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 (V) and CO₂ sensitivity (S). Breathing pattern was defined by the changes in tidal volume (ΔVt) and respiratory frequency (Δf) 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 (V, S, ΔVt, Δf, Vtmax). However, measurements of dynamic lung volume (FEV₁, FVC, IC) were found to be significantly correlated with the breathing pattern variables (ΔVt, Δf, Vtmax). Resting Pao₂ and Paco₂ were significantly correlated with ΔVt 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 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. 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. Each patient gave full informed consent. The presence of airway obstruction was defined as a reduction in the absolute FEV₁ to less than 50% predicted value, and FEV₁/FVC% less than 60%. No significant reversibility of airway obstruction (<15% change in FEV₁) could be obtained by the inhalation of aerosolised isoprenaline.

After an initial rest period, subjects were allowed to rebreathe a mixture of 7% CO₂ in 93% O₂ 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 cmH₂O l⁻¹ s).

Rebreathing was continued to the limit of tolerance determined by the patient or when the inspired CO₂ 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 (Vt) and end-tidal CO₂ concentration (PetCO₂) were re-
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corded on a multichannel linear recorder (Brush, Gould Instruments). Calibration of the pneumo-
tachograph volume signal was performed before
and after each procedure using a one-litre
displacement syringe. The accuracy of the pneumo-
tachograph 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
$\text{PETCO}_2$ 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 en-
sured 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 respira-
tory 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. Con-
version of mmHg (torr) to kPa requires a multi-
plcation factor of 0·133; for cmH$_2$O 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 air-
ways resistance (Raw) were measured using a
constant volume whole body plethysmograph
(Fenyves and Gut; Basle, Switzerland). For Raw
estimation, subjects breathe warm, moist air air
fulfilling BTPS conditions. 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 ob-
struction 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 $1^{-1}$ 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 ($p<0·1$) be-
tween 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 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| $\text{Age (yrs)}$ | $\text{Height (cm)}$ | $\text{FEV}_1$ (l) | $\text{FVC}$ (l) | $\text{FEV}_1$/FVC % |
| $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ |
| 61 | 170 | 0·93 | 1·84 | 50 |
| 7 | 5 | 0·32 | 0·51 | 7 |
| $\text{Raw (kPa} 1^{-1}\text{s)}$ | $\text{Pao}_2$ (kPa) | $\text{Paco}_2$ (kPa) | $\text{initial } V_t$ (l) | $\text{Vrmax}$ (l) | $\Delta V_t$ (l) | $\text{initial breath frequency (breath min}^{-1}$) | $\text{final breath frequency (breath min}^{-1}$) | $\Delta f$ (breath min$^{-1}$) | $\text{CO}_2$ sensitivity (1 min$^{-1}$ kPa$^{-1}$) |
| $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ | $\text{Mean}$ |
| 0·65 | 9·13 | 5·65 | 0·82 | 1·27 | 0·45 | 18·3 | 27·7 | 9·4 | 6·85 |
| 0·32 | 1·53 | 0·93 | 0·15 | 0·25 | 0·21 | 3·8 | 8·5 | 8·3 | 3·15 |

Figure 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 (Vmax) CO2 sensitivity (SV/Pco2) or pattern response to CO2 (ΔVT, ΔF, Vmax).

In contrast individual volumes (FEV1, 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 CO2. Although resting Pao2 and Paco2 were found to be significantly correlated with ΔVT (p<0.05 and p<0.01 respectively) no corresponding correlation was demonstrated with Δf (table 2).

| Table 2 | Correlations of breathing pattern indices (ΔVT, Δf, Vmax) with physiological variables of the 21 patients with chronic airway obstruction |
|-----------------|-----------------|---------------|-----------------|---------------|
|                | FEV1 (l) | FVC (l) | Pao2 (kPa) | Paco2 (kPa) |
| ΔVT (0)         | r=0.80    | r=0.81    | r=0.48      | r=−0.58      |
| Δf (breaths min−1) | r=−0.37   | r=−0.45   | r=0.07      | r=0.16       |
| (NS)            | p<0.05    | (NS)      | (NS)         | (NS)         |
| Vmax (l)        | r=0.63    | r=0.69    | r=0.09      | r=0.37       |
| (NS)            | p<0.01    | p<0.001   | (NS)         | (NS)         |

Discussion

After the work of early investigators into CO2 responsiveness in chronic bronchitis and emphysema,7–8 some authorities considered the mechanical impedance afforded by the airway obstruction to be of prime importance in diminishing ventilatory response to CO2,8–10 while others attributed this to an impaired CNS sensitivity to CO2.11–14 The inter-relationships of these two mechanisms were investigated and clarified by Lourenço and Miranda15 and Lane et al.16 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,17–19 we were unable to demonstrate a significant relationship between CO2 sensitivity (S) and the pulmonary function assessment of airway obstruction.

Our studies demonstrate that the diminished ventilatory response is caused primarily by the small Vmax values achieved, the higher respiratory frequencies failing to compensate sufficiently for these lower volumes. The markedly reduced Vt 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 Scott17 the largest Vt achieved by any of his subjects was 860 ml, and this diminished Vt 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 Vt who develop CO2 retention.22 However no data were obtained during respiratory stimulation to obtain values of Vmax.

Although the degree of airway obstruction did not correlate with total ventilatory or pattern responses to CO2 rebreathing, individual volumes (FEV1, FVC, IC) correlated well. This was particularly true for Vt which showed the strongest correlations with absolute values FEV1 and FVC. It may, therefore, be deduced that the mechanical constraints on the lungs determining Vt are of a restrictive rather than an obstructive nature.

Mean Vmax responses at the end of maximum tolerated levels of inspired Pco2 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 subjects24 we have shown Vmax never to be greater than IC and though Vmax 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 Vt may result, therefore, in tidal excursions actually exceeding TLC during hyperventilation.

Increased respiratory frequency in patients with obstructive lung disease has long been recognised. Rheinhardt17 recorded high resting respiratory frequencies (mean 23 breaths min−1). Scott17 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 subjects24 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
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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, pulmonary fibrosis, and pneumothorax. 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. A similar trend was seen in the relationship of AF and Pao2 from our data, but this negative correlation was not significant. Unlike the data presented here, Bradley et al 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

18 King TKC, Yu D. Factors determining the ventilatory response to carbon dioxide in chronic


