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 FEV₁=0.9 litre, mean FEV₁/FVC%=50%). Carbon dioxide rebreathing experiments were performed, the ventilatory response being defined in terms of total ventilation (V̇) and CO₂ sensitivity (S). Breathing pattern was defined by the changes in tidal volume (∆Vₜ) and respiratory frequency (∆f) and the maximum Vₜ achieved (Vₜmax). Contrary to some previous studies no significant relationship could be demonstrated between the severity of airway obstruction (FEV₁/FVC%, Raw) and the ventilatory response to rebreathing (V̇, S, ∆Vₜ, ∆f, Vₜmax). However, measurements of dynamic lung volume (FEV₁, FVC, IC) were found to be significantly correlated with the breathing pattern variables (∆Vₜ, ∆f, Vₜmax). Resting Pao₂ and Paco₂ were significantly correlated with ∆Vₜ but not ∆f. 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 Vₜ response, that appears to determine the ventilatory and breathing pattern response in patients with severe airway obstruction.

A reduced total ventilatory response to CO₂ in patients with chronic airway obstruction has long been recognised; 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 (Vₜ) 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 CO₂ rebreathing experiments.⁴ Each patient gave full informed consent. The presence of airway obstruc-

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Breathing pattern in chronic airway obstruction

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 \( V_T \), breath intervals (\( T_i \) and \( T_e \)), and \( P_{\text{ET.CO}_2} \) were measured by hand from the linear record. Breathing pattern was represented as the breath by breath plot of \( V_T \) against \( T_i \) and \( T_e \) (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 \( V_T \), \( T_i \) and \( T_e \) used in the statistical analyses were representative of each subject’s breathing pattern. Values of respiratory frequency and the changes in respiratory frequency (\( \Delta f \)) were derived from the values of \( T_i \) and \( T_e \).

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 \( \text{mmHg} \) (torr) to kPa requires a multiplication factor of 0.133; for \( \text{cmH}_2\text{O} \) to kPa, a factor of 0.1.

Forced expiratory volume in one second (\( \text{FEV}_1 \)), 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 \( \text{FEV}_1 = 0.93 \text{l} \) representing 50% of mean FVC. Mean Raw (inspiratory) for the group was 0.65 kPa 1\(^{-1}\) s (6.5 cmH\(_2\)O 1\(^{-1}\) s). Upper limit of adult value for our laboratory, 0.2 kPa 1\(^{-1}\) s (2 cmH\(_2\)O 1\(^{-1}\) s). No relationship could be demonstrated (p<0.1) between either the spirometric (\( \text{FEV}_1/\text{FVC} \)) or the plethysmographic (Raw) parameters of airway

<table>
<thead>
<tr>
<th>Mean</th>
<th>±1SD</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 5</td>
</tr>
<tr>
<td>( \text{FEV}_1 ) (l)</td>
<td>0.93 ± 0.32</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>1.84 ± 0.51</td>
</tr>
<tr>
<td>( \text{FEV}_1/\text{FVC} ) %</td>
<td>50 ± 7</td>
</tr>
<tr>
<td>Raw (kPa 1(^{-1})s)</td>
<td>0.65 ± 0.32</td>
</tr>
<tr>
<td>Paco(_2) (kPa)</td>
<td>9.13 ± 1.15</td>
</tr>
<tr>
<td>Paco(_2) (kPa)</td>
<td>5.65 ± 0.93</td>
</tr>
<tr>
<td>Initial ( V_T ) (l)</td>
<td>0.82 ± 0.15</td>
</tr>
<tr>
<td>Vrmax (l)</td>
<td>1.27 ± 0.25</td>
</tr>
<tr>
<td>d( V_T ) (l)</td>
<td>0.45 ± 0.21</td>
</tr>
<tr>
<td>Initial breath frequency (breath min(^{-1}))</td>
<td>18.3 ± 3.8</td>
</tr>
<tr>
<td>Final breath frequency (breath min(^{-1}))</td>
<td>27.7 ± 8.5</td>
</tr>
<tr>
<td>( \Delta f ) (breath min(^{-1}))</td>
<td>9.4 ± 3.3</td>
</tr>
<tr>
<td>( \text{CO}_2 ) sensitivity (1 min(^{-1}) kPa(^{-1}))</td>
<td>6.85 ± 3.15</td>
</tr>
</tbody>
</table>

Figure 1 Examples of breathing pattern plots in two of the patients studied as described by the tidal volume/breath interval (\( T_i \), \( T_e \)) relationship. Each symbol represents a single breath, some having been omitted for clarity. The example on the top shows little increase in \( V_T \) but significant shortening of both \( T_i \) and \( T_e \) (that is, increase in respiratory frequency) while below the increase in ventilation is achieved mostly by an increase in \( V_T \).
obstruction, and any of the indices chosen to represent total ventilatory (V\text{max}) CO\text{2} sensitivity (SV/P\text{CO2}) or pattern response to CO\text{2} (AV\text{T}, $\Delta F$, V\text{max}).

In contrast individual volumes (FEV\text{f}, FVC, and IC) showed varying but significant degrees of correlation with the indices of breathing pattern response (table 2). A reduction in lung volumes being associated with diminished response to CO\text{2}. Although resting PaO\text{2} and PaCO\text{2} were found to be significantly correlated with $\Delta V\text{T}$ ($p<0.05$ and $p<0.01$ respectively) no corresponding correlation was demonstrated with $\Delta f$ (table 2).

### Table 2 Correlations of breathing pattern indices ($\Delta V\text{T}$, $\Delta f$, $V\text{max}$) with physiological variables of the 21 patients with chronic airway obstruction

<table>
<thead>
<tr>
<th></th>
<th>FEV\text{f} (l)</th>
<th>FVC (l)</th>
<th>PaO\text{2} (kPa)</th>
<th>PaCO\text{2} (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta V\text{T}$ (0)</td>
<td>$r=0.80$</td>
<td>$r=0.81$</td>
<td>$r=0.48$</td>
<td>$r=-0.58$</td>
</tr>
<tr>
<td>$\Delta f$ (breaths min$^{-1}$)</td>
<td>$r=0.37$</td>
<td>$r=0.07$</td>
<td>$r=0.16$</td>
<td>(NS)</td>
</tr>
<tr>
<td>$V\text{max}$ (l)</td>
<td>$r=0.63$</td>
<td>$r=0.69$</td>
<td>$r=0.09$</td>
<td>$r=0.37$</td>
</tr>
</tbody>
</table>

### Discussion

After the work of early investigators into CO\text{2} responsiveness in chronic bronchitis and emphysema, some authorities considered the mechanical impedance afforded by the airway obstruction to be of prime importance in diminishing ventilatory response to CO\text{2}, while others attributed this to an impaired CNS sensitivity to CO\text{2}. The inter-relationships of these two mechanisms were investigated and clarified by Lourenço and Miranda and Lane et al. If mechanical factors alone are important, some correlation should be demonstrable between ventilatory response and indices reflecting the impaired mechanical status of the lungs, especially those relating to the degree of airway obstruction. Unlike other studies, we were unable to demonstrate a significant relationship between CO\text{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\text{max} values achieved, the higher respiratory frequencies failing to compensate sufficiently for these lower volumes. The markedly reduced V\text{r} 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 the largest V\text{r} achieved by any of his subjects was 860 ml, and this diminished V\text{r} response in patients with airway obstruction has subsequently been noted by several groups of workers. Sorli et al have proposed that it is only patients who have a lower than normal resting V\text{r} who develop CO\text{2} retention. However no data were obtained during respiratory stimulation to obtain values of V\text{max}.

Although the degree of airway obstruction did not correlate with total ventilatory or pattern responses to CO\text{2} rebreathing, individual volumes (FEV\text{i}, FVC, IC) correlated well. This was particularly true for V\text{r} which showed the strongest correlations with absolute values FEV\text{i} and FVC. It may, therefore, be deduced that the mechanical constraints on the lungs determining V\text{r} are of a restrictive rather than an obstructive nature.

Mean V\text{max} responses at the end of maximum tolerated levels of inspired PC\text{O2} reached a volume which represented 60% of VC, a somewhat higher value than that obtained by Potter et al and similar to the results obtained by Lane. In rebreathing studies in normal subjects we have shown V\text{max} never to be greater than IC and though V\text{max} 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. This increase in static lung volume together with the increase in V\text{r} 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 recorded high resting respiratory frequencies (mean 23 breaths min$^{-1}$). Scott 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 likewise show a lower resting frequency (13-9 breath min$^{-1}$) than that found here in patients with airway obstruction (18-3 breath 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. 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...
Breathing pattern in chronic airway obstruction

the rate. In pathological intrapulmonary airway obstruction it seems that this pattern is abandoned for an apparently 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 f and Pao₂ from our data, but this negative correlation was not significant. Unlike the data presented here, Bradley et al.35 were unable to demonstrate any differences in FEV₁ between the hypoxic patients with higher respiratory frequencies and those breathing more slowly. Arterial blood gases were seen to be better (higher Pao₂, lower Paco₂) in our subjects with the largest VT 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 Vd/VT ratio associated with larger values of VT.

Our findings would suggest therefore that, although the ventilatory response to CO₂ 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 VT appears to be closely related to the restriction of dynamic lung volumes.

References

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