

THE EFFECTS OF HYPOXIA AND HYPERCAPNIA ON PERCEIVED BREATHLESSNESS DURING EXERCISE IN HUMANS

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SUMMARY

1. The sensation of breathlessness increases when ventilation is reflexly stimulated but it is not clear whether different stimuli have specific effects in the genesis of this sensation.

2. Our aim was to compare subjective assessments of the intensity of breathlessness at the same levels of ventilation induced by different combinations of reflex ventilatory stimuli.

3. Against a background of progressive exercise (maximum workload 170 W) in 'blinded' normal naive subjects, normoxic hypercapnia (maximum end-tidal CO₂, P_{ET,CO_2} , 56 mmHg) or isocapnic hypoxia (minimum O₂ saturation 88%) was induced to achieve levels of ventilation (maximum 60 l min⁻¹) 'matched' with those resulting from a higher intensity of exercise alone. Subjective breathlessness was rated with a visual analogue scale.

4. For a given ventilation, compared with exercise alone, breathlessness scores were similar during hypercapnia and were lower during hypoxia.

5. These results do not support the idea that during exercise, hypercapnia or hypoxia has a specific role in the genesis of the sensation of breathlessness.

6. The findings are consistent with the hypothesis that the degree of reflex ventilatory activation, however achieved, is an important determinant of the intensity of perceived breathlessness in healthy humans.

INTRODUCTION

The neurophysiological basis of the common sensation of breathlessness is poorly understood. A number of studies have shown that in normal subjects exercise of increasing intensity induces ratings of perceived breathlessness which increase relatively linearly with the level of minute ventilation (Stark, Gambles & Lewis, 1981; Adams, Chronos, Lane & Guz, 1985*a*; Wilson & Jones, 1989*a*). However, recent studies have led to the proposal that the sensation of breathlessness may not derive from a perception of increased mechanoreceptive afferent activity from the respiratory apparatus but is a reflection of the degree of reflex stimulation of ventilation (Adams, Lane, Shea, Cockcroft & Guz, 1985*b*; Banzett, Lansing, Reid, Adams & Brown, 1989). Thus, an important question in elucidating the neural

mechanisms of this sensation is whether different reflex ventilatory stimuli elicit different intensities of perceived breathlessness for the same degree of ventilatory stimulation.

Early studies indicated that, with respect to ventilation, breathlessness was perceived earlier, and developed more rapidly, during progressive hypoxia or progressive hypercapnia at rest, than during progressively more intense exercise (Stark *et al.* 1981; Adams *et al.* 1985*a*). One interpretation of this is that chemical stimuli could indeed have a specific effect on the level of breathlessness. However, another possibility is that the different experimental conditions during exercise compared with those during hypercapnic and hypoxic rebreathing tests at rest could account for some of the differences in subjective responses at equivalent levels of ventilation.

The aim of the current study was to examine the effects on exercise-induced breathlessness of hypercapnia or hypoxia employing the methodology previously used in similar studies from this laboratory (Lane, Cockcroft & Guz, 1987). We wished to compare subjective ratings of breathlessness at the same levels of ventilation achieved with either hypoxia and exercise or hypercapnia and exercise, with those obtained during exercise alone. By employing a similar exercise protocol in all experimental conditions we hoped to examine the subjective effects of the interaction of these stimuli without the subject being aware from the experimental protocol of the different ventilatory stimuli.

This study has previously been presented in preliminary form (Adams & Lane, 1989).

METHODS

These studies were undertaken with the approval of the Ethical Committee of Charing Cross Hospital.

Subjects

Eighteen normal subjects (nine female) aged 20–35 years were studied. All had forced vital capacities (FVC) and forced expired volumes in 1 s ($FEV_{1.0}$) within their predicted normal range: two were smokers. None had taken part in previous studies of this kind and none was aware of the experimental design or the exact reason for the tests. Subjects were told that the tests were designed to investigate the effect of different gas mixtures on the sensation of breathlessness. They were told that all tests would be of identical format and that they would not be made aware of the changes in inspired gas concentrations. Subjects were aware that during certain tests they could be given hypoxic gas mixtures to breathe and had given informed consent prior to the study.

Preliminary protocol

During an initial test run subjects were familiarized with the experimental arrangement and in the use of the visual analogue scale (VAS) for breathlessness (Adams *et al.* 1985*a*). This required subjects, on request, to position a light on a 100 mm linear visual display relative to the two extremes which were labelled 'not at all breathless' and 'extremely breathless'; breathlessness was defined as 'an uncomfortable need to breathe'. Each subject then performed a second bicycle exercise test breathing air. After a 4 min period of cycling at 5 W, workload was increased at 1 min intervals by 20 W (females) and 25 W (males) to 'exhaustion'. Further familiarization with the scaling of breathlessness was attained in this test.

Study protocol

Four bicycle ergometer exercise tests were performed on each subject at the same time on separate days, within 1 week. Each test consisted of a 4 min 'run in' period (5 W), breathing air.

This was followed by an 8 min 'test period', during which the levels of workload and inspired CO_2 and O_2 could be altered by the experimenter at 15 s intervals in order to produce matched patterns of ventilation between tests. Changes in inspired gas concentrations were achieved by mixing CO_2 and/or N_2 into the room air flowing past the mouth. The study protocol is given below and is shown schematically in Fig. 1.

Test A: high workload

On the basis of the preliminary test to exhaustion, a pattern of workload was selected, for each subject, such that eight equal 1 min increments of workload would result in the subject reaching 90% of the heart rate attained in the maximal test. The size of increment ranged from 15 to 30 W dependent upon the sex and fitness of the subject. Air was inspired throughout the test.

Test B: lower workload

Each subject performed a 1 min incremental exercise test with increments of workload approximately 70% (range 67.7–75.0%) of those of test A. Air was inspired throughout.

Test C: lower workload with hypercapnia

This was a repeat of the workload protocol of test B, but the experimenter added CO_2 to the inspire, as necessary, in order to increase the level of ventilation to reproduce that of test A.

Test D: lower workload with hypoxia

The level of inspired O_2 was set at 15% for the duration of the test period. The experimenter adjusted the rate of increase in workload in order to match ventilation to that of test A. Additionally, CO_2 was titrated into the inspire, as necessary, to maintain end-tidal P_{CO_2} ($P_{\text{ET},\text{CO}_2}$) at isocapnic levels throughout.

The order of tests B, C and D was randomized between subjects, but was 'balanced' for the group overall.

At the end of each test subjects were asked to comment upon that test, and to compare their impressions with those of previous tests. They were specifically asked to describe their level of breathlessness and its quality, and how it changed, during the test. They were also asked to comment on how hard they found the level of work and how that compared to other tests.

Measurements

The experimental arrangement is shown in Fig. 2. Inspiratory and expiratory airflow was measured with a Fleisch No. 3 pneumotachograph (Validyne, MP45/CD12, USA) connected to a mouthpiece (total dead space = 150 ml); from this, the following variables were calculated: inspired minute ventilation (\dot{V}_I), respiratory frequency (f_R), inspiratory time (T_I), expiratory time (T_E) and tidal volume (V_T). Inspired and expired CO_2 and O_2 gas concentrations were measured by mass spectrometry (Centronics, MGA200, UK); from this $P_{\text{ET},\text{CO}_2}$ was measured and corrected to give an estimate of arterial P_{CO_2} (Jones, Robertson & Kane, 1979). Heart rate was derived from an ECG and arterial oxygen saturation (S_{a,O_2}) estimated using an ear oximeter (Ohmeda, Biox 3700, UK). All these variables were analysed breath by breath using an on-line computerized analysis system (Buxco Inc., Respiratory Gas Analyser, USA). Breathlessness was assessed every 30 s using the visual analogue scale.

Analysis

Comparisons of respiratory variables and breathlessness between tests

All analyses were performed upon the 8 min 'test period' for tests A, B, C and D. For each subject, mean levels of \dot{V}_I , V_T , T_I , T_E , f_R , $P_{\text{ET},\text{CO}_2}$ and S_{a,O_2} were calculated from breath-by-breath data over the final 15 s of each 30 s period. These measurements were considered to be representative of the period described by the discrete VAS assessments of breathlessness which were made during the last 5 s of each 30 s period.

Group mean levels of each variable were compared between tests using a repeated-measures two-way analysis of variance as follows: test type (factor 1; four levels) and time (factor 2; sixteen levels). The statistical significance of differences between any two mean levels between runs were

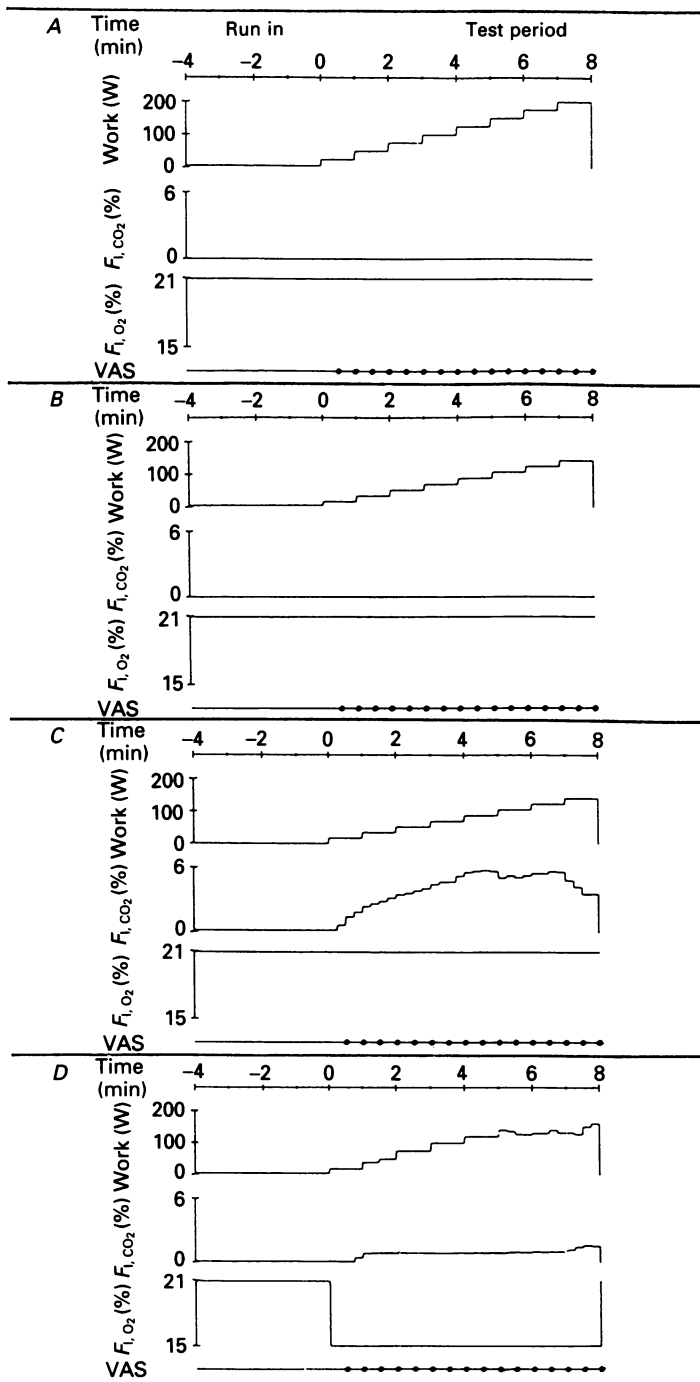


Fig. 1. Schematic representation of the four experimental protocols, showing workload (work) in watts (W), inspired percentage concentrations of CO_2 (F_{I,CO_2}) and O_2 (F_{I,O_2}) and timing of requests for assessments of breathlessness (VAS). *A*, high workload; *B*, lower workload; *C*, lower workload with hypercapnia; and *D*, lower workload with hypoxia.

tested for using Fisher's least significant difference statistic (LSD). A value of $P < 0.05$ was taken as indicating that conventional statistical significance had been attained.

Adequacy of matching of ventilation between tests

To test for the adequacy of the matching of ventilation between tests A, C and D, two analyses were performed. Firstly, for each subject, a linear regression analysis was performed between levels

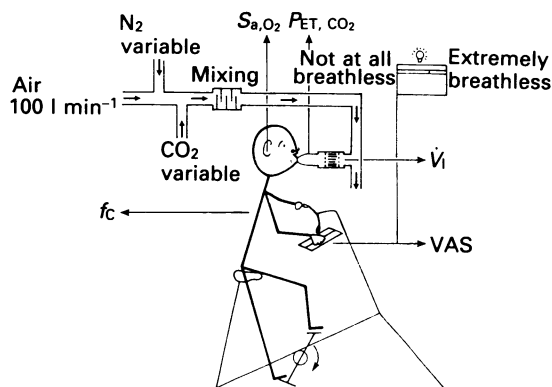


Fig. 2. Schematic representation of the experimental arrangement. The subject exercises on a cycle ergometer and breathes via a mouthpiece from a flow-past system. Respiratory airflow is measured at the mouth by a single pneumotachograph. Recordings are made of heart rate (f_c) from an ECG, arterial oxygen saturation (S_{a,O_2}) from an ear oximeter and end-tidal P_{CO_2} (P_{ET,CO_2}) from a mass spectrometer sampling from the mouthpiece. Inspiratory airflow is integrated 'on line' to give minute ventilation (\dot{V}_I) enabling the experimenter to adjust the levels of inspired CO_2 and O_2 (by controlling the flow rates of CO_2 and N_2 into the inspirate) in order to match \dot{V}_I between experiments.

of \dot{V}_I , measured over each 15 s, between tests A and C, and tests A and D. This analysis produced the slope (a), the 'y'-intercept (b) and the correlation coefficient (r). Individual r values were z-transformed to allow the mean r for the group to be calculated. Secondly, an analysis of differences in \dot{V}_I (every 15 s) between the same pairs of tests gave values of mean differences in \dot{V}_I both for individual subjects, and for the group as a whole (Bland & Altman, 1986).

Indices of chemosensitivity

Individual subjects' ventilatory sensitivities to hypoxia or hypercapnia were not measured directly during this study. However, indirect indices of sensitivity were derived (see below) to allow a rank order of individuals' chemosensitivities to be established.

Hypoxic sensitivity. The main component of the index of an individual's hypoxic sensitivity was calculated from the difference of the sums of the workload (taken every 15 s) between tests A and D ($W(A-D)$). This is justified if the levels of ventilation are matched between these tests, and the level of hypoxia during test D is relatively constant (constant inspired O_2 concentration, F_{I,O_2}). To allow for any imprecision in matching ventilation, a second component, calculated as the difference of the sums in workload which would have accounted for any differences in ventilation between the tests ($W(\Delta\dot{V}_I)$), was subtracted from this; this term is equivalent to the ventilatory sensitivity to exercise and was derived from the differences in the sums of workload and ventilation between the 'exercise-alone' tests (A and B). For the whole index, a value of zero would indicate no hypoxic sensitivity since this would imply the same workload was required to achieve a matched ventilation even in the presence of hypoxia; higher values reflect increasing hypoxic sensitivity.

Hypercapnic sensitivity. An index of an individual's hypercapnic sensitivity was calculated from two factors. Firstly, from the difference of the sums of the P_{ET,CO_2} (taken every 15 s) between tests A and C; secondly, from the difference in the sums of ventilation between tests C and B (taken

every 15 s; test B has the same workload protocol as the hypercapnic test C). Thus the index reflects the amount of CO_2 needed to match ventilations taking into account the reduced ventilation which would have occurred with the lower level of exercise had CO_2 not been given: a lower value for this index implies a higher ventilatory sensitivity to CO_2 .

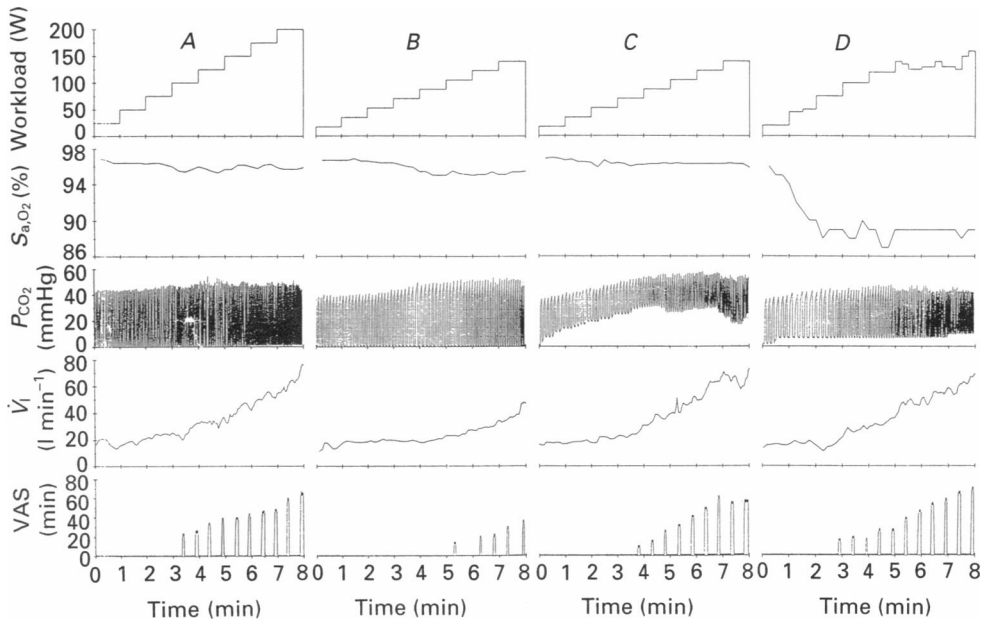


Fig. 3. 'Actual recordings' from one subject (No. 7) for the four exercise tests. *A*, test A, high workload. *B*, test B, lower workload. *C*, test C, lower workload with hypercapnia. *D*, test D, lower workload with hypoxia. This shows the workload in watts (W), arterial oxygen saturation (S_{a,O_2}) averaged over 15 s, P_{CO_2} measured continuously at the mouth, breath-by-breath ventilation (\dot{V}_I) and visual analogue scale (VAS) breathlessness scores taken every 30 s.

Indices of overall breathlessness

Two indices of an individual's overall breathlessness were calculated as the differences of the sums of VAS scores (taken every 30 s) between tests D (hypoxia) and A (exercise alone) (i.e. A–D), and tests C (hypercapnia) and A (i.e. A–C). A value of zero indicates no difference in breathlessness response; values less or greater than zero indicate respectively increased or decreased breathlessness during chemical stimulation compared with exercise alone.

Relationship between overall breathlessness and chemosensitivity indices

Spearman's rank correlation coefficient (r_s) was used to test for any statistically significant relationship between the indices for overall breathlessness, and those for hypoxic and hypercapnic sensitivity.

RESULTS

Subjects' comments

None of the subjects volunteered any information which suggested that they were aware of the exact format of any test. Compared to the first high-workload test (A), subjects described additional non-respiratory sensations during both hypercapnia (light-headed, five subjects; flushing, three subjects; headache, one subject) and hypoxia (feeling hot, three subjects).

Compared to the first high-workload test (A), sixteen subjects correctly identified that exercise was easier during the lower-workload protocol and one thought it was harder. For hypercapnia, five subjects thought the workload was less than in A, three felt it was the same and three felt it was more. For hypoxia, seven subjects thought the workload was less than in A, five felt it was the same and four thought it was more. In each comparison, the remainder of the subjects did not know which test was harder.

TABLE 1. Regression/correlation analysis between the levels of ventilation in the hypercapnic and hypoxic tests (y) each compared with the 'matched ventilation' exercise test (x) in individual subjects

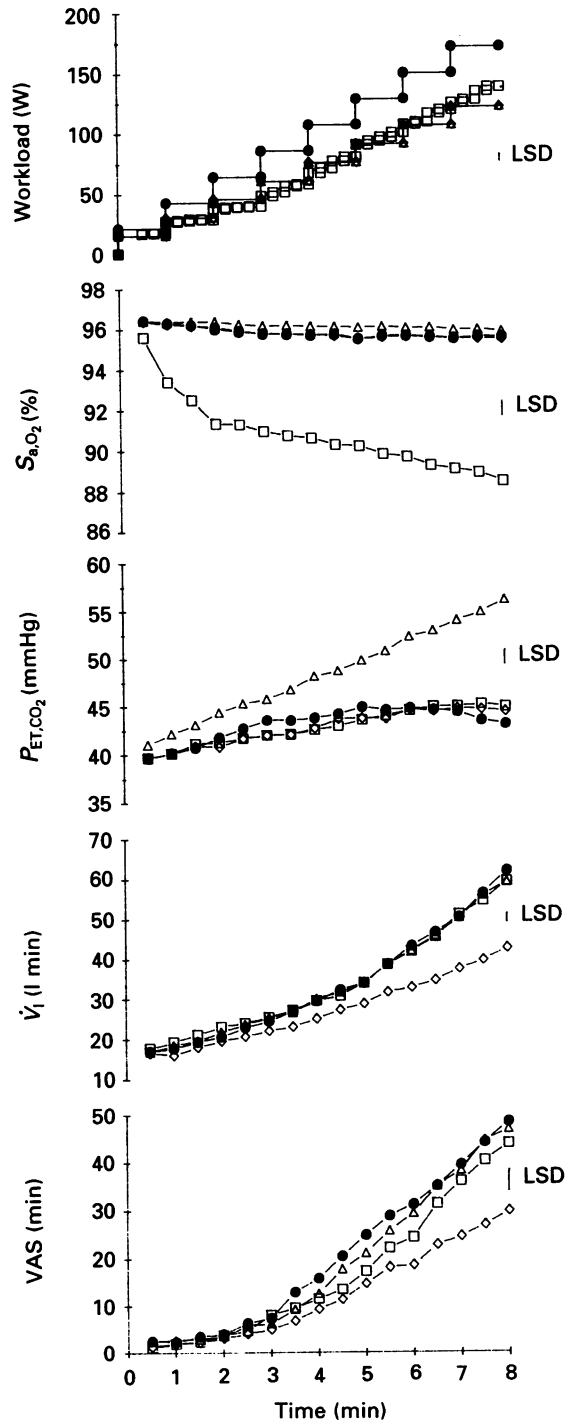
| Subject | Hypercapnia | | | | Hypoxia | | | |
|---------|-------------|-------------------------------|------|---|---------|-------------------------------|------|---|
| | a | b (l min ⁻¹) | r | $\Delta\dot{V}_1$ (l min ⁻¹) | a | b (l min ⁻¹) | r | $\Delta\dot{V}_1$ (l min ⁻¹) |
| 1 | 1.00 | -0.65 | 0.98 | 0.55 | 0.89 | 5.01 | 0.98 | -0.79 |
| 2 | 1.01 | -0.03 | 0.94 | -0.10 | 1.01 | -0.11 | 0.94 | -0.24 |
| 3 | 0.84 | 4.39 | 0.97 | 1.29 | 0.89 | 4.66 | 0.98 | -0.81 |
| 4 | 0.97 | 2.32 | 0.96 | -1.48 | 0.77 | 6.59 | 0.94 | -0.35 |
| 5 | 0.82 | 4.35 | 0.95 | 2.24 | 0.90 | 0.40 | 0.97 | 3.33 |
| 6 | 1.02 | -0.95 | 0.97 | 0.38 | 1.08 | -2.58 | 0.97 | 0.03 |
| 7 | 1.17 | -8.16 | 0.96 | 1.77 | 1.09 | -5.53 | 0.98 | 2.08 |
| 8 | 0.90 | 3.68 | 0.91 | -1.20 | 1.01 | 1.21 | 0.91 | -1.38 |
| 9 | 0.71 | 9.43 | 0.99 | -0.14 | 0.81 | 7.95 | 0.97 | -2.00 |
| 10 | 1.12 | -5.10 | 0.97 | 0.12 | 0.78 | 7.81 | 0.94 | 1.82 |
| 11 | 1.09 | -1.71 | 0.95 | -0.66 | 0.85 | 6.11 | 0.95 | -2.02 |
| 12 | 0.94 | 3.38 | 0.97 | -1.44 | 0.72 | 10.52 | 0.89 | -1.58 |
| 13 | 1.14 | -6.12 | 0.96 | 1.49 | 1.08 | -1.86 | 0.98 | -0.77 |
| 14 | 0.75 | 7.93 | 0.97 | 0.83 | 0.88 | 3.27 | 0.97 | 1.02 |
| 15 | 0.87 | 5.02 | 0.98 | 0.04 | 0.94 | 3.26 | 0.96 | -0.88 |
| 16 | 0.96 | 1.90 | 0.99 | -0.51 | 0.97 | 0.85 | 0.98 | 0.27 |
| 17 | 0.93 | 1.24 | 0.98 | 0.90 | 0.92 | 2.17 | 0.97 | 0.50 |
| 18 | 0.85 | 10.29 | 0.96 | -5.06 | 0.78 | 11.47 | 0.95 | -4.15 |
| Mean | 0.95 | 1.73 | 0.97 | -0.05 | 0.91 | 3.40 | 0.96 | -0.33 |

a = slope; b = 'y-intercept'; r = Pearson's correlation coefficient. The mean difference in ventilation between these pairs of tests ($\Delta\dot{V}_1$) is also shown.

All subjects were confident that they had correctly used the visual analogue scale to report their intensity of breathlessness. The pattern of VAS responses within a test was always consistent with subjects' post-test descriptions of their breathlessness during the test. During hypercapnia a few subjects identified different qualities of respiratory sensation compared to exercise alone; these were: 'fighting for air', 'like nothing there to breathe', 'couldn't get enough air in' and 'felt like chest would burst'. For hypoxia, comments of: 'fighting for air', and 'not getting fresh air' were offered.

Individual result

The results for one representative individual are presented in Fig. 3. This shows that the experimenter was successful in manipulating the different ventilatory stimuli to achieve a good match of ventilation (\dot{V}_1) between test A (high-workload exercise), test C (hypercapnia) and test D (hypoxia). \dot{V}_1 for test B (low-workload exercise) was substantially lower than for any of the other tests. The magnitude of the additional hypercapnia necessary to maintain \dot{V}_1 is indicated by the elevation of



P_{ET,CO_2} in test C compared to test A. The magnitude of the effect of hypoxia (indicated by the lower S_{a,O_2}) on \dot{V}_I is reflected by the difference in workloads between tests A and D. The levels of subjective breathlessness were similar in tests A, C and D (where ventilations were matched) and markedly lower during test B when workload and \dot{V}_I were lower.

Group results

Adequacy of matching of ventilation

A comparison between the levels of \dot{V}_I during the hypercapnic (test C) and hypoxic (test D) tests against the high-workload test (test A) for each subject is given in Table 1. This indicates a consistently high level of correlation and low mean differences in \dot{V}_I in all subjects reflecting good matching in both hypercapnia and hypoxia tests compared with exercise alone.

Ventilatory stimuli, ventilation and breathlessness

The group mean levels of workload, S_{a,O_2} , P_{ET,CO_2} , \dot{V}_I and VAS breathlessness scores against time are shown in Fig. 4.

By design, the pattern of workload during hypercapnia (test C) was identical to that of the low-workload test (test B); with hypoxia (test D) the workload was similar to that of test B although there were a few points over the final 3 min of the test when it became significantly higher.

There was no difference in S_{a,O_2} between tests A, B and C with a mean level of 95.9% throughout these tests. The experimentally induced fall in S_{a,O_2} during test D was significant from 30 s onwards and gradually fell throughout the test, reaching a minimum level of 88.5% by 8 min.

During each of tests A and B the mean levels of P_{ET,CO_2} were 43.1 and 42.7 mmHg respectively; in each case there was a small but significant increase over the duration of the test. During the hypoxic test (D) the experimenter was successful in maintaining P_{ET,CO_2} at the same mean level (42.8 mmHg) as for test A, although there was a small but significant overshoot during the last minute of the test. During the hypercapnic test (C) P_{ET,CO_2} was significantly greater than in the other tests from 30 s onwards; it reached a level of 56.1 mmHg by the end of the test.

The accuracy of the matching of ventilation by the experimenter for individual subjects has been assessed above. Except for isolated points at 2 min (hypoxia) and 8 min (hypoxia and hypercapnia) the analysis of group data confirms close matching of \dot{V}_I between tests A, C and D. The low-workload test (B) produced a mean level of \dot{V}_I which was statistically significantly lower than any of the other tests from 2.5 min onwards, reaching a final level which was 19.3 l min⁻¹ below that of test A.

Mean VAS breathlessness scores were similar during the hypercapnic (C) and hypoxic (D) tests compared with the exercise-alone (matched ventilation) test (A).

Fig. 4. Mean results for eighteen subjects derived from measurements over 30 s periods. ● = test A, high workload; ◇ = test B, lower workload; △ = test C, lower workload with hypercapnia; □ = test D, lower workload with hypoxia. This shows workload in watts (W), arterial oxygen saturation (S_{a,O_2}), end-tidal P_{CO_2} (P_{ET,CO_2}), ventilation (\dot{V}_I) and breathlessness scores (VAS). LSD = Fisher's least significant difference between runs ($P = 0.05$).

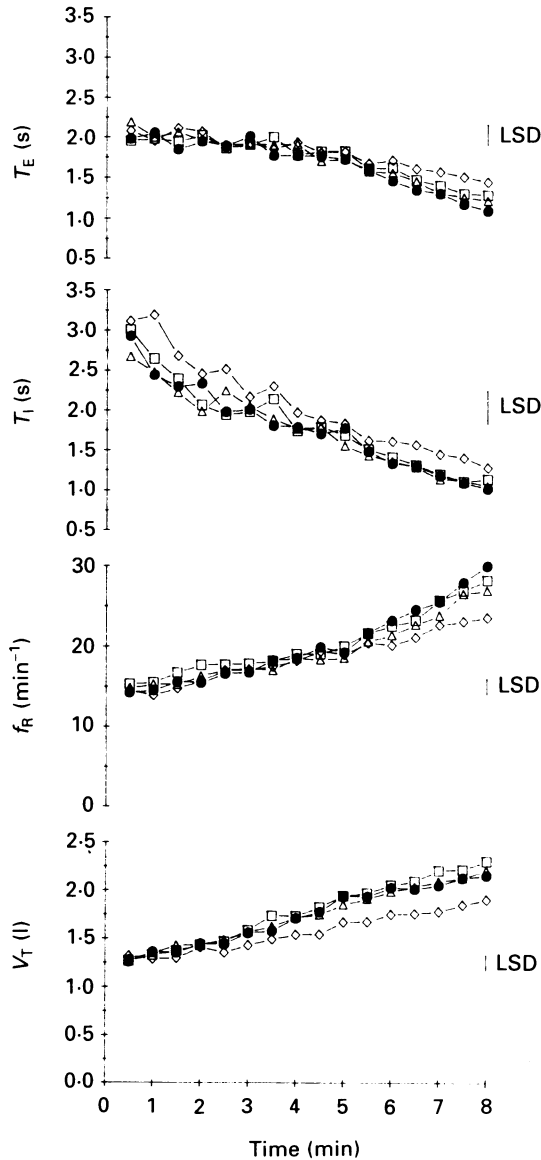


Fig. 5. Mean results for eighteen subjects derived from measurements over 30 s periods. ● = test A, high workload; ◇ = test B, lower workload; △ = test C, lower workload with hypercapnia; □ = test D, lower workload with hypoxia. This shows expiratory and inspiratory times (T_E and T_I), respiratory frequency (f_R) and tidal volume (V_T). LSD = Fisher's least significant difference between runs ($P = 0.05$).

Comparison of the exercise and hypercapnic test reveals a significant difference only at 5 min, whereas the hypoxic test was associated with significantly less breathlessness than the exercise test during much of the latter half of the test. The low-workload test (B) was associated with significantly lower levels of breathlessness than the high-workload test (A) from 3.5 min onwards, and from 6 min onwards compared with the hypoxic test.

A comparison of the levels of ventilation and breathlessness achieved in the two

exercise tests with different workload protocols (A and B; Fig. 4) shows that towards the end of these tests there are no statistically significant differences between the mean levels of breathlessness (A = 32.2 mm; B = 29.8 mm) for the same level of ventilation (A = 42.9 l min⁻¹; B = 42.7 l min⁻¹) at statistically significantly different times (A = 6 min; B = 8 min).

TABLE 2. Indices of ventilatory chemosensitivity and overall breathlessness in individual subjects derived from tests A, B, C and D

| Subject | Hypercapnia | | Hypoxia | |
|---------|-----------------------------------|----------|-------------------------------|----------|
| | $P_{ET,CO_2}(C-A)/\dot{V}_I(C-B)$ | VAS(A-C) | $W(A-D) - W(\Delta\dot{V}_I)$ | VAS(A-D) |
| 1 | 0.39 | 27.4 | 1037 | 39.3 |
| 2 | 0.73 | 148.7 | 251 | 321.4 |
| 3 | 1.02 | -48.0 | 1306 | 70.4 |
| 4 | 0.37 | 0.8 | 1051 | 17.5 |
| 5 | 1.09 | 30.5 | 642 | -95.0 |
| 6 | 0.57 | -45.8 | 313 | -122.9 |
| 7 | 0.75 | 97.1 | 446 | -1.8 |
| 8 | 1.25 | -52.9 | 998 | 11.9 |
| 9 | 1.01 | -22.5 | 1356 | 5.7 |
| 10 | 1.00 | -124.2 | 1177 | 45.4 |
| 11 | 1.38 | 72.4 | 1893 | 65.8 |
| 12 | 0.83 | -53.9 | 2086 | -76.5 |
| 13 | 0.88 | -49.0 | 385 | 38.9 |
| 14 | 1.25 | -33.5 | 557 | 50.1 |
| 15 | 0.63 | 143.3 | 1189 | 284.2 |
| 16 | 0.51 | 201.5 | 482 | 79.3 |
| 17 | 0.59 | 4.0 | 438 | 118.4 |
| 18 | 0.39 | 122.7 | 1627 | 166.6 |
| r_s | -0.38 ($P = 0.12$) | | 0.02 ($P = 0.99$) | |

For hypercapnia, $P_{ET,CO_2}(C-A)/\dot{V}_I(C-B)$ is the chosen index of chemosensitivity (see text); for hypoxia, $W(A-D) - W(\Delta\dot{V}_I)$ is a measure of the reduction in workload 'resulting' from the hypoxic stimulus allowing for the differences in ventilation (see text). VAS(A-C) and VAS(A-D) are measures of the overall breathlessness indices resulting from chemical ventilatory stimulation. r_s = Spearman's rank correlation coefficient for the group between indices of chemosensitivity and breathlessness.

Pattern of breathing

Figure 5 shows group mean results for T_E , T_I , f_R and V_T . There were no significant differences for any of these variables between hypercapnic (C), hypoxic (D) and exercise-alone (A) tests where ventilations were matched.

Indices of chemical sensitivity and overall breathlessness

The results for individual subjects are given in Table 2. Spearman's rank correlation analysis failed to show any significant relationship between either hypercapnic sensitivity or hypoxic sensitivity and overall breathlessness.

DISCUSSION

The main finding of this study was that during progressive exercise, normal subjects rated an increasing intensity of perceived breathlessness which depended on the level of ventilation but was relatively independent of the nature of the reflex

ventilatory stimulus. Thus, the substitution of a portion of an exercise ventilatory stimulus by a hypoxic or hypercapnic ventilatory stimulus, to achieve the same level of ventilation, did not result in a greater degree of subjective breathlessness. These results lend no support to the idea that changes in arterial blood gas levels have a specific effect on the sensation of breathlessness other than via their stimulation of ventilation.

An important feature of the results of this study is the clear reduction in perceived breathlessness when the intensity of exercise was reduced to a level equivalent to that in the hypercapnic and hypoxic tests but in the absence of a second ventilatory stimulus. In this case, the visual analogue scale demonstrated its sensitivity in detecting a reduction in the sensation of breathlessness associated with a fall in ventilation. The fact that breathlessness ratings were greater at lower workload with chemical stimulation lends weight to the argument that the sensation being scored was related to the degree of ventilatory stimulation. However, the lower breathlessness scores at relatively higher ventilations during hypoxia, compared with exercise alone, suggest that the degree of exertion may influence perceived breathlessness (although the result with hypercapnia does not support this) or that hypoxic ventilatory stimulation induces *less* breathlessness than exercise or hypercapnia.

The findings of the present study are not consistent with earlier studies in normal subjects which documented greater intensities of breathlessness for given ventilations achieved separately with hypercapnia (Stark *et al.* 1981; Adams *et al.* 1985*a*) or hypoxia (Adams *et al.* 1985*a*) compared with exercise. The present study aimed to deal with the problem in previous studies, of comparing subjective estimates obtained under the very different experimental situations of rebreathing and exercise. Thus, we used exercise as the basis of the experimental protocol and 'blinded' the subjects from knowing when inspired gas concentration was altered. The 'shortfall' in exercise intensity during the 'lower-workload' tests was perceived by most subjects. However, with 'chemical stimulation' tests, similar reductions in exercise intensity were not consistently identified by subjects; this would reduce the likelihood of any effects due to individuals' anticipation. We took care in only recruiting naive subjects with no expectation of the outcome of these studies. Another possible explanation for the greater breathlessness with a 'pure' chemical stimulus compared with the current 'mixed' stimulus approach could relate to the sensitivity of the sensory scaling technique; thus, if there was any difference in intensity of breathlessness for a given degree of ventilatory stimulation induced by hypercapnia or hypoxia, then this might be more evident if this stimulus caused the whole rather than a part of the ventilatory response. In the context of the present study, however, the levels of blood gas changes attained with alterations in inspired gas concentrations (i.e. P_{ET,CO_2} up to 56 mmHg; S_{a,O_2} below 90%) are significant in terms of those occurring during respiratory disease or at altitude (hypoxia) when breathlessness on exertion becomes a problem. We therefore feel that in view of the sensitivity of our scaling technique for breathlessness demonstrated in this study (see above), it is unlikely that hypoxia or hypercapnia constitute an important specific dyspnoegenic factor in exertional breathlessness, at least in normal subjects.

Other evidence that blood P_{O_2} and P_{CO_2} levels *per se* are not crucial to the intensity of the sensation of breathlessness comes from a study using hypercapnic and hypoxic

ventilatory stimulation in normal subjects at rest (Adams *et al.* 1985*b*). Oscillating these stimuli at different frequencies resulted in a temporal dissociation between the magnitudes of the stimulus and the ventilatory response; for both hypercapnia and hypoxia, the intensity of breathlessness was found to correlate more closely with the prevailing ventilation rather than the degree of reflex chemical activation. Although this approach was not able to address the importance of the hypercapnic stimulus at the central chemosensitive site in the genesis of the sensation of breathlessness, it did suggest that the hypoxic ventilatory stimulus from peripheral chemoreceptors was not directly perceived as breathlessness.

Recently, Ward & Whipp (1989) reported on a series of experiments in normal subjects which were very similar to those presented here. These authors also reported that for a given level of ventilatory stimulation, the intensity of subjectively assessed 'breathing difficulty' induced by a combination of hypercapnia and exercise, was not different from that resulting from higher intensity exercise alone. However, a similar protocol, but with a combination of hypoxia and exercise, induced a markedly greater level of discomfort compared with the same ventilation resulting from exercise alone. Despite significant experimental differences between the present study and that of Ward & Whipp (1989), it is not easy to identify a reason for the fundamentally different observations relating to the putative dyspnoenic effect of hypoxia during exercise. One difference that may be important is that Ward & Whipp (1989) compared breathlessness during hypoxia with control measurements (exercise alone) obtained during hyperoxia (inspired O₂ concentration = 100%); our comparisons of breathlessness were between hypoxia and normoxia. Although not investigated in either of these studies, any specific effect of hyperoxia in reducing breathlessness for a given ventilation could account for the differences between the studies. A second possible source of these discrepant findings is the definition of what to scale given by the investigators to their subjects; we asked our subjects to scale breathlessness and defined this as 'an uncomfortable need to breathe', whereas Ward and Whipp requested ratings of 'breathing difficulty'. Recently, Wilson & Jones (1989*b*) have pointed out that the words used to describe the sensation of breathing discomfort which subjects should scale, crucially affects the subjective responses elicited under a given set of experimental conditions.

Further support for a direct dyspnoenic effect of hypoxia during exercise comes from a previous study on normal subjects from this laboratory (Chronos, Adams & Guz, 1988). A step hypoxic stimulus (inspired O₂ concentration = 15%) given for 4 min during steady-state exercise induced changes in perceived breathlessness which occurred more rapidly than the changes in ventilation during both the on- and off-transients. However, this study did not address the question of whether hypoxia in the steady state would result in a disproportionate increase in breathlessness compared with its effect on ventilation. The present study suggests that this is not the case; in fact perceived breathlessness was lower with hypoxia than at the same ventilation induced by exercise alone (Fig. 4). However, in view of the opposite conclusions from the careful study of Ward & Whipp (1989), it is clear that this issue merits further investigation.

For the group as a whole there was no evidence of a dyspnoenic effect of either chemical stimulus, but it is evident that there was a range of sensitivities for breathlessness amongst the subjects for both stimuli (Table 2). However, there was

no evidence from our results that those individuals who were most sensitive to hypoxia, and who thus had a relatively greater hypoxic ventilatory stimulus at matched ventilations, responded in a consistently different way from other subjects in their relative subjective responses between the hypoxic and exercise tests with matched ventilation. Similarly, there was no correlation between an individual's index of hypercapnic sensitivity and ratings of breathlessness in the appropriate tests; a similar finding has been observed at rest (Adams *et al.* 1985*a*). We therefore feel it unlikely that in the present study the findings in the group as a whole are hiding an important effect in individuals with extreme levels of ventilatory chemosensitivity. In addition there was no evidence of any difference in the pattern of breathing adopted in the three tests where overall ventilation was matched (Fig. 5); this fact helps to justify our interpretation of these results with respect to differences in the reflex ventilatory stimuli used in this study.

A further interesting observation made in the present study was that for a given level of ventilation during exercise, the intensity of breathlessness is independent of duration of exercise. This observation is not consistent with the finding of O'Neill, Stark, Allen & Stretton (1986), although our study was not designed to address this question and the difference in exercise duration was relatively small.

The results of the present study, taken in isolation, are consistent with the view that the intensity of breathlessness during ventilatory stimulation could depend on the perception of mechanoreceptive afferent information from the lungs or chest wall. However, a recent study from this laboratory (Lane *et al.* 1987) employed a similar protocol to that of the present study except that ventilation resulting from exercise alone was matched at a lower workload by subjects' voluntary activation of their breathing. In this case, the intensity of breathlessness was lower than that at the same ventilation with exercise alone and the same as that recorded at a lower ventilation at the same exercise intensity. Taking account of these findings, the present results indicate that the magnitude of perceived breathlessness reflects the degree of reflex ventilatory activation but that specific stimuli confer no additional source of dyspnoegenic information. However, in analysing other studies, a specific role for hypoxia in the genesis of breathlessness remains an intriguing question. The ability of hypoxia during exercise to induce rapid changes in breathlessness before the consequent ventilatory response is fully developed (Chronos *et al.* 1988) is consistent with the view that reflex ventilatory stimulation is important in the genesis of breathlessness but indicates that the subsequent increase in ventilation is an associated rather than a contributory event. On the other hand, the findings of Ward & Whipp (1989) suggest that afferent information deriving from hypoxic chemoreceptors may have direct sensory effects over and above its reflex stimulation of ventilation.

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