

# Lung function, breathing pattern, and gas exchange in interstitial lung disease

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## Abstract

**Background** The aim of this study was to determine the relation between the severity of abnormalities in ventilatory function tests and tidal breathing pattern and gas exchange indices in interstitial lung disease.

**Methods** Pulmonary function, ventilation, carbon dioxide production, oxygen consumption, arterial blood gas tensions, and pH were measured during resting steady state conditions in 60 patients with proved interstitial lung disease. Patients were categorised by forced vital capacity (FVC) (percentage of predicted values) as having a mild, moderate, or severe restrictive defect with means (SD) of 71% (4%), 57% (4%), and 41% (7%) of predicted values, respectively.

**Results** FVC varied from 29% to 79% of predicted values and from 0.99 l to 4.32 l. The two measurements of FVC correlated strongly with most static lung volumes and with transfer factor for carbon monoxide. Mean respiratory rates (per minute) and tidal volumes (ml) were 17 (4) and 484 (131), 20 (4) and 460 (139), and 23 (5) and 377 (109) in mild, moderate, and severe restrictive defects, respectively. FVC correlated negatively with respiratory rate and positively with tidal volume. Arterial carbon dioxide tension ranged from 30 to 49 mm Hg; only two patients were hypercapnic. Mean arterial oxygen tensions were not significantly different among the three groups, and there were no significant correlations between forced expiratory volume in one second or FVC and arterial carbon dioxide tension or carbon dioxide production.

**Conclusion** Low values of FVC were associated with increased respiratory rate and decreased tidal volume; this pattern of breathing mimics external elastic loading, suggesting that mechanoreceptors may contribute to the rapid and shallow pattern of breathing in interstitial lung disease. Hypercapnia seems to be rare in interstitial lung disease even when functional impairment is severe and tidal volume is small. The increased respiratory rate is important in maintaining adequate ventilation. In the face of a severe restrictive defect carbon dioxide production did not increase, which also contributed to the maintenance of eucapnia.

The relation between lung function test values, breathing pattern, and gas exchange has been studied in patients with chronic obstructive lung disease. Carbon dioxide retention in these patients is usually associated with a forced expiratory volume in one second (FEV<sub>1</sub>) of less than 1.0 litre<sup>1-4</sup>, and the same is true in asthma.<sup>5-7</sup>

The pattern of breathing may contribute to carbon dioxide retention. Hypercapnic patients with chronic obstructive lung disease breathe faster and more shallowly than eucapnic patients,<sup>4,8</sup> causing an increase in the ratio of dead space to tidal volume (V<sub>D</sub>/V<sub>T</sub>) and in dead space ventilation (V<sub>D</sub>) with a decrease in alveolar ventilation (V̇<sub>A</sub>); this results in hypercapnia.

Few studies have examined the pattern of breathing in diffuse interstitial lung disease.<sup>9-13</sup> Although it is commonly believed that patients with interstitial lung disease breathe more rapidly and shallowly than normal subjects, previous studies have reported considerable variation in both breathing frequency and tidal volume. In the original study of Lourenco *et al*, for example, the respiratory rate varied from 13 to 40 breaths/min, and tidal volume from 306 to 612 ml.<sup>9</sup> In a more recent study Renzi *et al* showed that changes in respiratory rate and tidal volume were related to stiffness (elastance) of the lungs in 12 patients with interstitial lung disease and suggested that variations in breathing pattern were probably related to differences in the severity of the disease.<sup>13</sup>

The main aim of this study was to determine the relation between the pattern of breathing and gas exchange during steady state breathing at rest and ventilatory lung function in a large group of carefully selected patients with proved interstitial lung disease.

## Methods

We reviewed the results of pulmonary function tests in patients with a restrictive lung defect (forced vital capacity <80% predicted) and an established diagnosis of interstitial lung disease. The patients were referred for diagnosis and treatment of interstitial lung disease. The diagnosis was made by open lung biopsy or from the presence of specific historical findings such as occupational exposure. Methods of diagnosis have been reported in detail.<sup>14,15</sup>

We excluded all patients with (a) a ratio of FEV<sub>1</sub> to forced vital capacity (FVC) of <75%; (b) neuromuscular disorders; (c) kyphoscoliosis, (d) pulmonary emboli; (e) lung car-

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Accepted 10 September 1991

cinoma; (f) acute respiratory alkalosis or metabolic acidosis or alkalosis<sup>16,17</sup>; and (g) obesity. Obesity was defined as a body mass index (body weight (kg)/(height(m))<sup>2</sup>) greater than 27.8 and 27.3 in men and women, respectively.<sup>18</sup> Finally, the respiratory exchange ratio had to be 0.83 (0.05).

#### MEASUREMENT OF LUNG FUNCTION

The technical details, methods of analysis, precautions, and calibrations used in our laboratory have been outlined previously.<sup>19</sup>

Spirometric measurements were obtained with a Stead-Wells spirometer while the patient was seated. Functional residual capacity (FRC) was measured by helium equilibration, and residual volume (RV) and total lung capacity (TLC) were calculated.

The single breath carbon monoxide transfer factor (TLCO) was measured as described.<sup>20</sup> Ventilation and arterial blood gas tensions and pH were determined with the patient supine and comfortable. An arterial cannula was placed in the radial or brachial artery. The patient then breathed through a mouthpiece connected to a two way valve (Hans-Rudolf, Kansas City, Missouri) into a Douglas bag. The respiratory rate and tidal carbon dioxide tension were monitored with an infrared analyser or a mass spectrometer (1100 Medical Gas Analyzer, Perkin Elmer, Pomona, California). When end tidal carbon dioxide was stable, after an initial wash out, expired air was collected for two minutes. The volume of expired air was determined in a Tissot spirometer and oxygen and carbon dioxide concentrations in expired air by a mass spectrometer. An arterial blood sample was obtained for determination of arterial blood gas tensions and pH. A calculator was used to calculate plasma bicarbonate concentration (Severinghaus Calculator, Radiometer, Copenhagen).

From these measurements, minute ventilation ( $\dot{V}_E$ ), respiratory rate, tidal volume, dead space (VD), alveolar ventilation ( $\dot{V}_A$ ), oxygen consumption ( $\dot{V}_{O_2}$ ), carbon dioxide production ( $\dot{V}_{CO_2}$ ), and respiratory exchange ratio were calculated.

Normal values for the spirometric data were taken from Kory *et al*,<sup>21</sup> and regression equations for TLCO from Gaensler and Smith.<sup>20</sup>

#### ANALYSIS

Patients were divided into three groups on the basis of the FVC representing mild, moderate, and severe restrictive defect: 79% to >65%, 65% to >50%, and  $\leq$ 50% of predicted values, respectively. The groups were compared by analysis of variance and multiple *t* tests adjusted by the Bonferroni method. Patients with

moderate (group 2) and severe (group 3) restrictive defects were compared with those having a mild restrictive defect (group 1) (two comparisons), and  $p \leq 0.025$  was considered to be significant. Data are presented as means with standard deviations in parentheses.

We also determined Pearson linear correlations for certain variables and then considered a *p* value below 0.05 to be significant. The SAS computer software of the University of Cincinnati was used for the calculations.

#### Results

Sixty patients met the criteria, with 27, 18, and 15 in groups 1, 2, and 3, respectively. The major diagnoses were idiopathic pulmonary fibrosis (25 patients), sarcoidosis (11), asbestosis (eight), collagen vascular disease (six), berylliosis and silicosis (three), and chronic eosinophilic pneumonia and eosinophilic granuloma (four). The distribution of disease was similar among the three groups.

Morphometric data are shown in table 1. Although mean values for height, weight, and body surface area were lower in group 3 than in groups 1 and 2 the differences were not significant.

FVC ranged from 79% to 29% of predicted values. There were significant differences in most spirometric and lung volume measurements between the groups (table 2). FVC, FEV<sub>1</sub>, and TLC were significantly lower in groups 2 and 3 when compared with group 1 whether expressed as percentages of predicted values or as absolute values (table 2). The only measurements that did not differ significantly between the three groups were small differences in residual volume (RV) (and RV percentages of predicted values) and FEV<sub>1</sub> to FVC ratio.

Although arterial carbon dioxide tension (Paco<sub>2</sub>) varied from 30 mm Hg (4.0 kPa) to 49 mm Hg (6.5 kPa) in individual patients, mean values of Paco<sub>2</sub> (table 3) did not differ between the three groups. Mean values for carbon dioxide production and oxygen consumption (per surface area) also did not differ significantly in the three groups (table 3).

Although minute and alveolar ventilation (per surface area) did not differ between the three groups (table 3), breathing pattern varied considerably with a significant and progressive rise in respiratory rate and a progressive fall in tidal volume.

#### CORRELATIONS BETWEEN VARIABLES

FVC correlated significantly with other lung volumes, the highest correlation occurring with inspiratory capacity and TLC, and the lowest with RV (table 4). Similar correlations were

Table 1 Demographic data on three groups of patients with interstitial lung diseases categorised according to percentage of predicted forced vital capacity. Values are means (SD)

	Age (years)	Height (cm)	Weight (kg)	BSA (m <sup>2</sup> )	BMI (kg/m <sup>2</sup> )
Group 1 (n = 27)	46.2 (17.2)	170.9 (11.2)	70.0 (13.4)	1.81 (0.22)	23.9 (3.9)
Group 2 (n = 18)	47.2 (17.1)	167.1 (9.9)	65.1 (10.5)	1.73 (0.18)	23.2 (2.5)
Group 3 (n = 15)	39.7 (17.0)	165.4 (10.0)	59.7 (13.0)	1.65 (0.21)	21.7 (3.0)

BSA = body surface area; BMI = body mass index.

Table 2 Mean (SD) lung volumes in three groups of patients with interstitial lung diseases categorised according to percentage of predicted forced vital capacity

Lung volume	Group 1 (n = 27)	Group 2 (n = 18)	Group 3 (n = 15)
FVC { litres	2.88 (0.76)	2.17 (0.53)*	1.54 (0.32)*
% predicted	71 (4)	57 (5)*	41 (7)*
FEV <sub>1</sub> { l/s	2.42 (0.68)	1.82 (0.42)*	1.35 (0.31)*
% predicted	73 (8)	59 (8)*	41 (7)*
FEV <sub>1</sub> /FVC (%)	84 (6)	84 (5)	87 (9)
TLC { litres	4.31 (1.01)	3.38 (0.86)*	2.54 (0.39)*
% predicted	91 (11)	74 (13)*	57 (12)*
FRC (l)	2.18 (0.60)	1.86 (0.53)	1.48 (0.39)*
RV { litres	1.30 (0.44)	1.17 (0.41)	0.96 (0.40)
% predicted	108 (31)	103 (43)	88 (36)
IC (l)	2.12 (0.69)	1.52 (0.59)*	1.06 (0.34)*
RV/TLC (%)	31 (9)	35 (10)	38 (12)

\*p &lt; 0.025 v group 1.

FVC = forced vital capacity; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; IC = inspiratory capacity.

Table 3 Mean (SD) gas exchange and ventilation values in three groups of patients with interstitial lung diseases categorised according to percentage of predicted forced vital capacity

	Group 1	Group 2	Group 3
Pao <sub>2</sub> (mm Hg)	76 (12)	71 (14)	74 (17)
Paco <sub>2</sub> (mm Hg)	37 (4)	36 (3)	39 (5)
[H <sup>+</sup> ] (nEq/l)	39.0 (2.4)	37.6 (1.8)	38.0 (2.0)
[HCO <sub>3</sub> <sup>-</sup> ] (mEq/l)	23 (2)	24 (2)	25 (3)
Vo <sub>2</sub> /BSA (ml/min/m <sup>2</sup> )	135 (17)	147 (28)	142 (21)
Vo <sub>2</sub> /BSA (ml/min/m <sup>2</sup> )	109 (14)	120 (24)	115 (21)
RER	0.81 (0.03)	0.82 (0.04)	0.81 (0.04)
TLCO { (ml/min/mmHg)	17 (7)	14 (7)	12 (6)
(% predicted)	64 (20)	54 (26)	49 (34)*
RR (min)	17 (4)	20 (4)**	23 (5)***
V <sub>T</sub> (ml)	484 (131)	460 (139)	377 (109)***
V <sub>D</sub> (ml/kg)	2.4 (1.1)	2.7 (1.2)	2.7 (0.8)
V <sub>D</sub> /V <sub>T</sub> (%)	34 (12)	37 (10)	42 (7)
VE/BSA (l/min/m <sup>2</sup> )	4.4 (0.8)	5.2 (1.5)	5.1 (0.9)
VA/BSA (l/min/m <sup>2</sup> )	2.8 (0.3)	3.2 (0.4)	3.0 (0.4)

\*p &lt; 0.025; \*\*p &lt; 0.017; \*\*\*p &lt; 0.01 (all v group 1).

BSA = body surface area; Vo<sub>2</sub> = oxygen consumption; Vco<sub>2</sub> = carbon dioxide production; TLCO = transfer factor for carbon monoxide; RER = respiratory exchange ratio; VE = minute ventilation; VA = alveolar ventilation. Vo<sub>2</sub>, Vco<sub>2</sub>, and TLCO are at STPD. Ventilatory values are at BTPS.

Conversion to SI unit: 1 mm Hg ≈ 0.133 kPa.

found between FVC as a percentage of predicted values and other predicted values (data not shown).

Both FVC and FVC % predicted correlated with respiratory rate and tidal volume (figures 1 and 2).

The correlations between both Paco<sub>2</sub> and Pao<sub>2</sub> and other variables are summarised in table 5. In addition, there were no significant correlations between Paco<sub>2</sub> and V<sub>D</sub>, V<sub>D</sub>/V<sub>T</sub> ratio, body weight, FEV<sub>1</sub>, FEV<sub>1</sub> % predicted, FVC, and FVC % predicted. However, Pao<sub>2</sub> correlated significantly with FVC (r = 0.28, p = 0.035) and TLCO (r = 0.39, p = 0.003).

There was no correlation between Vo<sub>2</sub> and Vco<sub>2</sub> (or Vo<sub>2</sub> and Vco<sub>2</sub> in relation to body surface area) and FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC ratio, RV/TLC ratio, or their respective predicted values.

## Discussion

To obtain reliable measures of the pattern of breathing, ventilation, and arterial blood gas tensions in patients with pulmonary disease, steady state criteria must be met.<sup>4</sup> Applying a noseclip and mouthpiece<sup>22</sup> and sampling arterial blood may change the pattern of breathing. In our study several precautions were taken to ensure the presence of a steady state. Measurements of ventilation were started only after the patient had already breathed for several minutes through the mouthpiece and shown stable end tidal carbon dioxide concentrations. Normal values of respiratory exchange ratio were required. Arterial blood was obtained through an indwelling cannula, and the strong linear correlation (r = 0.85) between Paco<sub>2</sub> and bicarbonate concentration with a slope of 0.58 indicates that changes in Paco<sub>2</sub> were long term.

We studied 60 patients, 11 of whom had a severe restrictive defect with an FVC below 1.5 l. Among these 60 patients two had a high Paco<sub>2</sub> of 44 mm Hg (5.9 kPa), one had 45 mm Hg (6.0 kPa) and one 49 mm Hg (6.5 kPa). Chronic hypercapnia therefore seems to be rare in ambulatory patients with interstitial lung disease. Severe V̇/Q̇ mismatch impairs carbon dioxide elimination,<sup>23 24</sup> but our patients were generally capable of increasing their minute ventilation and, hence, alveolar ventilation, to prevent hypercapnia. In addition, V̇co<sub>2</sub> (table 2), another determinant of Paco<sub>2</sub>, remained relatively constant even in patients with marked impairment of FVC.

Several factors probably help to maintain VE and VA in these patients. One factor, not looked at in this study, is the low to mid position of the chest wall in patients with a low FVC. This position places the inspiratory muscles at a mechanical advantage. Two factors identified in this study were the low values of Pao<sub>2</sub> and high respiratory rate. We found a significant negative correlation between Pao<sub>2</sub> and minute ventilation (table 5), perhaps suggesting that hypoxaemia may augment resting ventilation in patients with more severe interstitial lung disease. A major factor, however, contributing to maintenance of ventilation was the increase in respiratory rate.

Our results show that in interstitial lung disease breathing pattern changes, lower values of FVC being associated with an increased respiratory rate and decreased tidal volume. Previous studies have reported considerable variation in respiratory rate and tidal volume in patients with interstitial lung disease, though the number of patients was usually small and the variation reported is probably related to the differences in severity of restriction between studies. In our study respiratory rate varied

Table 4 Pearson correlations of forced vital capacity versus other lung function values in interstitial lung disease

	FEV <sub>1</sub>	FEV <sub>1</sub> /FVC	TLC	RV	RV/TLC	IC	ERV	FRC	TLCO
r	0.98	-0.2	0.90	0.26	-0.52	0.89	0.53	0.58	0.52
p	0.0001	0.2	0.0001	0.04	0.0001	0.0001	0.0001	0.0001	0.0001

ERV = expiratory reserve volume; TLCO = single breath transfer factor for carbon monoxide; other abbreviations as in table 3.

Table 5 Pearson correlations of  $Paco_2$  and  $PaO_2$  versus results of ventilatory and gas exchange tests in interstitial lung disease

	$\dot{V}_E/BSA$ (l/min/m <sup>2</sup> )	$\dot{V}_A/BSA$ (l/min/m <sup>2</sup> )	RR (min)	$V_T$ (ml)	$\dot{V}_{CO_2}/BSA$ (l/min/m <sup>2</sup> )	$[HCO_3^-]$ (mEq/l)	$[H^+]$ (nEq/l)	$TLCO$ (ml/min/mmHg)
					$Paco_2$			
r	-0.2	-0.29	-0.2	0.1	0.2	0.85	0.1	0.1
p	0.1	0.02	0.2	0.4	0.2	0.0001	0.4	0.2
					$PaO_2$			
r	-0.41	-0.1	-0.04	-0.27	-0.2	-0.1	0.01	0.39
p	0.001	0.4	0.74	0.04	0.2	0.3	0.9	0.003

$\dot{V}_E$  = minute ventilation;  $\dot{V}_A$  = alveolar ventilation; BSA = body surface area; RR = respiratory rate;  $V_T$  = tidal volume;  $TLCO$  = single breath transfer factor for carbon monoxide;  $\dot{V}_{CO_2}$  = carbon dioxide.

from eight to 33 per minute and tidal volume from 214 to 829 ml in individual subjects and were often normal in patients with minimally abnormal FVC values (group 1). When rapid and shallow breathing is clinically obvious the patients characteristically have severe mechanical impairment.

The mechanisms mediating the rapid and shallow breathing in interstitial lung disease

have been reviewed by several authors.<sup>25-28</sup> They include the mechanical effects of increased lung elastance, perceived as increasing load by mechanoreceptors, and stimulation of intrapulmonary receptors—for example, rapidly adapting and J receptors.

External elastic loading of the respiratory system (breathing from a rigid chamber) has been used to study the role of mechanoreceptors in determining the pattern of breathing. External elastic loading is thought to represent the mechanical analogue of diffuse interstitial lung disease (internal elastic loading). Several studies have shown that normal subjects breathe shallowly and rapidly in response to an external load and that respiratory rate increases progressively and tidal volume falls as the magnitude of the external elastic load increases.<sup>29-33</sup> Our results show similar differences in the pattern of breathing in relation to lower values of FVC, which are consistent with those of studies on external elastic load.

Intrinsic elastic loading does not seem to account fully for the pattern of breathing in our patients. Despite a significant correlation between FVC and respiratory rate and tidal volume, the results show a considerable scatter. Several factors, such as stimulation of both mechanoreceptors and other intrapulmonary receptors,<sup>25-28</sup> may have contributed to the pattern of breathing we observed. Intrapulmonary receptors may be stimulated by inflammatory mediators<sup>25-26</sup> released from cells which accumulate in the lung parenchyma of patients with interstitial lung disease,<sup>34</sup> and studies by Guz *et al* in humans<sup>27,28</sup> and by Phillipson *et al* in dogs<sup>35</sup> indicate that stimulation of these receptors contributes to tachypnoea.

Irrespective of the mechanisms involved, in the face of severe interstitial lung disease a raised respiratory rate is important in maintaining adequate ventilation because tidal volume is small and gas exchange impaired. This pattern of breathing is appropriate to the mechanical properties of the respiratory system in interstitial lung disease.<sup>36</sup> It enables patients to maintain ventilation with a smaller inspiratory muscle force and less mechanical work per breath,<sup>36</sup> which should minimise the work of breathing. Mean values of  $\dot{V}_{CO_2}$  and  $\dot{V}_{O_2}$  in relation to body surface area did not differ in our three groups of patients. Indices of metabolic rate did not correlate with ventilatory impairment in contrast to the findings in patients with chronic obstructive lung disease.<sup>37</sup> In normal subjects the increase in

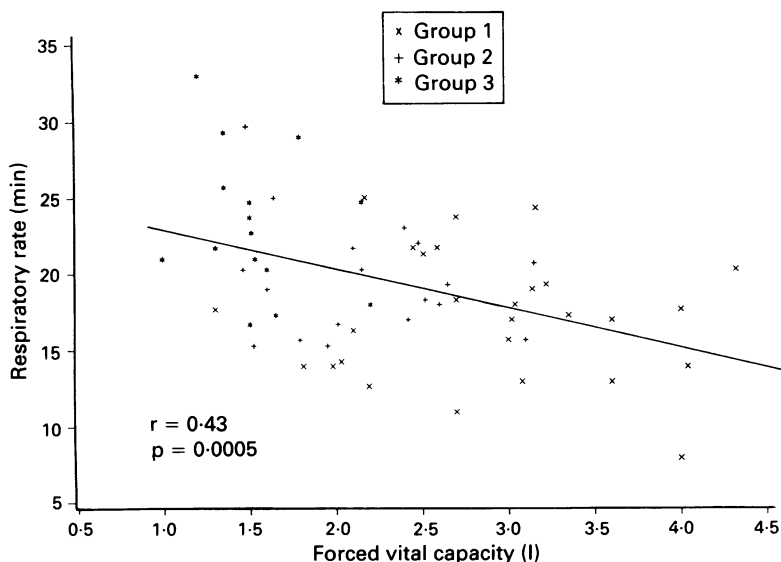


Figure 1 Linear regression between forced vital capacity (FVC) and respiratory rate (RR).

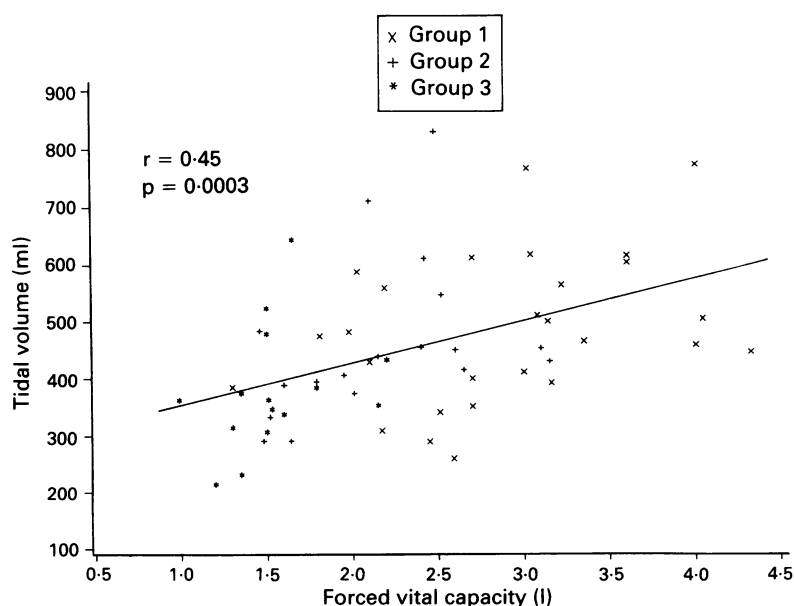


Figure 2 Linear regression between forced vital capacity and tidal volume ( $V_T$ ).

oxygen consumption caused by an added inspiratory external elastic load is less than that seen with a resistive load,<sup>38</sup> an effect attributed to preferential recruitment of faster and less efficient muscle fibres during breathing with a resistive load.

From our results in 60 patients with interstitial lung disease we draw several conclusions. With respect to gas exchange, FVC correlates with impairment in TLCO more strongly than with hypoxaemia. Changes in  $P_{aCO_2}$  do not relate to severity of impairment of any spirometric values—for example, FEV<sub>1</sub> or FVC in absolute terms or as percentage of predicted values. Low values of FVC are associated with higher respiratory rates and lower tidal volumes; in the face of severe impairment in gas exchange, changes in respiratory rate are important for maintaining adequate ventilation and eucapnia. This pattern of breathing minimises the work of breathing, and carbon dioxide production and oxygen consumption remain relatively constant even when mechanical impairment is severe. The lack of a rise in carbon dioxide production in the face of increasing functional impairment (increasing mechanical and gas exchange defects) is important in preventing the development of hypercapnia in interstitial lung disease.

We thank Dr E A Gaensler for allowing us to report the data collected in his laboratory. The authors also thank Mrs Sandra K Eversole for her excellent secretarial help, Mr Robert J Mohrman for his careful review of the manuscript, and Dr P Gartside for his help in the statistical analysis.

- 1 Burrows B, Sakesena FB, Diener CF. Carbon dioxide tension and ventilatory mechanics in chronic obstructive pulmonary disease. *Ann Intern Med* 1966;65:685-700.
- 2 Howell JBL. Breathlessness in pulmonary disease. In: Howell JBL, Campbell EJM, eds. *Breathlessness*. Oxford: Blackwell Scientific Publications, 1966;165-77.
- 3 Javaheri S. Premorbid hypercapnic ventilatory response and  $P_{aCO_2}$  in emphysema. *Pflügers Arch* 1987;408:S29.
- 4 Javaheri S, Blum J, Kazemi H. Pattern of breathing and carbon dioxide retention in chronic obstructive lung disease. *Am J Med* 1982;71:228-34.
- 5 McFadden ER Jr, Lyons HA. Arterial-blood gas tension in asthma. *N Engl J Med* 1968;278:1027-32.
- 6 Rebeck AS, Read J. Assessment and management of severe asthma. *Am J Med* 1971;51:788-98.
- 7 Kelsen SG, Kelsen DP, Fleegler BF, Jones RC, Rodman T. Emergency room assessment and treatment of patients with acute asthma. *Am J Med* 1978;64:622-8.
- 8 Sorli J, Grassino A, Lorange G, Milic-Emili J. Control of breathing in patients with chronic obstructive lung disease. *Clinical Science and Molecular Medicine* 1978;54:295-304.
- 9 Lourenco RV, Turino GM, Davidson LAG, Fishman AP. The regulation of ventilation in diffuse pulmonary fibrosis. *Am J Med* 1965;38:199-216.
- 10 Snider GL, Doctor RL. The mechanics of ventilation in sarcoidosis. *Am Rev Respir Dis* 1964;89:897-908.
- 11 Young RC, Carr C, Shelton TG, Mann M, Ferrin A, Laurey FJR, Harden KA. Sarcoidosis: relationship between changes in lung structure and function. *Am Rev Respir Dis* 1966;95:224-38.
- 12 Marshall R, Karlsh AJ. Lung function in sarcoidosis. *Thorax* 1971;26:402-5.
- 13 Renzi G, Milic-Emili J, Grassino AE. The pattern of breathing in diffuse lung fibrosis. *Bull Eur Physiopathol Respir* 1982;18:461-72.
- 14 Gaensler EA, Carrington CB, Coutu RE, Fitzgerald MX. Radiographic, physiologic, pathologic correlations in interstitial pneumonias. *Progress in Respiration Research* 1974;8:223-41.
- 15 Gaensler EA, Carrington CB, Coutu RE, Tomasian A, Hoffman L, Smith AA. Pathological, physiological and radiological correlations in the pneumoconioses. *Ann NY Acad Sci* 1972;200:574-607.
- 16 Goldberg M, Green SB, Moss ML, Marbach CB, Garfinkel D. Computer-based instruction and diagnosis of acid-base disorders. *JAMA* 1973;223:269-75.
- 17 Javaheri S, Kazemi H. Metabolic alkalosis and hypoventilation in humans. *Am Rev Respir Dis* 1987;136:1011-6.
- 18 Itallie TBV. Health implications of overweight and obesity in the United States. *Ann Intern Med* 1985;103:983-8.
- 19 Gaensler EA, Macklem P, Cherniak R, Permutt S, Ferris B. Pulmonary function in epidemiology standardization project. *Am Rev Respir Dis* 1978;188:7-112.
- 20 Gaensler EA, Smith AA. Attachment for automated single breath diffusing capacity measurements. *Chest* 1973;63:136-45.
- 21 Kori RC, Callahan R, Boren HG, Syner JC. The Veterans Administration-Army Cooperative Study of Pulmonary Function. I. Clinical spirometry in normal man. *Am J Med* 1961;30:243-58.
- 22 Gilbert R, Auchincloss JH Jr, Brodsky J, Bowden W. Changes in tidal volume, frequency and ventilation induced by their measurement. *J Appl Physiol* 1972;33:252-4.
- 23 West JB. Causes of carbon dioxide retention in lung disease. *N Engl J Med* 1971;284:1232-6.
- 24 West JB. Assessing pulmonary gas exchange. *N Engl J Med* 1987;316:1336-8.
- 25 Kornbluth RS, Turino GM. Respiratory control in diffuse interstitial lung disease and diseases of the pulmonary vasculature. *Clin Chest Med* 1980;1:91-102.
- 26 Rebeck AS, Stulsky AS. Control of breathing in diseases of the respiratory tract and lungs. In: Fishman AP, ed. *Handbook of physiology. Vol 2. The respiratory system*. Bethesda, Maryland: American Physiological Society, 1986;771-91.
- 27 Guz A, Noble MIM, Eisele JH, Trenchard D. Experimental results of vagal block in cardiopulmonary disease. In: Porter R, ed. *Breathing: Hering-Breuer centenary symposium*. London: Churchill, 1970;17-40.
- 28 Guz A, Noble MIM, Eisele JH, Trenchard D. Experimental results of vagal block in cardiopulmonary disease. In: Porter R, ed. *Breathing: Hering-Breuer centenary symposium*. London: Churchill, 1970;315-36.
- 29 Freedman S, Campbell EJM. The ability of normal subjects to tolerate added inspiratory loads. *Respir Physiol* 1970;10:213-35.
- 30 Bland S, Lazerou L, Dyck G, Cherniak RM. Influence of the "chest wall" on respiratory rate and depth. *Respir Physiol* 1967;3:47-54.
- 31 Agostoni E, D'Angelo E, Piolini M. Breathing pattern in men during inspiratory elastic loads. *Respir Physiol* 1978;34:279-393.
- 32 Pope H, Holloway R, Campbell EJM. The effects of elastic and resistive loading of inspiration on the breathing of conscious man. *Respir Physiol* 1968;4:363-72.
- 33 Remmers JE, Marttila I. Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. *Respir Physiol* 1975;24:31-41.
- 34 Turner-Warwick M, Haslan PL. The value of serial bronchoalveolar lavages in assessing the clinical progress of patients with cryptogenic fibrosing alveolitis. *Am Rev Respir Dis* 1987;135:26-34.
- 35 Phillipson EA, Murphy E, Kozar LF, Schultze RK. Role of vagal stimuli in exercise ventilation in dogs with experimental pneumonitis. *J Appl Physiol* 1975;39:76-85.
- 36 Mead J. Control of respiratory frequency. *J Appl Physiol* 1960;15:325-36.
- 37 Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;140:385-91.
- 38 Cala SJ, Wilcox P, Edyvean J, Rynn M, Engel LA. Oxygen cost of inspiratory loading: resistive v elastic. *J Appl Physiol* 1991;70:1983-90.