Methods to assess breathlessness in healthy subjects: a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide

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(Received 7 August 1980; 26 February 1981; accepted 16 April 1981)

Summary

1. Methods were devised and evaluated for inducing breathlessness by submaximal graded exercise in healthy subjects while objective measurements of cardiorespiratory function were made. Breathlessness was assessed with serial visual analogue scales (VAS), but with various measures to enhance repeatability.

2. A high level of reproducibility was obtained in spite of the subjective nature of the assessment. Individual responses were described by the relationship between breathlessness and ventilation. The sensitivity of the method was demonstrated by the use of inspiratory resistances which disturbed this relationship and caused greater breathlessness for a given level of ventilation.

3. These methods were applied to six healthy subjects to analyse the effects of acute doses of diazepam and promethazine on breathlessness induced by graded exercise or by rebreathing carbon dioxide in a double-blind study.

4. During exercise, diazepam and promethazine did not reduce breathlessness, although there was a minor trend with promethazine. During exposure to elevated levels of carbon dioxide, diazepam and promethazine had no effect on breathlessness. Diazepam and promethazine produced similar levels of sedation, but neither drug had significant effects on the ventilatory response to carbon dioxide. These preliminary findings contrast with those reported for chronic diazepam in 'pink puffers'.

5. Raised levels of carbon dioxide caused greater breathlessness in relation to ventilation than did exercise.

Key words: breathlessness, carbon dioxide, diazepam, dyspnoea, exercise, promethazine, ventilation, visual analogue scales.

Abbreviations: VAS, visual analogue scales.

Introduction

Dyspnoea is a distressing and disabling symptom. Analysis of the effects of drugs on dyspnoea per se is hindered by the lack of methodology with which to measure dyspnoea. The difficulties are those inherent in assessing a sensation and attempting to do this on a quantitative basis. Aitken [1, 2] described the use of visual analogue scales (VAS) to study various sensations and applied them to assess dyspnoea in subjects breathing through respiratory resistances. A rectilinear relationship between dyspnoea and the logarithm of the resistance of the valve was described.

In the present study we have extended the use of VAS for the appraisal of breathlessness and assessed its reproducibility and sensitivity. Although the ultimate aim is to assess drugs in patients with dyspnoea, the development and validation of methods is performed more easily in...
healthy subjects. These methods can then be modified for the assessment of patients. A description of our methods and differences between the breathlessness of exercise and that during rebreathing carbon dioxide have been presented previously [3, 4].

A clinical report has shown that diazepam reduces dyspnoea and improves the exercise tolerance in patients with emphysema [5]. In addition, the slope of the ventilatory response to carbon dioxide decreased with diazepam, indicating a diminished responsiveness to carbon dioxide. In these studies diazepam was administered chronically and the effects on dyspnoea were apparent by day 4 of treatment. The possibility that these changes were due to the desmethyl metabolite of diazepam was considered. Reports that a drug in clinical use reduces dyspnoea are of interest both therapeutically and pharmacologically. Possibilities concerning the mode of this action of diazepam have been discussed already [5], but experimental exploration of this problem is now required. As a starting point we have used our new methodology to examine the simplest situation, namely the effects of single doses of diazepam on breathlessness in normal subjects. Breathlessness was induced by exercise or by rebreathing carbon dioxide and the effects of diazepam were compared with those of placebo. A difference in response might be attributable to non-specific sedation from diazepam. Therefore, a further control was included by administration of promethazine, which was likely to induce sedation, but has never been shown to benefit clinical dyspnoea. Sedation was assessed with a standard questionnaire and any effect on breathlessness or breathing was related to this.

Methods

Subjects

The subjects included in this study were healthy males aged 20–39 years who fulfilled the requirement of a clinical examination and who had a normal electrocardiogram (ECG). Subjects with evidence of cardiorespiratory disease were excluded, as were those with prior knowledge of the project and its aims. All gave informed consent in accordance with the Declaration of Helsinki. Information on the subjects is shown in Tables 1 and 2. Different groups were used for the validation and for the drug study.

Induction of breathlessness by exercise

Walking was used to induce breathlessness. Work load was varied by changing the speed and slope of a treadmill to produce peak heart rates of about 85% of the maximum predicted rate [6]. The slope was 5–10° depending on the fitness of the subject and exercise continued for 6 min. The first 2 min of exercise were at a speed of 2 km/h, the next 2 min at 4 km/h and the final 2 min at 6 km/h. Most volunteer subjects were moderately breathless at the end of the test. No attempt was made to attain a steady-state condition during exercise.

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<th>Height (cm)</th>
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<th>Exercise</th>
<th>Max. predicted heart rate (beats/min)</th>
<th>Max. heart rate (beats/min)</th>
<th>Max. ( PO_{2} ) (ml/min)</th>
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The effects of the treatments under test were compared by repeating the exercise under conditions which were as similar as possible. All subjects refrained from smoking for 2 h before study and were studied at the same time of day after a standard meal. At least 1 week between assessments was allowed to minimize any training effects. Room temperature was held constant. The same staff ran the study on each occasion and studies were performed on a double-blind basis.

Expired gas was passed through a pneumotachograph (Fleisch head no. 3 or 4) and then through a mixing cone from which gas was sampled and passed through a paramagnetic oxygen analyser (Morgan 252 D, Chatham, Kent, U.K.) and an infrared carbon dioxide analyser (Morgan 801). A microprocessor presented the data as oxygen consumption standardized to STP (standard temperature and pressure). Respiratory rate, tidal volume and expired minute ventilation ($V_e$) were corrected to BTPS (body temperature and pressure, saturated) and presented at intervals of 1 min during the period of study. Calibration of the gas analysers and pneumotachograph preceded every study. ECG readings were monitored continuously and heart rate was derived from this. In the study on diazepam and promethazine the pneumotachograph output was recorded on a pen recorder (Gould 2600, Hainault, Essex, U.K.) and ventilation was calculated from the expired volumes over a period of 30 s.

Subjects were connected to the system with a facemask (Martindale MP-1) which was comfortable in use and it was possible to eliminate leaks. These were found by surveying the edges of the mask in situ with a sampling tube connected to the carbon dioxide analyser. The study did not proceed until all leaks were eliminated. Inspiration was from the atmosphere through a low resistance valve (Martindale MP-3).

**Induction of breathlessness by rebreathing carbon dioxide**

This procedure was based on the method described by Read [7]. One difference, however, was that the subjects were connected to a facemask to provide consistency with the situation during exercise. An anaesthetic facemask (Medishield) was used and its position was adjusted to exclude leaks at the junction with the face. Subjects were connected to a 6 litre bag

### Table 2. Diazepam and promethazine: general information on subjects and their responses to exercise and treatment

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>R</th>
<th>Sedation difference from placebo</th>
<th>BHT (s)</th>
<th>CO$_2$ (kPa)</th>
<th>Exercise</th>
<th>PEFR (l/min)</th>
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* Equipment failure.
**n=5.
containing a mixture of CO$_2$ + O$_2$ (5:95, v/v) or to the atmosphere through a three-way tap. The circuit included a Fleisch head (no. 3 or 4 as in exercise) connected to a Godart pneumotachograph (no. 17212) recording on the Gould 2600 pen recorder. Ventilation was measured as cumulative inspiratory volume over a period of 30 s. Gas was sampled continuously from the rebreathing circuit and returned to it after passage through a Morgan 901 Mk 2 high-speed carbon dioxide analyser and a Morgan 252 D paramagnetic oxygen analyser. These measurements together with the ECG were recorded continuously on the pen recorder. The gas analysers were calibrated with standard gas mixtures before each study. End-tidal P$_{CO_2}$ was calculated in the usual way.

At the start of the test, the subject breathed with the tap open to atmosphere until a regular pattern of breathing was established. Then the subject was connected to the rebreathing bag. Rebreathing continued for 4 min or until the end-tidal CO$_2$ concentration reached 10%. On each day of study, a carbon dioxide response was measured before the treatment was given and approximately 2 h after administration. As for exercise, environmental factors were held constant during the study.

Linear regression was used to assess the ventilatory response to carbon dioxide and the slope and x-axis intercept of the regression line was computed for each drug and placebo both before and after administration. These slopes and intercepts were then compared by Wilcoxon’s signed rank-sum tests. The results before each treatment were compared with those after treatment and the changes on each active agent were compared with the changes on placebo.

Assessment of breathlessness during exercise

During the period of increasing and then decreasing breathlessness, VAS were administered at intervals. It seemed likely that the changes in score with time would be a more reliable index than any single score, since the latter might be affected by many factors including personality and environment. The top score of the VAS was anchored by applying a standard stress to produce breathlessness of greater severity than that which occurred during the remainder of the assessment. The subject could then relate his subsequent feelings to this point. Comparisons of responses on the VAS were made within the same subject and not between subjects.

The VAS were used as follows. A horizontal straight line measuring 20 cm was presented to the volunteer subject and he was asked to mark the line to show the severity of his breathlessness. Full explanation was given to the subject to ensure his understanding and co-operation. The minimum point was ‘not at all breathless’ and this related to the feelings of the subject at rest. The maximum point was ‘very breathless’ and this was set by the subject’s assessment of his own breathlessness at the end of a standard period of exercise performed before administration of the treatment at the start of each study. The exercise load of 12–15° at 6–8 km/h for 1 min was selected to produce greater breathlessness than that which occurred during the 6-min period of graded exercise.

The VAS were presented at intervals of 1 min on a television screen suspended on the treadmill at eye level. The marker on the scale was controlled by buttons operated by the thumbs of the subject. The scale was removed from the screen after the volunteer subject had responded. The television screen was connected to a PET (Personal Electronic Transactor) and data were displayed as percentages.

Assessment of breathlessness during rebreathing of carbon dioxide

VAS were used to assess the severity of the breathlessness at intervals of 1 min during rebreathing of carbon dioxide. In this part of the study the maximum point was ‘very breathless’ and this was set by the subject’s assessment of his own breathlessness at the end of a period of rebreathing carbon dioxide at the start of each study before treatment was administered. This produced greater breathlessness than occurred during exercise (see the Results section). At the end of exercise and rebreathing carbon dioxide, a questionnaire directed at exploring the quality of the breathlessness was administered to the subject through the PET and television screen.

Validation of VAS method

Reproducibility. Six healthy volunteer subjects participated in a study to assess the method critically: particular attention was paid to repeatability. Each subject attended the laboratory on three occasions separated by an interval of at least 1 week. On the first occasion the procedures were rehearsed to familiarize the subjects. On the two subsequent occasions identical ‘runs’ were performed to permit within-subject comparison of the responses.

Sensitivity. It was necessary to investigate whether the methods were sufficiently sensitive to
show an effect of treatment on breathlessness and it was easier to test this by increasing rather than decreasing the severity of breathlessness. For this study, the subject breathed from a valve-box through a mouthpiece with a noseclip in position. After the VAS had been set, the subjects undertook two periods of exercise. During one of these, an inspiratory resistance (0.67 cm water) was in situ and during the other there was no such resistance; the order was randomized and the study was performed double-blind.

**Design and analysis of the drug study**

Six healthy subjects participated in a double-blind comparison of diazepam, promethazine and placebo with the order of treatments randomized and an interval of 1 week between treatments. Single doses of diazepam (10 mg; Valium, Roche Products) and promethazine (25 mg; Phenergan, May and Baker) were given by mouth. Matching tablets for placebo were not available, but the double-blind nature of the study was maintained with the help of a third party who inserted the treatment directly into the mouth of the subject. Subjects were carefully supervised during procedures such as exercise. Measurements started 75 min after tablet administration.

Sedation was assessed after the exercise test and before rebreathing carbon dioxide in each subject with a series of VAS [8]. Total scores for each of the treatments were calculated and those for placebo were subtracted from those for the drugs to provide relative scores.

Breath-holding time was measured on two occasions after each of the treatments. This was done after a full inspiration and recordings were made of ventilation and the carbon dioxide concentration at the end of the ensuing expiration. Peak expiratory flow rate was measured with a Wright peak-flow meter at the start of the study, before and after exercise. In this way, any effect of exercise or the test drugs on bronchomotor tone could be detected.

The levels of breathlessness on drug and on placebo were compared statistically at the maximal value of ventilation achieved during exercise common to both drug and placebo; linear interpolation was used when necessary. This was done separately for diazepam and promethazine. A simple count was made of the number of times breathlessness was higher on each active agent than on placebo and vice versa. This was tested for significance by a sign test. Inspection of the data did not indicate that the potentially greater sensitivity of parametric methods would have had any effect on the conclusions.

**Results**

**Breathlessness during exercise and validation of method**

Table 1 shows general information on the six subjects who participated in the investigation of reproducibility. Peak expiratory flow rates before exercise were not significantly different on the two occasions and the responses of the subjects in terms of maximum heart rate and maximum oxygen uptake were similar.

The ventilations and scores for breathlessness for three subjects are shown in Fig. 1. Breathlessness was at a very low level before exercise and started to increase within 2 or 3 min of the start of exercise. Generally breathlessness increased with ventilation above a threshold with lay between 20 and 40 litre/min, but varied from subject to subject. The increase in breathlessness was marked at the highest work load. As soon as exercise ceased, breathlessness decreased and came towards baseline levels in 3–5 min. Different subjects used the VAS in different ways, some operating on the complete scale and others on a fraction of it.

The mean scores for breathlessness and ventilation for the first and second experiments were very similar as shown in Fig. 2. There were no statistically significant differences between the mean scores at any point (Student’s paired t-test) as can be seen by comparing the mean differences with their standard errors. At peak breathlessness a difference of 20% on the VAS would have been required for statistical significance ($P < 0.05$) and this illustrates the potential sensitivity of the method in this limited number of six subjects. By increasing the number of subjects sensitivity would be increased.

Breathlessness showed associations with heart rate, oxygen uptake, respiratory rate, tidal volume and $V_e$. The latter seemed most relevant at this stage and in Fig. 3 this relationship has been shown. The response of each of the subjects is included to show the variation in the findings. Breathlessness increased steeply above a threshold which varied between individuals and satisfactory reproducibility within subjects was apparent. Comparison between subjects would be hazardous because of the individualistic use of the VAS.

In four subjects the sensitivity of the method was checked by comparing the relationship between breathlessness and ventilation in the presence and absence of an inspiratory resistance (Fig. 4). Breathlessness was more severe with the inspiratory resistance in situ. This suggests that the plot of breathlessness against ventilation is
sensitive to external factors and that the subjects did not respond in a fixed way on the VAS.

**Breathlessness during raised CO₂ and comparison with exercise**

Information on the subjects is provided in Table 2. Breathlessness was at a low level as subjects breathed from the atmosphere but after connection to the rebreathing bag there was a rise in ventilation and this was accompanied by increasing breathlessness (Fig. 5).

The same VAS and calibration were used to assess the breathlessness of exercise and of elevated carbon dioxide. The subjects did not
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encounter difficulties in comparing the severity of breathlessness during the two procedures although qualitatively the sensations were different. Greater breathlessness for a given level of ventilation occurred during rebreathing (Fig. 6; \( P < 0.05 \)), although the mean maximum ventilation was 42.2 litre/min for rebreathing which was lower than 47.8 litre/min for exercise. Questions directed at exploring the quality of breathlessness in the two situations showed two trends during rebreathing of carbon dioxide. Subjects noted some difficulty in getting air into the chest and also indicated that the gas they breathed was unsatisfying. Questions concerning the site of the breathlessness did not show a clear separation between exercise and carbon dioxide.

Effects of diazepam and promethazine

Most subjects were sedated by diazepam and promethazine (Table 2). One subject, however, scored less after promethazine than after placebo. Four subjects were more sedated with diazepam than promethazine and two had the reverse

![Fig. 4. Sensitivity. Effect of breathing through an inspiratory resistance on relationship between breathlessness and ventilation. O, No resistance; ●, resistance.](image)

![Fig. 5. Effects of diazepam, promethazine and placebo on breathlessness vs ventilation during rebreathing carbon dioxide \((n = 6)\). O, Diazepam; △, promethazine; ●, placebo.](image)

![Fig. 6. Breathlessness vs ventilation during exercise (■) and rebreathing carbon dioxide (□) in the presence of placebo, diazepam and promethazine \((n = 6)\).](image)
situation. No effects on peak expiratory flow rate attributable to the treatments were found. The physiological responses in terms of maximal heart rate and maximal oxygen uptake to exercise were similar for the three tests in all subjects.

During exercise, ventilation increased to 40–50 litre/min and this was accompanied by an increase in breathlessness at ventilation levels above 20 litre/min (Fig. 7). Mean values for each of the treatments show that slightly less breathlessness in relation to ventilation occurred after promethazine, but this did not reach statistical significance. The responses after placebo and diazepam were identical.

During rebreathing of carbon dioxide, no significant differences between treatments occurred and the trend in favour of promethazine during exercise was not repeated for exposure to carbon dioxide (Fig. 5). After diazepam, there was a minor depression of the relationship between breathlessness and ventilation (Fig. 5).

Table 3 shows the ventilatory responses to carbon dioxide. Single doses of diazepam and promethazine were without significant effects either on the slope or on the intercept.

Breath-holding time was not prolonged in the presence of diazepam or promethazine and the carbon dioxide tensions at the end of the following expiration were similar (Table 2).

**Discussion**

VAS have proved to be of considerable value in the assessment of states which do not lend themselves to study by objective means. The range of applications is wide but particular usefulness occurs in assessing the function of higher levels of the central nervous system and the effects of drugs thereon (e.g. [8,9,10]).

Aitken [11] studied the effects of respiratory resistances on the feeling of dyspnoea in normal subjects. A rectilinear relationship was found between the subjective assessment and the logarithm of pressure gradient across the resistance. In a subsequent study [2] the dyspnoea scores on VAS were related to the expiratory pressure loading in three groups of subjects: normal, asthmatic and neurotic. The extremes of the scales were 'no resistance to

**TABLE 3. Effects of placebo, diazepam and promethazine on the ventilatory response to carbon dioxide**

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<th>Diazepam</th>
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breathing' and 'impossible to exhale'. The differences between the groups were small, but it was clear that VAS could provide a useful tool with which to study respiratory sensations in health and disease.

Use of VAS in the present study was influenced by the published findings of others as well as by experience in our own pilot studies. We decided to focus attention on the dynamic situation during exercise and to make serial assessments of breathlessness. It seemed important to follow the scores on the scales as the breathlessness increased rather than to rely on a single assessment on maximal exercise. In many situations (e.g. assessment of depression) it is not possible to administer a 'calibration dose' of the sensation, but this is quite feasible in the study of breathlessness. In our studies we anchored the maximum point by asking the subject to undertake a short period of strenuous exercise before administration of the test treatment. Clearly, it was important that greater breathlessness occurred during this procedure than during the subsequent period of exercise. During the latter, subjects occasionally scored 100% but, it was confirmed after, that they would not have given a greater score had more scale been available. Anchoring the scale with a level of breathlessness greatly in excess of that in the main assessment would have reduced the sensitivity of the scales.

A high level of reproducibility of the methodology was obtained during the present studies. Such findings were a little surprising and an explanation might be that the system lacked sensitivity and each subject responded to the VAS in a stereotyped fashion which would not have varied even with an effective treatment. Clearly, one method of demonstrating sensitivity is by testing with a drug which is known to reduce breathlessness in human subjects. The treatments tested in this study did not have such an effect. The alternative means of testing sensitivity was to increase breathlessness for a given level of ventilation by use of inspiratory resistances. A low resistance was used which was not detected at rest and hence did not interfere with the 'blinding' of the test. At the higher ventilation levels during exercise the severity of breathlessness increased more sharply in the presence of the resistance and this suggested that the methods had adequate responsiveness.

The relationship between ventilation and breathlessness was a convenient means of expressing the results of exercise tests. In this system there should be clear differences between a treatment which reduces breathlessness by decreasing ventilation and one which reduces breathlessness without an effect on ventilation. The latter presents some therapeutic appeal.

We believe the methods we have described for study of breathlessness in healthy subjects can provide the basis for assessment of dyspnoea in patients with cardiorespiratory disease. Assessment of dyspnoeic patients is generally directed towards determining the limits of tolerance with clinical history or with exercise tests. In particular, the 12-min test [11, 12] allows for discontinuity of effort and may therefore relate more to the situation of the dyspnoeic patient in everyday life. The use of serial VAS during exercise based on our methods would permit more detailed study, since it can examine not only the onset and development of breathlessness but also the rate of recovery. We believe that such a system may promote fuller analysis of the effects of drugs such as diazepam in dyspnoea.

Interest had been stimulated by the results of Mitchell-Heggs et al. [5], showing that chronic administration of diazepam relieved dyspnoea in patients with emphysema. We investigated the effects of single oral doses of diazepam in healthy subjects. Clearly, this was a different situation from that studied by Mitchell-Heggs et al. [5] but, nonetheless, one which might be relevant to probing the mode of action of diazepam. Promethazine was included as another agent which could induce sedation; its other properties include antagonism of histamine.

In our study diazepam had no significant effect on breathlessness during exercise or during exposure to raised levels of carbon dioxide. The effects were tested between 75 and 120 min after oral administration at which stage maximal serum levels of diazepam would be expected and the desmethyl metabolite of diazepam would be at a low level [13, 14]. The slower increase in desmethyldiazepam has been considered as a reason for the lag in improvement of dyspnoea in patients with emphysema [5].

We have made no assumptions that similar mechanisms operate in healthy subjects and patients with respiratory disease [15] and would not extrapolate from the effects of drugs in health to the situation in disease.

An unexpected result in the present study was the small trend towards reduction of breathlessness of exercise after promethazine (Fig. 5). Although not statistically significant in a study of six subjects, it merits further consideration. The ventilation values during exercise were similar for promethazine and placebo and therefore any effect on breathlessness was not the result of a reduction in ventilation. The possibility that the effects of promethazine were simply secondary to...
sedation can be studied by comparing diazepam and promethazine. Both drugs caused sedation, the effect being slightly greater with diazepam, which did not reduce breathlessness. This suggests that any effect of promethazine may relate to some other pharmacological property. A major effect of promethazine on the calibre of the airways was unlikely, since peak expiratory flow rate was unchanged. Promethazine is an antihistamine and, although a role for histamine in the genesis of breathlessness of exercise has never been established, it would be of considerable interest to test whether antihistamines of other chemical classes have similar effects on breathlessness. Promethazine did not reduce the breathlessness in relation to ventilation associated with raised carbon dioxide.

Promethazine did not have significant effects either on the slope or threshold of the ventilatory response to carbon dioxide. Such findings are in accordance with those of Pleuvry & Maddison [16] who tested oral doses of 50 mg. Diazepam, chronically administered, reduced the slope of the ventilatory response to carbon dioxide in patients with emphysema [5]. In healthy subjects a single oral dose of 5 mg caused no change in intercept, but a small decrease in slope, and 10 mg caused an increase in threshold, but no change in slope [17]. We have found neither a change in intercept nor a change in slope after a dose of 10 mg. Similar findings were reported after intravenous administration of diazepam [18].

An interesting finding in the present study was that greater breathlessness occurred during exposure to raised carbon dioxide than occurred during exercise. This was not due to differences in ventilation during the two procedures. As far as possible, the same apparatus was used for exercise and for rebreathing and in both situations subjects used a facemask. It therefore seems unlikely that the difference in breathlessness was due to technical factors. Subjects generally considered that the quality of the breathlessness during rebreathing was different from that of exercise although a questionnaire directed at testing this showed minor differences only. Guz [19] has indicated differences in the quality of these sensations and the feeling of being unable to breathe deeply enough in the presence of carbon dioxide.

The use of one system of VAS to assess breathlessness in the two conditions is perhaps open to question, but the subjects had little difficulty on the three occasions each made the comparison. While breathlessness on exercise is a common and known experience to all, exposure to elevated levels of carbon dioxide by rebreathing is less pleasant and unfamiliar and might be associated with some anxiety. It is therefore of interest that diazepam had only minor effects on the separation and promethazine, by decreasing breathlessness of exercise, increased the separation. It is possible that the mechanisms vary in the two types of breathlessness.

Acknowledgments

We are grateful for the patient co-operation of the subjects who participated in this study. Professor A. Guz, Professor J. M. Bishop, Dr R. C. Joshi and our colleagues at ICI provided constructive criticism and encouragement at all stages. Mr A Shore devised the computer programme for the assessment of breathlessness and Miss S. E. Pickford typed the manuscript.

References

Diazepam, promethazine and breathlessness


