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Relationship between ventilation and breathlessness during exercise in chronic obstructive airways disease is not altered by prevention of hypoxaemia

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Summary

1. We have examined the hypothesis that hypoxaemia contributes to breathlessness by a mechanism distinct from its action as a ventilatory stimulant.

2. Five patients who developed arterial oxygen desaturation during incremental exercise were studied. Exercise tests were performed on a cycle-ergometer. Breathlessness was measured by using a visual analogue scale technique. All five patients had considerable previous experience of these procedures.

3. Two identical exercise tests were performed by each patient, breathing either room air or 60% oxygen in a blind randomized study.

4. Breathing air, arterial saturation at rest was 93% and fell by 7% during exercise. Breathing 60% oxygen, resting saturation was 98% and there was no fall during exercise.

5. Breathing oxygen, ventilation for a given work load was reduced and exercise duration was increased when compared with air breathing.

6. In each of the five patients the relationship between breathlessness and minute ventilation was the same whether breathing air or 60% oxygen, despite the reduction in ventilation for a given work rate.

Key words: airways obstruction, dyspnoea, hypoxaemia, ventilation.

Introduction

Breathlessness is a frequent symptom of cardiopulmonary disease and the mechanisms responsible for its appreciation are incompletely understood and probably multifactorial [1]. The relationship between ventilation and breathlessness, measured with the visual analogue scale technique [2], shows wide inter-subject variation. Within a given subject, however, the relationship is reproducible on repeated testing and, in asthmatic patients, it has been shown to change with bronchodilatation [3]. Hypoxaemia is a powerful ventilatory stimulus in health and disease. There has been a recent suggestion that it may also have a 'dyspnogenic' effect that alters the perception of breathlessness. This concept, that hypoxaemia may cause more breathlessness than is appropriate to the degree of ventilation, was based on the observation that, during heavy exercise in normal subjects, the induction of hypoxaemia by inhalation of 15% oxygen caused an increase in perceived breathlessness that preceded the ventilatory response [4].

This study was designed specifically to investigate whether hypoxia, in addition to its known action as a ventilatory stimulant, also changed the relationship between perceived breathlessness and ventilation in patients with chronic obstructive airways disease who were known to develop arterial desaturation during exercise.

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Methods

Patients

Two male and three female patients, mean age 65 years (range 53–72), were studied. Spirometry and resting arterial oxygen saturation are shown in Table 1. All had advanced obstructive airways disease but were in a stable clinical state. They had all previously performed at least eight cycle-ergometer exercise tests as part of an earlier study

TABLE 1. *Measurements made during exercise while breathing room air and 60% oxygen, and spirometry performed on room air before each test*

Results are means ± SD. Comparisons between air and oxygen breathing were made by using Student's *t*-test for paired data. NS, Not significant.

	Air	60% O_2	Paired *t*-test
FEV_1 (l)	0.8 ± 0.2	0.8 ± 0.1	NS
FVC (l)	1.8 ± 0.4	1.9 ± 0.4	NS
Resting SaO_2 (%)	93.2 ± 0.8 (range 92–94)	97.6 ± 0.5 (range 97–98)	
Fall in SaO_2 on exercise (%)	7.0 ± 1.9 (range 5–10)	Zero Zero	
Maximum ventilation reached on exercise (l/min)	25.9 ± 5.9	25.6 ± 6.6	NS
Duration of exercise (s)	364 ± 73	444 ± 105	$P < 0.02$

and had each demonstrated good reproducibility in the relationship between their subjective estimate of breathlessness and their measured ventilation.

Protocol

The patients performed two identical cycle-ergometer exercise tests, separated by a 3 h interval. They were randomized to perform the first exercise test breathing either 60% oxygen (three patients) or room air (two patients); the inspired gas mixtures were then reversed for the second test. Salbutamol (200 μg) was administered by metered-dose inhalation 1 h before each test. FEV_1 and FVC were recorded breathing air immediately before each exercise test.

Once positioned on the cycle-ergometer, the patients inspired from one of a pair of large Douglas bags, one of which contained 60% oxygen and the other air. Neither gas was humidified. A tap enabled the patient to be connected to the appropriate gas mixture. The Douglas bags were continuously trickle-fed with the appropriate gas mixture to prevent depletion during exercise.

The patients were informed that the purpose of the study was to investigate the effects of different gas mixtures on exercise performance. No specific effects were mentioned. Written informed consent was obtained from each patient. Two physicians and a technician were present. One of the physicians was blind to the gas mixture being used and to the ear oximeter reading. This physician had supervised all the patients' previous exercise tests and was responsible for encouraging the patients to reach their maximum performance. All the patients stated that exercise was limited by breathlessness.

Exercise tests

The incremental exercise protocol in this study was identical with that with which the patients were familiar. The tests were performed on an electrically braked cycle-ergometer (Lanooy). Heart rate was recorded on an ECG and arterial oxygen saturation was measured with an ear oximeter (Hewlett Packard type 47201 A). A nose-clip was worn and expired gas was collected via a mouthpiece and 115 ml dead space two-way valve (Hans Rudolf type 2700). Ventilation was measured every 20 s with a computerized system that incorporated a rolling-seal spirometer and dynamic mixing of the expired gas (Gould 9000 IV Exercise Laboratory). The resistance of the system was 1.5 cm water l/s at 12 litres/s. It was not technically possible to measure oxygen uptake during oxygen breathing.

Breathlessness was measured by using the visual analogue scale technique. A sliding scale potentiometer was attached to the ergometer handlebar. The ends of the slider scale on the potentiometer were labelled 'minimum' and 'maximum'. Minimum breathlessness was explained to the patient as 'not at all breathless' and maximum breathlessness 'as breathless as you can imagine'. Movement of the potentiometer slide control from base position ('minimum') caused a proportional illumination of a row of 30 light-emitting diodes, length 10 cm, situated in front of the patient. This thermometer-type display was used for ease of viewing by rather elderly patients. The visual analogue score (VAS) expressed as a percentage of the maximum possible score was read from a digital display that was not visible to the patient. The slide control was then returned to base

position (no diodes illuminated) by the supervising physician.

The exercise period was preceded by a 4 min rest period on the mouthpiece. The ergometer was set running by an investigator so that the patients did not have to overcome the inertia of the machine. The work rate was increased by 10 W every minute, starting at a setting of 10 W. Patients were instructed to maintain a pedal frequency of 50–60 rev./min and to continue pedalling until they indicated their desire to stop. Readings of breathlessness score were made at the end of each complete minute of exercise, and immediately before cessation of exercise.

Analysis of ventilatory response to exercise

In each patient the relationship between ventilation and work rate was compared over the duration of exercise common to both air and oxygen breathing tests. This comparison was made by using analyses of variance and covariance, employing a generalized linear modelling technique (GLIM 3.11, Royal Statistical Society, London). Statistical significance was accepted at the 5% level.

Calibration of ear oximeter

Calibration was performed in other patients by simultaneous measurements of saturation measured at the ear lobe and of arterial blood saturation measured with an OSM 2 Hemoximeter (Radiometer).

Results

Calibration of ear oximeter

Calibration was performed over a range of haemoglobin oxygen saturation of 80–100%. The slope of the relationship between the ear lobe measurements and arterial blood measurements of saturation was 0.97 ($r = 0.98, P < 0.001$). The ear oximeter measure was on average 1.0 ± 0.8 (SD)% saturation lower than the arterial blood measurement.

Exercise response on air and oxygen

The results are summarized in Table 1. Resting arterial saturation breathing air was 93.2% and fell by 7% during exercise. Breathing 60% oxygen, resting saturation was 97.6% and there was no fall during exercise. Exercise duration increased while breathing oxygen by an average of 80 s, equivalent to $1\frac{1}{3}$ work loads. Although the duration of exercise was increased by oxygen breathing, the peak ventilation reached at the end of exercise was the same whether breathing air or oxygen [mean difference $= 0.2 \pm 1.1$ (SD) l/min].

In all five patients at any given work rate, ventilation while breathing air was higher than

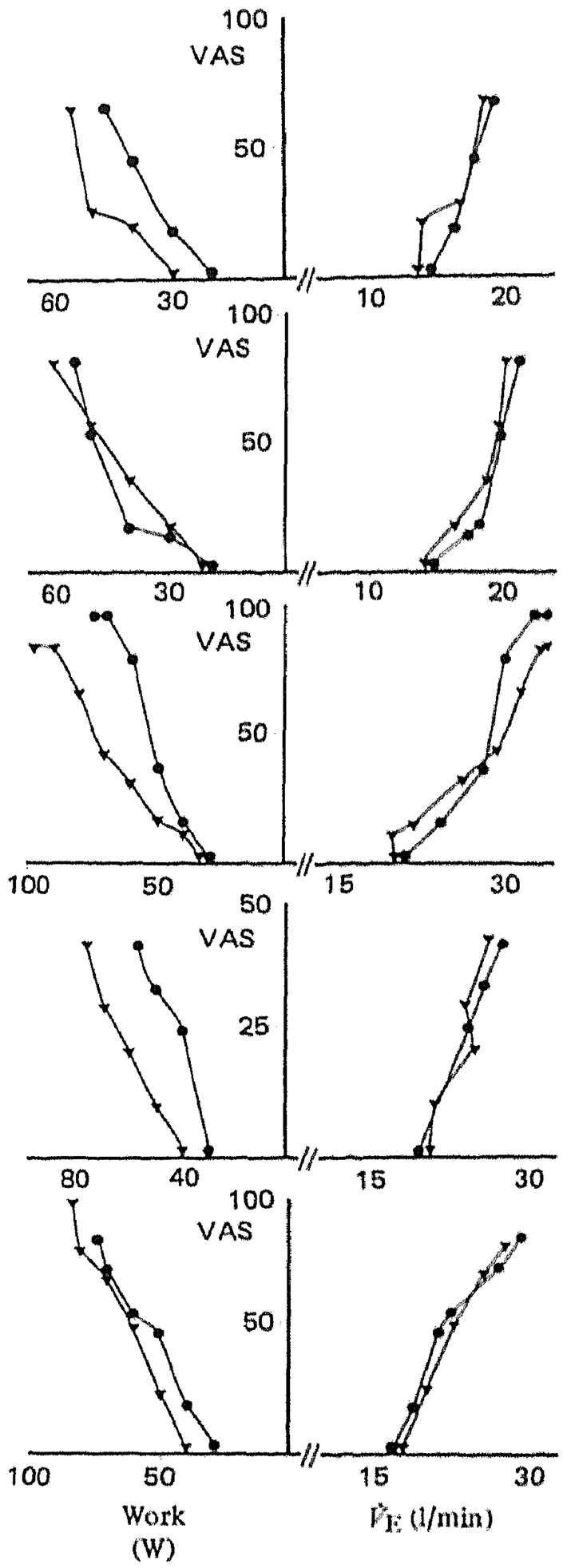

FIG. 1. Relationship between breathlessness measured as visual analogue score (VAS) and work rate (W) (left-hand panels), and VAS and minute ventilation ($\dot{V}_E$) (right-hand panels) in five patients breathing air (●) and 60% oxygen (▼). The patients are numbers 1 to 5 from top to bottom of the Figure.

while breathing 60% oxygen [mean difference 7.9 ± 5.8 (SD)%]. In three patients (patients 1, 3 and 4; Fig. 1) this difference reached statistical significance.

Relationship between breathlessness and ventilation

The prevention of hypoxaemia did not alter the relationship between breathlessness and ventilation. The right-hand panel of Fig. 1 displays the plots of this relationship from all five patients. In each patient the air and oxygen breathing plots were almost superimposed on each other. At peak ventilation when hypoxaemia was greatest during air breathing, the VAS score breathing oxygen was lower in two patients and higher in three patients than when breathing air.

Relationship between breathlessness and work rate

In contrast to the constancy of the breathlessness-ventilation relationship, oxygen breathing reduced breathlessness relative to work rate in three patients (patients 1, 3 and 4; Fig. 1), with little or no change in the other two patients.

Patients' subjective impressions

At the end of the second test, the patients were asked "how was that compared with the first test?". Four were unaware of any difference, and one felt that the air breathing test was easier.

Discussion

In this study the relationship between ventilation and perceived breathlessness during exercise was the same whether or not hypoxaemia was present. This does not support the hypothesis that hypoxaemia contributes to breathlessness by a mechanism distinct from its effect as a ventilatory stimulant. The pathway for the ventilatory response to hypoxaemia involves the carotid chemoreceptors and brain stem nuclei, and reflex responses to hypoxaemia occur in decerebrate animals. Breathlessness on the other hand is a perception that must involve cerebral cortical activity. Hypoxia could act to alter this perception at a number of sites, and there is no *a priori* reason why the classical chemoreflex pathways should be involved. Furthermore the original observation that 'dyspnogenic' and stimulatory effects of hypoxia could be separated [4] may suggest different sites of action. In three patients (1, 3 and 4) in the current study, ventilation at a given work rate was significantly lower when breathing oxygen, indicating that their hypoxic drive to breathe was preserved, but even in these patients there were no consistent changes in the breathlessness–ventilation relationship. These patients did, however, show a clear change in the breathlessness–work rate relationship, suggesting that they were using the visual analogue scale to indicate breathlessness rather than perceived muscular exertion.

Our results are at variance with those of Adams *et al.*, but the experiments were very different in design. In our study, the changes in ventilation and breathlessness were sustained over a whole exercise test whereas in the study of Adams *et al.*, breathlessness was perceived to have changed in the brief period between the change to a hypoxic gas mixture and the ensuing ventilatory response. There were a number of other differences. In the patients, hypoxaemia developed progressively, whereas the switch to breathing a hypoxic gas mixture would have presented a more rapid change in arterial saturation. The exercise tests were also different in that Adams' subjects were exercising at a constant high level of work above their 'anaerobic threshold'. It is also possible that daily exposure to hypoxaemia in patients with advanced lung disease may have modified their perception of breathlessness.

We have no measurements of arterial or end-tidal CO_2 levels during these studies. It is probable that these would have risen during oxygen breathing in those patients in whom ventilation was reduced. However, as the reduction in ventilation was on average less than 8%, any changes in alveolar CO_2 would have been correspondingly small. In a recent study, Adams *et al.* were unable to find any evidence for a 'dyspnogenic' action of CO_2 distinct from its effects on ventilation [5], and it is therefore unlikely that the small changes in arterial CO_2 which may have occurred in this study would have influenced the results.

In summary, this study further illustrates the importance of measuring ventilation when assessing the effects of treatment on breathlessness. It provides no evidence for the hypothesis that the arterial hypoxaemia of severe pulmonary disease contributes to breathlessness, other than by hypoxic stimulation of ventilation.

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