Ventilation during steady-state exercise in patients with chronic obstructive pulmonary disease

A preliminary study

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Summary

In this preliminary study 20 patients with chronic obstructive pulmonary disease (COPD) walked on the treadmill until symptoms limited further exercise. When minute volume exceeded 60% of the predicted maximum breathing capacity the arterial carbon dioxide partial pressure was frequently low, thus indicating hyperventilation; the arterial oxygen partial pressure also declined on exercise. In only 2 patients was there alveolar hypoventilation. Although other factors may be operative, the hyperventilation in some patients with COPD may be induced by an exertional decline in alveolar oxygen partial pressure. In 4 patients the exercise tidal volume exceeded the resting inspiratory capacity, indicating a decline in functional residual capacity and increased work of breathing. It is concluded that there is a need further to assess patients with COPD in respect of the association between exertional dyspnoea, alveolar ventilation and lung mechanics.

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Of all the possible mechanisms operative in the limitation of exercise tolerance in patients with chronic obstructive pulmonary disease (COPD), ventilatory limitation has received the most attention.[1-6] It is generally accepted that ventilatory capacity is reduced in these patients because of limitation of expiratory airflow. There may also exist an increase in ventilatory demand owing to the mechanical disadvantage (increased oxygen consumption), elevated alveolar dead space, or both. These considerations have led to the conclusion that this elevated ventilatory demand/capacity ratio is directly related to the observed limitation of exercise tolerance. An exercise ventilatory demand/capacity ratio in excess of 0,6 has been clearly related to the advent of dyspnoea which, in itself, may limit exercise.[1] What is not clear from the literature[1-6] is the relationship of dyspnoea to the adequacy of alveolar ventilation (and blood gases) in these patients. Data relating exercise ventilation to arterial blood gases in this class of patient are limited.[1,7,8]

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This study was undertaken to identify the factors which limit exercise in patients with COPD, with special reference to the adequacy of the ventilatory response. Attention was given to the pattern and level of ventilation and not to the objective quantification of dyspnoea.

Patients and methods

Twenty patients with the clinical features of COPD who had been referred for assessment of exercise tolerance were investigated. All the subjects had objective evidence of fixed expiratory airflow limitation, the forced expiratory volume of the first second/forced vital capacity (FEV_1/FVC) ratio being less than the predicted value − 1,65 SD.[9] The patients, none of whom was asthmatic, were clinically stable at the time of investigation and were not in overt right or left ventricular failure. Patients were tested while on their usual maintenance aerosol bronchodilator therapy (salbutamol) taken 2 - 4 hours before the exercise test.

Voluntary signed consent was obtained from all the subjects before the exercise study after the indications for and the nature, extent, benefits and possible complications of the test and procedures had been explained to them.

After a prior non-invasive progressive exercise test to establish the exercise tolerance of each subject, the patients were studied during steady state at rest and at approximately 75% of their maximal work capacity. Exercise was in the form of walking on the treadmill. Steady state was assumed when the mixed expired carbon dioxide concentration varied by less than 0,1% over a 30-second period. Measurements were taken during steady state only, but the ECG, ventilation and oxyhaemoglobin saturation (using an ear oximeter) were monitored throughout the test.

Before the steady-state test an arterial cannula (20G intravenous catheter) was inserted percutaneously into a radial artery after adequate flow through the ipsilateral ulnar artery had been assured (Allen's test). Arterial blood samples drawn from the catheter were analysed immediately for arterial oxygen partial pressure (Pa_{O_2}), arterial carbon dioxide partial pressure (Pa_{CO_2}) and pH, using calibrated conventional electrodes (Instrument Laboratories pH/blood gas analyser, IL 613).

The patients breathed through a low-resistance, two-way, non-rebreathing valve assembly with an internal dead space of 90 ml (Hans Rudolf Valve No. 2700). Expired gas was passed through a 6-litre mixing chamber. This gas, and the respired gas at the mouth, were analysed for oxygen, carbon dioxide, nitrogen and argon using a quadruple mass spectrometer (Centronix MGA 200), which had been calibrated before the test against two gases of known composition. Minute volume and pulmonary gas exchange were measured by the inert gas dilution method described in detail by Davies and Denison.[10] Respiratory rate and the ratio of inspiratory to expiratory time

were obtained from the capnographic tracing taken at the mouth.

In view of the relatively small sample size and non-normal distribution of the data, statistical analysis was done using the Mann-Whitney *U*-test.

Results

Some patients had difficulty identifying the specific symptom which prevented their continuing exercise to a higher grade. Eleven of the subjects identified excessive dyspnoea as the dominant symptom limiting exercise. Of the remainder, 6 complained of exhaustion/tiredness and 3 of a variety of symptoms including intermittent claudication, pleuritic-type chest pain, and discomfort with the apparatus at higher grades.

In the light of the aims of this study, the subjects were divided into two groups according to the ratio of the minute ventilation ($\dot{V}_E$) to the maximal breathing capacity (MBC). The MBC was derived from the measured FEV_1, using the equation given by Jones and Campbell.[11] A $\dot{V}_E$/MBC in excess of 60%, which is uncommon in normal subjects even during maximal exercise, has been used as an index of dyspnoea, and may be associated with the onset of diaphragmatic fatigue.[1,11] In group 1 the $\dot{V}_E$/MBC was in excess of 60% ($N = 11$) while in group 2 it was less than 60% ($N = 9$). Group 1 subjects are the same 11 who complained of excessive dyspnoea as the factor limiting exercise.

In group 1 the resting expiratory airflow limitation was very much worse as gauged by the FEV_1 and the FEV_1/FVC ratio (Table I). It is also evident that there was no clear difference in the pattern of ventilation at symptom-limited exercise in respect of the tidal volume, ratio of the latter to the resting inspiratory capacity, respiratory frequency and inspiratory/expiratory time ratio. The dead space/tidal volume ratio did not differ between the two groups. It is also clear from Table I that in the dyspnoeic subjects, who also utilized more of their ventilatory reserve, there was a significant degree of hypocapnia. There was no pH difference between the two groups of patients, nor was the $\dot{V}CO_2$ different. This confirms that the $\dot{V}_E$/MBC is the independent variable and that a different level of CO_2 production could not be implicated in the ventilatory difference between the two groups. The level of work done by each group did not differ significantly, since there was no difference in the $\dot{V}O_2$ (Table I) or body surface area (BSA) values.

The hyperventilation in group 1 patients was also associated with a lower exertional PaO_2. The latter reflected a decline in the PaO_2 during exercise, while in the other group the PaO_2 remained almost constant (see Table I). In Fig. 1 the association between the exertional change in PaO_2 and the $\dot{V}_E$/MBC is clearly demonstrated: when the $\dot{V}_E$/MBC exceeded 100%, exertional arterial hypoxia was inevitable, whereas when this value was less than 50%, a decline in PaO_2 was unlikely to develop. Using the pooled data from both groups, it was possible to demonstrate a correlation between the $\dot{V}_E$/MBC at symptom-limited exercise, and the change in PaO_2 in the transition from rest to exertion:

$\dot{V}_E/MBC\ (\%) = 66{,}9 - 20{,}25\ \Delta\ PaO_2\ (kPa)$ ($r = 0{,}50$ and $P < 0{,}01$)

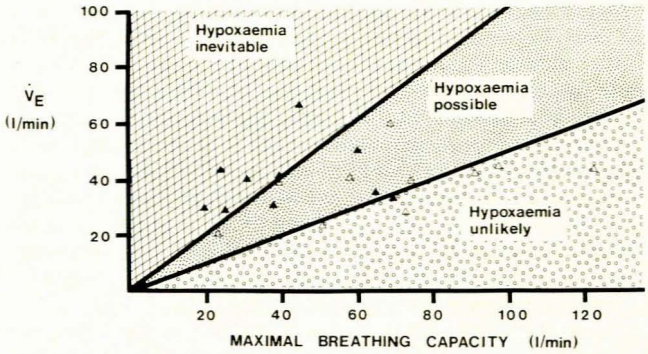

Fig. 1. When $\dot{V}_E$/MBC exceeded 100%, exertional hypoxia inevitably occurred. When the ratio was less than 50%, the Pa_{O_2} was unlikely to decline on exertion. The response of the Pa_{O_2} was variable when the $\dot{V}_E$/MBC had intermediate values (Δ = patients whose Pa_{O_2} did not decline on exercise; ▲ = patients whose Pa_{O_2} declined on exercise by at least 10% of the resting value).

TABLE I. LUNG MECHANICS, EXERCISE VENTILATION AND ARTERIAL BLOOD GAS AND ACID-BASE STATUS

	Group 1	Group 2	Sig.
No. of patients	**11**	**9**	
Age (yrs)	**57,1 ± 11,0**	**51,4 ± 5,4**	**S**
BSA (m^2)	**1,82 ± 0,16**	**1,75 ± 0,24**	**NS**
FEV_1 (litre)	**1,12 ± 0,42**	**2,24 ± 0,64**	**HS**
FEV_1/FVC (%)	**45,40 ± 13,60**	**66,20 ± 5,80**	**HS**
$\dot{V}_E$/MBC (%)	**109,70 ± 32,50**	**47,20 ± 9,70**	**HS**
$\dot{V}O_2$ (ml/min)	**923,30 ± 474,30**	**922,60 ± 282,6**	**NS**
$\dot{V}CO_2$ (ml/min)	**868,50 ± 403,50**	**912,30 ± 368,10**	**NS**
$\dot{V}_E$ (l/min)	**39,55 ± 14,3**	**36,01 ± 7,07**	**NS**
V_T (l)	**1,52 ± 0,49**	**1,50 ± 0,36**	**NS**
f_R (/min)	**27,30 ± 8,90**	**27,80 ± 6,20**	**NS**
V_D/V_T	**0,36 ± 0,13**	**0,32 ± 0,15**	**NS**
T_I/T_E	**0,86 ± 0,16**	**0,97 ± 0,09**	**NS**
V_T/IC	**0,76 ± 0,05**	**0,79 ± 0,18**	**NS**
$PaCO_2$ (kPa)	**4,38 ± 0,80**	**5,09 ± 0,69**	**S**
pH	**7,43 ± 0,05**	**7,39 ± 0,04**	**NS**
Pa_{O_2} (kPa)	**9,08 ± 1,91**	**11,20 ± 1,92**	**S**
Δ Pa_{O_2} (kPa)	**−1,36 ± 1,19**	**−0,09 ± 0,72**	**HS**

Pathophysiological profile of patients with and without exertional dyspnoea — group 1: $\dot{V}_E$/MBC > 60%; group 2: $\dot{V}_E$/MBC < 60%.
BSA = body surface area; V_T = tidal volume at symptom-limited exercise; f_R = ventilatory frequency; T_I/T_E = ratio of inspiratory to expiratory time; V_T/IC = V_T defined above as ratio of the resting inspiratory capacity (IC); $\dot{V}_E$/MBC = minute ventilation/maximal breathing capacity ratio; $\dot{V}O_2$ = oxygen consumption (ml/min); $\dot{V}CO_2$ = carbon dioxide elimination (ml/min); V_D/V_T = physiological dead space to tidal volume ratio; Δ Pa_{O_2} = change in Pa_{O_2} from rest to exercise; Sig. = statistical significance; HS = $P < 0{,}01$; S = $0{,}01 < P < 0{,}05$; NS = $P > 0{,}05$.

Discussion

That the $\dot{V}_E$/MBC on exercise in patients with COPD is frequently elevated is well established,[1] as is the fact that this ratio may exceed unity.[8] The latter indicates the inability of the MBC to reflect accurately the level of ventilation at maximal exercise. The explanation of this apparent paradox lies in the difference between ventilatory mechanics of maximal forced expiration, and submaximal expiratory effort at maximal exertion. In patients with severe airflow obstruction (and collapsing airways) submaximal effort may lead to higher flow rates than will be the case on maximal expiratory effort. Apart from the fact that on exercise patients may utilize submaximal pleural pressures and even increase their functional residual capacity (FRC), it seems reasonable to suppose that the $\dot{V}_E$/MBC may still reflect the degree of mechanical disadvantage and the use of ventilatory reserve during exercise. This index has also been used in the assessment of exertional dyspnoea,[1] and our finding of dyspnoea in all subjects in group 1 confirms the value of this index.

The greater severity of disease in the patients of group 1 may reflect their more advanced age and longer duration of illness. It was a surprising finding of this study that these

patients with the worst resting pulmonary mechanics and who encroached more on their ventilatory reserve on exercise (a high demand/capacity ratio) exhibited a degree of hyperventilation. This finding indicates that a significant part of their ventilatory response was inappropriately elevated relative to the CO_2 production. A partial explanation for this finding may reside in the significant correlation between the $\dot{V}_E$/MBC and the change in Pa_{O_2}. The peripheral chemoreceptors may partially be responsible for the hyperventilation because of their sensitivity to acute changes in the Pa_{O_2} on exercise. That lung and/or chest wall mechanoreceptors may be involved in this augmented drive is possible but difficult to separate from other factors, let alone quantitate, in the context of the present study. This finding of exertional hyperventilation is to be compared with that of Raffestin *et al.*;[12] a number of their patients with severe dysfunction exhibited an exertional increase in Pa_{CO_2}. In only 2 patients in this study (1 from each group) was this phenomenon observed. This difference may possibly be ascribed to a greater degree of airflow limitation in the patients in the study of Raffestin *et al.*[12]

The FRC has been reported to increase on exercise[6] and this may also be operative in the genesis of dyspnoea because of its effect on ventilatory muscle and chest wall mechanics. It is of interest that in this study there were 4 subjects in whom the V_T/IC exceeded unity, and this can only be explained by a decrease in the FRC from rest to exercise. Such a decline in FRC would be accompanied not only by increased ventilatory work in deforming the chest wall, but also by a higher airway resistance. The reduced FRC may, however, be of benefit in respect of diaphragm function in COPD patients with resting lung hyperinflation. Change in FRC need not necessarily be accompanied by an altered tidal volume/inspiratory capacity and the FRC may therefore well have changed in other patients. Further analysis was not possible in this study, but this decline in FRC, which has not been reported previously,[1,11] certainly requires investigation in future studies.

Since the relationship of the $\dot{V}_E$/MBC to the Pa_{O_2} was appreciated retrospectively, the effect of ambulant O_2 therapy was not systematically investigated. It may well be that such treatment, apart from its primary effect on arterial oxygenation, may have the secondary effect of reducing the ventilatory response of those hypoxic subjects in whom the ventilation was excessive. This is one possible mechanism by which ambulant O_2 therapy could bring about the documented improvement in exercise tolerance.[1]

Conclusion

Exertional dyspnoea in patients with COPD was an important factor limiting exercise but was accompanied by a variable and unpredictable level of alveolar ventilation as gauged by Pa_{CO_2}. In the majority of patients in this study who developed exertional arterial hypoxia on exercise there was an accompanying hyperventilation in spite of $\dot{V}_E$/MBC values which indicate gross ventilatory mechanical disadvantage. It is clear from these preliminary findings that there is a need to distinguish between the symptoms of exertional dyspnoea and actual hypo- or hyperventilation observed during exercise.

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Nuus en Kommentaar/News and Comment

The tubercle bacillus is alive and well in the USA

We are only too well aware of the menace of tuberculosis in this country and nobody can afford to be complacent about the situation. But it is a little surprising to hear about the misplaced complacency in the USA. Many doctors there apparently regard tuberculosis as a rare disease only of historical interest. Nevertheless, nearly 25 000 cases were reported in 1983 and the number has been declining only slowly. Incidentally, the decline antedates modern drug therapy and control measures by decades, which makes one think.

Conventional wisdom is that in a developed country such as the USA the only cases of pulmonary tuberculosis are likely to be found in the elderly and epidemic spread from them is unlikely. However, as often happens, conventional wisdom has been shaken by a study of nearly all the nursing-home (a euphemism for old-age home) residents in Arkansas by Stead *et al.* (*N Engl J Med* 1985; **312:** 1483).

They skin-tested the 31 421 residents of 223 homes with tuberculin and took radiographs of all those with positive tests. Among those tested within 1 month of admission to a home only 12% were tuberculin-positive, but when residents of longer standing (average 30 months) were tested the rate rose to 20,8%. Moreover, the infection rate rose with every year of stay in the home. Hence these people were becoming infected in the home, and old-age homes in Arkansas and probably elsewhere may represent a fertile source of tuberculosis and of its transmission.