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Pattern of carbon dioxide stimulated breathing in patients with chronic airway obstruction

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ABSTRACT The pattern of stimulated breathing during carbon dioxide inhalation was studied in a group of 21 patients with severe irreversible airways obstruction (mean FEV_1=0·9 litre, mean $FEV_1/FVC\%$=50%). Carbon dioxide rebreathing experiments were performed, the ventilatory response being defined in terms of total ventilation ($\dot{V}$) and CO_2 sensitivity (S). Breathing pattern was defined by the changes in tidal volume (ΔV_T) and respiratory frequency (Δf) and the maximum V_T achieved ($V_{T}max$). Contrary to some previous studies no significant relationship could be demonstrated between the severity of airway obstruction ($FEV_1/FVC\%$, Raw) and the ventilatory response to rebreathing ($\dot{V}$, S, ΔV_T, Δf, $V_{T}max$). However, measurements of dynamic lung volume (FEV_1, FVC, IC) were found to be significantly correlated with the breathing pattern variables (ΔV_T, Δf, $V_{T}max$). Resting Pa_{O_2} and Pa_{CO_2} were significantly correlated with ΔV_T but not Δf. Results indicate that the degree of airway obstruction does not dictate the ventilatory or breathing pattern response to carbon dioxide induced hyperpnoea. In contrast it is the restriction of dynamic lung volume, by limiting the V_T response, that appears to determine the ventilatory and breathing pattern response in patients with severe airway obstruction.

A reduced total ventilatory response to CO_2 in patients with chronic airway obstruction has long been recognised[1]; however, surprisingly little attention has been paid to the pattern of breathing.

In recent years considerable progress has been made in understanding the factors controlling tidal volume (V_T) and breath intervals (total breath duration Tt, inspiratory duration Ti, and expiratory duration Te, in experimental animals and in normal man.[2 3] It is, therefore, a logical step to consider the impaired ventilatory response in patients with chronic airways obstruction in terms of abnormalities in breathing pattern.

Methods

Twenty-one male patients with severe, chronic, irreversible, airway obstruction underwent CO_2 rebreathing experiments.[4] Each patient gave full informed consent. The presence of airway obstruction was defined as a reduction in the absolute FEV_1 to less than 50% predicted value, and $FEV_1/FVC\%$ less than 60%. No significant reversibility of airway obstruction (<15% change in FEV_1) could be obtained by the inhalation of aerosolised isoprenaline.

After an initial rest period, subjects were allowed to rebreathe a mixture of 7% CO_2 in 93% O_2 contained within a six-litre anaesthetic bag. The rebreathing bag was connected via a three-way tap to a heated Fleisch (no 3) pneumotachograph and rubber mouthpiece. The tap was turned so as to connect with either ambient air or the rebreathing mixture. The resistance of the rebreathing circuit was 0·025 kPa l^{-1} s (0·25 cmH_2O l^{-1} s).

Rebreathing was continued to the limit of tolerance determined by the patient or when the inspired CO_2 level reached 10%. After reaching the limit of tolerance the patient was again allowed to breathe air. Rebreathing times ranged between four and six minutes between individuals.

Airflow, its integral, tidal volume (V_T) and end-tidal CO_2 concentration ($P_{ET}CO_2$) were re-

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corded on a multichannel linear recorder (Brush, Gould Instruments). Calibration of the pneumotachograph volume signal was performed before and after each procedure using a one-litre displacement syringe. The accuracy of the pneumotachograph was confirmed using air, the initial rebreathing mixture, and a mixture equivalent to that achieved at the end of rebreathing. No significant differences in volume calibration could be demonstrated between these gas mixtures.

Values of VT, breath intervals (Ti and Te), and $P_{ET}CO_2$ were measured by hand from the linear record. Breathing pattern was represented as the breath by breath plot of VT against Ti and Te (figure). Lines of best fit were drawn by hand through each plot so as to pass through the mean values for five initial and final breaths. This ensured that the mean values of VT, Ti and Te used in the statistical analyses were representative of each subject's breathing pattern. Values of

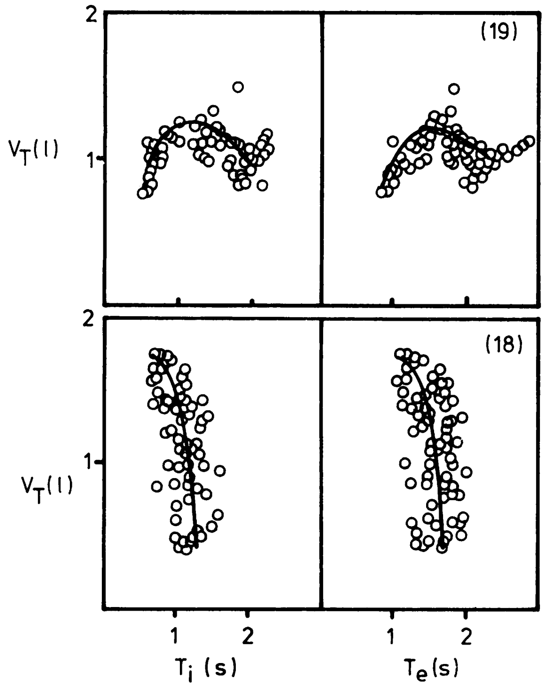

Figure *Examples of breathing pattern plots in two of the patients studied as described by the tidal volume/breath interval (Ti, Te) relationship. Each symbol represents a single breath, some having been omitted for clarity. The example on the top shows little increase in VT but significant shortening of both Ti and Te (that is, increase in respiratory frequency) while below the increase in ventilation is achieved mostly by an increase in VT.*

respiratory frequency and the changes in respiratory frequency (Δf) were derived from the values of Ti and Te.

Statistical analysis of group mean data was made using Student's *t* test, linear regressions by least squares regression analysis. SI units are quoted with standard units in parentheses. Conversion of mmHg (torr) to kPa requires a multiplication factor of 0·133; for cmH_2O to kPa, a factor of 0·1.

Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), inspiratory capacity (IC), functional residual capacity (FRC), and airways resistance (Raw) were measured using a constant volume whole body plethysmograph (Fenyves and Gut; Basle, Switzerland). For Raw estimation, subjects breathe warm, moist air fulfilling BTPS conditions.[5 6] Measurements were made during resting breathing so that panting manoeuvres were avoided.

Blood gas analysis was made immediately after radial artery blood sampling using Radiometer equipment.

Results

Anthropometric and physiological characteristics of the 21 patients with airway obstruction are given in table 1. The severity of the airway obstruction is indicated by the group mean FEV_1= 0·93 l representing 50% of mean FVC. Mean Raw (inspiratory) for the group was 0·65 kPa l^{-1} s (6·5 cmH_2O l^{-1} s). Upper limit of adult value for our laboratory, 0·2 kPa l^{-1} s (2 cmH_2O l^{-1} s). No relationship could be demonstrated ($p<0·1$) between either the spirometric (FEV_1/FVC) or the plethysmographic (Raw) parameters of airway

Table 1 *Anthropometric and physiological data of the 21 patients studied. Values expressed as the mean ±1 SD*

	Mean	*±1SD*
Age (yrs)	61	7
Height (cm)	170	5
FEV_1 (l)	0·93	0·32
FVC (l)	1·84	0·51
FEV_1/FVC %	50	7
Raw (kPa l^{-1}s)	0·65	0·32
Pa_{O_2} (kPa)	9·13	1·53
Pa_{CO_2} (kPa)	5·65	0·93
Initial VT (l)	0·82	0·15
VTmax (l)	1·27	0·25
ΔVT (l)	0·45	0·21
Initial breath frequency (breath min^{-1})	18·3	3·8
Final breath frequency (breath min^{-1})	27·7	8·5
Δf (breath min^{-1})	9·4	8·3
CO_2 sensitivity (l min^{-1} kPa^{-1})	6·85	3·15

obstruction, and any of the indices chosen to represent total ventilatory ($\dot{V}max$) CO_2 sensitivity ($S\dot{V}/PCO_2$) or pattern response to CO_2 (ΔV_T, ΔF, V_Tmax).

In contrast individual volumes (FEV_1 FVC, and IC) showed varying but significant degrees of correlation with the indices of breathing pattern response (table 2), reduction in lung volumes being associated with diminished response to CO_2. Although resting PaO_2 and $PaCO_2$ were found to be significantly correlated with ΔV_T ($p<0.05$ and $p<0.01$ respectively) no corresponding correlation was demonstrated with Δf (table 2).

Table 2 *Correlations of breathing pattern indices (ΔV_T, Δf, V_Tmax) with physiological variables of the 21 patients with chronic airway obstruction*

	FEV_1 (l)	FVC (l)	PaO_2 (kPa)	$PaCO_2$ (kPa)
ΔV_T(l)	r=0·80 p<0·001	r=0·81 p<0·001	r=0·48 p<0·05	r=−0·58 p<0·01
Δf (breaths min^{-1})	r=−0·37 (NS)	r=−0·45 p<0·05	r=0·07 (NS)	r=0·16 (NS)
V_Tmax (l)	r=0·63 p<0·01	r=0·69 p<0·001	r=0·09 (NS)	r=0·37 (NS)

Discussion

After the work of early investigators into CO_2 responsiveness in chronic bronchitis and emphysema,[1 7 8] some authorities considered the mechanical impedance afforded by the airway obstruction to be of prime importance in diminishing ventilatory response to CO_2,[9 10] while others attributed this to an impaired CNS sensitivity to CO_2.[11-14] The inter-relationships of these two mechanisms were investigated and clarified by Lourenço and Miranda[15] and Lane *et al.*[16] If mechanical factors alone are important, some correlation should be demonstrable betwen ventilatory response and indices reflecting the impaired mechanical status of the lungs, especially those relating to the degree of airway obstruction. Unlike other studies,[17-19] we were unable to demonstrate a significant relationship between CO_2 sensitivity (S) and the pulmonary function assessment of airway obstruction.

Our studies demonstrate that the diminished ventilatory response is caused primarily by the small V_Tmax values achieved, the higher respiratory frequencies failing to compensate sufficiently for these lower volumes. The markedly reduced V_T response to respiratory stimuli in patients with chronic airway obstruction does not initially appear to be unexpected especially in view of the greatly impaired total ventilatory response. In the early study by Scott[7] the largest V_T achieved by any of his subjects was 860 ml, and this diminished V_T response in patients with airway obstruction has subsequently been noted by several groups of workers.[20-21] Sorli *et al*[22] have proposed that it is only patients who have a lower than normal resting V_T who develop CO_2 retention.[22] However no data were obtained during respiratory stimulation to obtain values of V_Tmax.

Although the degree of airway obstruction did not correlate with total ventilatory or pattern responses to CO_2 rebreathing, individual volumes (FEV_1, FVC, IC) correlated well. This was particularly true for V_T which showed the strongest correlations with absolute values FEV_1 and FVC. It may, therefore, be deduced that the mechanical constraints on the lungs determining V_T are of a restrictive rather than an obstructive nature.

Mean V_Tmax responses at the end of maximum tolerated levels of inspired PCO_2 reached a volume which represented 60% of VC, a somewhat higher value than that obtained by Potter *et al*[21] and similar to the results obtained by Lane.[23] In rebreathing studies in normal subjects[24] we have shown V_Tmax never to be greater than IC and though V_Tmax exceeded IC in three subjects in the present study this was only by small volumes (50 ml), which probably fall within the experimental error of the measurements. End-expiratory lung volumes (FRC) do not remain fixed during stimulated breathing in patients with airway obstruction, FRC increasing significantly.[25-27] This increase in static lung volume together with the increase in V_T may result, therefore, in tidal excursions actually exceeding TLC during hyperpnoea.

Increased respiratory frequency in patients with obstructive lung disease has long been recognised. Rheinhardt[7] recorded high resting respiratory frequencies (mean 23 breaths min^{-1}). Scott[6] found a similar relationship (18 breaths min^{-1} for patients with airway obstruction and 12·5 breaths min^{-1} for normal subjects). Our own data in normal subjects[24] likewise show a lower resting frequency (13·9 breath min^{-1}) than that found here in patients with airway obstruction (18·3 breaths min^{-1}).

This increased frequency of breathing at rest in patients with chronic airway obstruction contrasts with the slow deep breathing observed at rest in normal people subjected to non-elastic loading of expiration.[28 29] Mechanical considerations suggest that slowing the rate of respiration is more economical in terms of respiratory work in the face of airway obstruction than increasing the rate. In pathological intrapulmonary airway obstruction it seems that this pattern is abandoned for an apparenly inefficient mode of rapid shallow breathing. The present data confirm that this discrepancy is even more marked during ventilatory stimulation.

Since this response appears to be inappropriate in purely mechanical terms there may be other factors involved in the tachypnoea. Lung conditions characterised by a resistive defect have disproportionately high respiratory frequencies at rest or during exercise. This is observed for example in mitral stenosis,[30] pulmonary fibrosis,[31 32] and pneumothorax.[33] Is there then a restrictive component influencing breathing pattern in patients with chronic airflow obstruction? This could be so if "restrictive" is interpreted not in the accepted sense of stiff lungs with reduced lung volumes but as a loss of compliance associated with breathing at high lung volume. Apart from the purely mechanical problems of breathing at high lung volumes, associated reflex phenomena involving lung stretch receptors may also be implicated in the production of tachypnoea.

Recently it has been shown that patients with chronic obstructive lung disease who were hypoxic achieved higher respiratory frequencies than those who were not.[34] A similar trend was seen in the relationship of Δf and Pa_{O_2} from our data, but this negative correlation was not significant. Unlike the data presented here, Bradley *et al*[34] were unable to demonstrate any differences in FEV_1 between the hypoxic patients with higher respiratory frequencies and those breathing more slowly. Arterial blood gases were seen to be better (higher Pa_{O_2}, lower Pa_{CO_2}) in our subjects with the largest V_T values. This may be an inevitable correlation because of the superior pulmonary function values in these subjects, but on the other hand may reflect the lower V_D/V_T ratio associated with larger values of V_T.

Our findings would suggest therefore that, although the ventilatory response to CO_2 rebreathing in severe airway obstruction is not directly related to the degree of obstructive pulmonary function impairment, the breathing pattern components are dependent on lung mechanics. In particular, the maximum increase in V_T appears to be closely related to the restriction of dynamic lung volumes.

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