenced by changes in breathing pattern and was considered not to influence comparison between the patients and normal controls.

Arterial oxygen saturation (SaO_2) was monitored by ear oximetry[7] (Hewlett Packard) in 31 patients and recordings of SaO_2 were made at the end of each power output.

The ventilatory response to exercise was assessed by calculating the group mean $\dot{V}I$ at each power output. Analysis of the pattern of breathing was undertaken by comparing the group mean VT, respiratory rate, Ti, and Ttot for 10 l/min intervals of $\dot{V}I$. Predicted maximum power output was calculated from a standard regression equation.[6]

Linear relationships were determined by the method of least squares and compared by analysis of variance.

Details of 32 patients and 32 control subjects

	Age (y)	*Height (cm)*	*FEV_1 (l)*	*VC (l)*	*PO_{max} (kpm/min)*
Patients					
Mean	48	165	1·94	2·38	556
SD	14·3	18·1	0·61	0·78	248
Controls					
Mean	47	166	3·50	4·09	1050
SD	14·4	7·5	0·88	0·96	424

FEV_1—forced expiratory volume in one second; VC—vital capacity; PO_{max}—maximum power output.
Conversion: Traditional to SI units—Power output: 1 kpm/min ≈ 0·16 w.

Results

Maximum power output (PO_{max}) was reduced to below 80% of that predicted on the basis of sex, age, and size in all but one patient. In comparison with the matched control group of healthy subjects, the patients achieved only 53% of the maximum power output (table). Both the maximum power output (fig 1) and maximum ventilation (fig 2) were linearly related to the vital capacity.

Oxygen saturation (SaO_2) was measured during exercise in 31 subjects; significant reductions (grea-

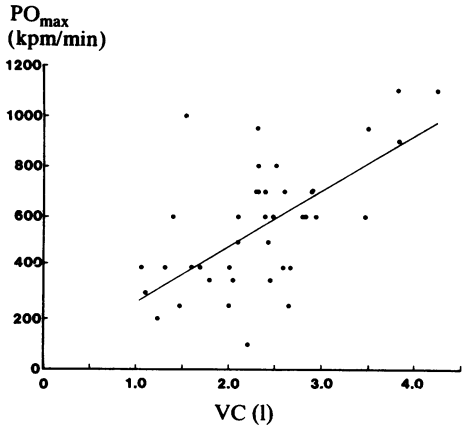

Fig 1 *Maximum power output (PO_{max}) related to vital capacity (VC). Regression equation: PO_{max} (kpm/min) = 41 + 220 VC (r = 0·564, p < 0·05). Conversion: Traditional to SI units—Power output: 1 kpm/min ≈ 0·16 w.*

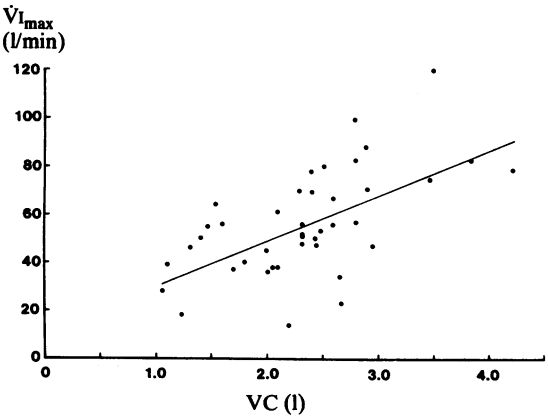

Fig 2 *Ventilation at maximum power output related to vital capacity. Regression equation: $\dot{V}I_{max}$ (l/min) = 12·1 + 18·9 VC (r = 0·614, p < 0·001).*

ter than 5%) occurred in 13 patients. Neither SaO_2 at PO_{max} nor change in saturation during exercise (ΔSaO_2) correlated with PO_{max} expressed as a percentage of the predicted normal average value (fig 3).

The heart rate responses to exercise were within the expected normal range in all but seven patients. These seven showed a slightly greater reduction in VC (mean 49% (SD 13·6%) predicted) and lower PO_{max} (mean 378 (71) kpm/min) than the group as a whole and all but one showed a fall in SaO_2 (mean fall 5%).

Ventilation ($\dot{V}I$) increased linearly with increasing power output in all subjects. The group mean ventilatory response to exercise was best described by the equation $\dot{V}I = 9·29 + 0·07$ PO (r = 0·98), where $\dot{V}I$ is in l/min and PO in kpm/min. To ensure that no undue bias was placed on this relationship by subjects with low maximum power output (less than 50% predicted) the ventilatory response for these subjects (n = 14) was compared with those whose exercise capacity was 50% predicted or more (n = 27). Although $\dot{V}I$ in subjects with low maximum power output was 5–10 l/min higher at each power output (fig 4), this difference did not reach significance (p = 0·27). Increases in $\dot{V}I$ during exercise were a result of increases in both VT and

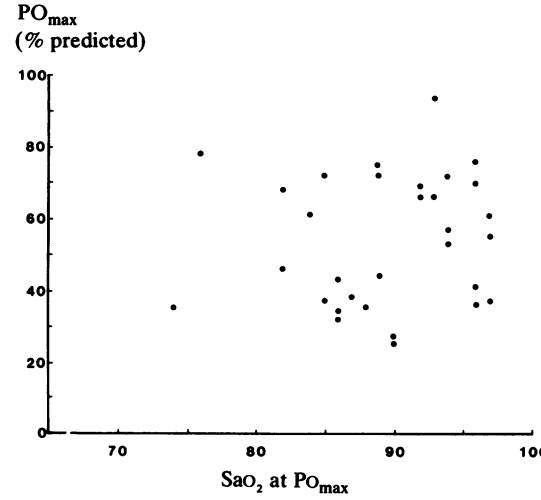

Fig 3 *Arterial oxygen saturation (SaO_2) during exercise showing no significant association with maximum power output (PO_{max}) (n = 31).*

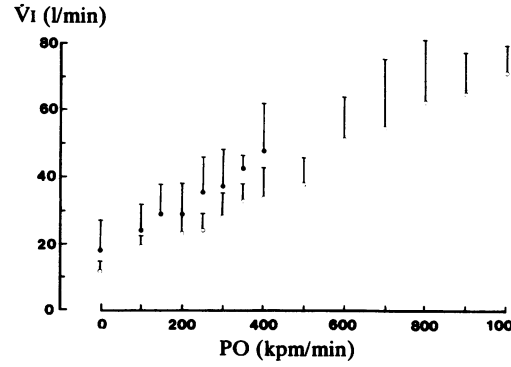

Fig 4 *Mean ventilation + SD at each power output (PO) in those with a maximum power output (PO_{max}) of less than 50% of the predicted normal (n = 14: ●) and in those with a PO_{max} of 50% predicted or more (n = 27: ○). Conversion: Traditional to SI units—Power output: 1 kpm/min ≈ 0·16 w.*

respiratory rate, but at all levels of $\dot{V}_I$ V_T was smaller in patients than healthy subjects (fig 5). The tidal volume at maximum power output ($V_{T_{max}}$) was linearly related to VC (fig 6).

Ti and Ttot decreased progressively throughout exercise in the patients and healthy subjects (fig 7). The decrease in Ti paralleled that of Ttot, resulting in a constant Ti/Ttot ratio in patients (0·35 (SD 0·07) at rest; 0·34 (0·11) at PO_{max}), whereas in the control subjects Ti decreased less than Ttot, and

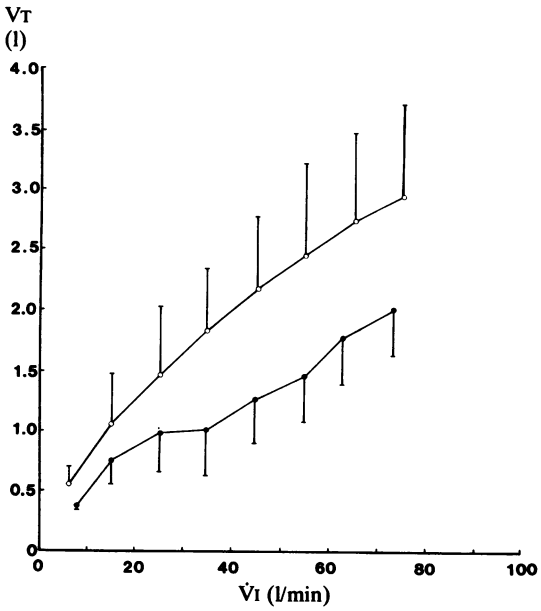

Fig 5 *Tidal volume (V_T) during exercise in patients (●) and matched controls (○): mean values and 1 SD for increments in ventilation ($\dot{V}_I$) of 10 l/min.*

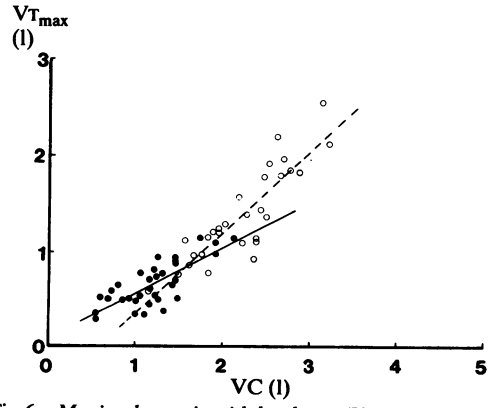

Fig 6 *Maximal exercise tidal volume ($V_{T_{max}}$) related to vital capacity (VC) in patients (●) and controls (○). Regression equation for data on patients (———): $V_{T_{max}}$ = 0·11 + 0·50 VC (r = 0·725, p < 0·001).*

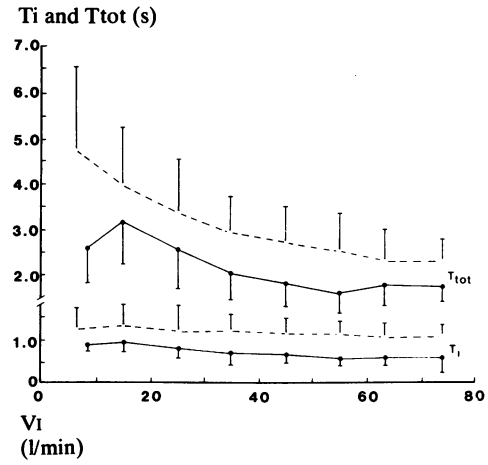

Fig 7 *Inspiratory (Ti) and total breathing cycle (Ttot) duration: mean values and 1 SD in patients (●) and matched controls (○) for 10 l/min increments in ventilation ($\dot{V}_I$).*

Ti/Ttot showed an increase (from 0·25 (0·09) at rest to 0·43 (0·03)). The Ti/Ttot ratio during exercise associated with $\dot{V}_I$ above 40 l/min was lower in patients than in the normal subjects.

Discussion

Although there have been few formal studies of exercise limitation in diffuse pulmonary parenchymal disease, the factors underlying functional impairment are well recognised. Effort intolerance and dyspnoea are characteristic early symptoms and are related to reductions in ventilatory capacity, impaired pulmonary gas exchange, and in some patients pulmonary hypertension. Often these abnormalities combine to produce an additive effect in which impairment of exercise performance is more severe than might be expected from measurements of pulmonary function made at rest. In the present study we used maximal exercise testing to identify the relative importance of some of these factors, but our main focus was the pattern of breathing expressed in terms of the tidal volume (V_T), frequency of breathing, and timing of inspiration (Ti) relative to the total respiratory cycle duration (Ttot).

Although a fall in SaO_2 may be a contributory factor in exercise limitation we did not find a relationship between either the absolute SaO_2 during maximum exercise (fig 3) or the exercise related fall in SaO_2 and the reduction in maximum power output. Impairment in pulmonary oxygen transfer has been recognised as the hallmark of pulmonary

alveolar disorders, leading to the concept of "alveolocapillary block."[8] The gas exchange disturbance, which is now considered to be mainly secondary to gross dispersion of ventilation: perfusion ratios,[9] was severe enough to cause a fall in SaO_2 of more than 5% in 13 of the 31 patients in whom SaO_2 was measured (45%). There was no correlation between the degree of exercise oxygen desaturation and the reduction in lung volumes (VC and total lung capacity), suggesting that measurement of the change in SaO_2 with exercise may help in assessing the independent effects of gas exchange disturbances in these patients. Of interest were several patients with severe oxygen desaturation who were able to achieve relatively high power outputs, the most extreme being one who reached a power output of 75% of the predicted normal value in the face of a 20% fall in SaO_2. Presumably in such patients an increase in cardiac output maintains muscle oxygen delivery despite low SaO_2, as occurs in normal people breathing low oxygen gas mixtures.[10]

Pulmonary hypertension may impair exercise performance owing to associated reductions in cardiac stroke volume and maximal cardiac output. A small stroke volume is associated with a high heart rate response to exercise, but this was found in only seven patients. Generally these patients had severe impairment of pulmonary function and severe disability as measured by the reduction in maximum power output; four showed a significant (greater than 5%) fall in SaO_2. The falls in SaO_2, however, were too small to account for the increases in heart rate,[10] and an impaired cardiac stroke volume response to exercise is likely to have been present in these patients.

The major factor contributing to a reduced exercise capacity was a limited ventilatory capacity. A relationship was found between maximum power output and vital capacity (fig 1); ventilation at the maximum exercise load was also correlated with the vital capacity (fig 2). Furthermore, more disabled patients showed a higher ventilatory response to exercise (fig 4), a finding which was probably influenced by oxygen desaturation on exercise and by the high dead space:tidal volume ratio which is characteristic of patients with interstitial pulmonary disorders.[11] Thus the ventilatory impairment in exercise was a combination of an increase in the ventilation and a reduction in the ventilatory capacity to meet the demand, as reflected in the vital capacity (fig 2).

Early physiological studies of diffuse pulmonary fibrosis showed that most patients showed a low tidal volume and a high frequency pattern of breathing, seen as an adaptation for small, stiff lungs.[2,11] In contrast, Patton and Freedman[12] found normal VT responses to carbon dioxide inhalation at rest in pulmonary fibrosis despite increases in respiratory mechanical work. In the present study the VT response to increases in ventilation was lower than in normal subjects matched for size (fig 5). The maximum VT during exercise was linearly related to vital capacity, but when the values in the patients were compared with the relationship found for the normal subjects, whose results were similar to those obtained in previous studies,[13,14] many were above the normal range (fig 6). That many of our patients showed a higher VT_{max} for a given VC than normal subjects is at first sight surprising. Such a comparison, however, contrasts patients with small lungs in a potentially normal sized thoracic cage[15] with subjects in whom the size of the lungs is appropriate to that of the thoracic cage. If, as seems likely,[15] the mechanical properties of the chest wall in fibrosing alveolitis are unaffected, an unusually good mechanical advantage of the inspiratory muscles may allow patients to generate a more negative pleural pressure at a given relative lung volume, thus tending to maintain VT.

Factors influencing the pattern of breathing were investigated by Clark and von Euler,[4] who made measurements of the timing of the respiratory cycle in cat and man. At low levels increases in $\dot{V}I$ were the result of increasing VT, the inspiratory time remaining constant ("range 1"). Subsequent increases in $\dot{V}I$ were associated with increases in VT and reductions in Ti, with a linear relationship between VT and the reciprocal of Ti ("range 2"). Taken at face value the results obtained in the present studies (figs 5 and 7) suggest a shift downwards (smaller VT) and to the left (lower Ti) in the VT/Ti relationship in patients with pulmonary fibrosis, the results of patients and normal subjects lying in range 2 of Clark and von Euler. Although studies similar to those of Clark and von Euler[4] have not been carried out in normal subjects with lungs as small as those of our patients, it seems reasonable to infer that a short inspiratory time and high respiratory rate (short Ttot) are adopted as a response to the elastic load presented by stiff lungs.

Inspiratory elastic loads in healthy subjects usually,[16,17] but not always,[18] are associated with increases in respiratory rate and reductions in tidal volume. Although few studies have reported Ti/Ttot, this ratio may be calculated from the results presented by Agostoni and colleagues[19]; elastic loading progressively reduced Ti, but the Ti/Ttot ratio remained constant in their subjects studied during carbon dioxide breathing. The responses to elastic loading have also been studied in normal subjects undergoing cycle ergometer exercise[20]; all subjects showed a low VT at a given $\dot{V}I$. In patients with

pulmonary fibrosis at rest, during 5% carbon dioxide breathing[12] and during exercise,[2 14] a low VT, high frequency pattern of breathing has been found and usually ascribed to stimulation of pulmonary irritant or stretch receptors. Bradley and Crawford[14] reported that Ti/Ttot at high levels of ventilation during exercise was about 0·5 in normal subjects and 0·4 in patients with restrictive diseases. In our subjects Ti decreased progressively with increasing $\dot{V}I$ up to 40 l/min, but changed little at higher levels (fig 7); Ti was about one second less at all exercise levels in the patients than in the normal subjects. The average inspiratory flow (VT/Ti) was similar in the patients and controls at all levels of exercise, reaching about 3·5 l/s at the higher levels of $\dot{V}I$. If, however, these flow rates are considered in relation to the lung volume at which they were generated, the possibility arises that maximum inspiratory flows were reached[21] by the patients.

The depth and rate of breathing normally are linked to maintain normal gas exchange at a minimal cost in terms of respiratory muscle force[22] and work.[23] The receptors which signal the increase in respiratory muscle force to enable this adaptive response have been the subject of speculation; but recent research which has quantified the sense of respiratory effort in response to elastic loading of the inspiratory muscles suggests that there may be a behavioural or "learned" component to the mechanisms concerned.

The increased elastance associated with pulmonary fibrosis imposes an impedance to the action of the inspiratory muscles; the peak inspiratory force is the product of the tidal volume and the elastance of the respiratory system. The maintenance of a given tidal volume in the face of high elastance requires a large peak intensity of inspiratory force which could result in diaphragm fatigue, despite normal maximal respiratory muscle power.[24] Thus the pattern of breathing adopted in our patients, with reduced tidal volume, was that expected to reduce peak force and delay the onset of fatigue.

The reduction in peak force was accompanied by an increase in the frequency of force development—that is, in the respiratory rate—and a reduction in Ttot, an adaptation which will tend to increase the total force developed. Nevertheless, a shortening of the duration of force development in each breath (reduction in Ti/Ttot, fig 7) served to minimise the total force generated by respiratory muscles over a given time and maximise the ability of the respiratory muscles to maintain force development without fatigue.[25]

When inspiratory elastic loads are presented to healthy subjects, their perception of the magnitude of the added elastance is only indirectly related to the actual size of the elastance, and directly related to the effort generated against the load.[26 27] The perceived magnitude (ψ) bears a power function to both the intensity (P) and the duration (t) of force development as expressed in the equation[26]

$$\psi = K_0 \times P^{1.3} \times t^{0.56}.$$

Thus by minimisation of the peak intensity of force and the time for which it is sustained the perceptual magnitude of the load is also minimised. The results of these sensory experiments suggest that the pattern of force development by inspiratory muscles may be behaviourally selected in the light of sensory information regarding the impedance to breathing. Thus patients with pulmonary fibrosis, when faced with the increased breathing demands of exercise, minimise the peak intensity of force (smaller VT), the duration of force development (shorter Ti) and the time spent in force development in relation to the time of recovery (decreased Ti/Ttot). This pattern may be selected or conditioned as a behavioural response rather than on the basis of reflex mechanisms.

We are grateful to Dr J Morse for permitting us to study records of exercise studies carried out in the regional chest and allergy unit at St Joseph's Hospital. Dr JGW Burdon held a fellowship in applied health sciences (National Health and Medical Research Council, Australia).

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