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SHORT REVIEW

Dyspnoea: Assessment and pharmacological manipulation

R.D. Stark*

A recent meeting of the European Society for Clinical Respiratory Physiology, held in Antwerp, focused on the mechanisms and management of respiratory symptoms. Dyspnoea received particular attention and this review is based on a talk presented at that meeting.

The clinical problem posed by dyspnoea, or breathlessness, is of considerable magnitude. Precise data on its prevalence are lacking but it is the most common symptom in patients with cardiorespiratory disease. Many chronic diseases are associated with dyspnoea, notably cardiac failure and chronic obstructive pulmonary disease. Extrapolation from the epidemiological survey of the Respiratory Diseases Study Group of the RCGP [1] would suggest that, in the UK alone, approximately 750,000 patients with chronic bronchitis experience dyspnoea induced by walking on level ground.

A therapeutic agent which reduces the sensation of dyspnoea would be expected to improve the quality of life for the patient by delaying the restrictions on lifestyle imposed by breathlessness and by mitigating a symptom which causes distress and induces anxiety. This would be no substitute for specific therapy directed at the underlying disease process, but could be of value when the pathology is not reversible. Close analogies exist with the use of analgesics to treat pain.

Discovery of drugs to reduce dyspnoea is difficult because the pathophysiological mechanisms are still in dispute. In addition, animal models are limited in the study of sensations. In this laboratory known pharmacological agents were used in studies on man to discover the possible mechanisms of dyspnoea.

No progress could be made until methods were available for assessing breathlessness. Precision was necessary in these assessments and there had to be knowledge of the reliability and limitations of the method in view of its subjective nature. Over about ten years, experience has been gained which provides opportunities to optimize future experimental design and to appreciate when credibility has been overstretched! This review records what has been learned from these experiences.

Assessment of dyspnoea

Methods not involving visual analogue scales

The traditional clinical assessment of dyspnoea involves grading according to the degree of limitation of daily activities [2]. This method is widely used but lacks sensitivity since significant changes can occur without being reflected in the grades.

Dyspnoeic index depends on the relationship between exercise ventilation and maximal breathing capacity [3] but does not take account of the sensations experienced by the patient.

Exercise testing enables the patient's sensation of breathlessness to be related to objective physiological measurements. In studies on patients, assessment during walking seems preferable since this more closely resembles normal daily activities than does pedalling on a bicycle ergometer. With the latter, discomfort in the exercising muscles may limit exercise capacity and distract from the measurement of dyspnoea.

The 12-min walking test has proved a useful and relevant measure of a patient's disability and has the advantage that the distance covered is quantitative and less-obviously subjective [4, 5]. Variations on the test have been introduced which allow use of shorter walking times [6]. For specific study of dyspnoea, the 12-min walking test has the disadvantage that other sensations such as general muscle fatigue or pain may determine the performance. However, such a test may yield more useful information than a visual analogue scale in clinical situations such as assessing a patient being considered for pneumonectomy.

Rating of perceived exertion with the method of BORG and LINDERHOLM [7] is in wide use but, as with the walking tests, it does not have specificity for dyspnoea.

Visual analogue scales

Visual analogue scales (VAS) have been used for many years to assess sensations such as pain and sedation. AITKEN in 1969 [8] was first to apply VAS to respiratory sensations, when he studied the effects of breathing against resistances. In 1980, the assessment of breathlessness during exercise using VAS was described [9]. The objective was to measure breath-

* Clinical Pharmacology Unit, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK.

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lessness as it increased during sub-maximal exercise and decreased during recovery and to relate the intensity of these sensations to ventilation and its components or to oxygen uptake. In this way, it was possible to study dyspnoea without taking the subjects to the limits of their exercise tolerance.

In this laboratory, the VAS is a horizontal straight line labelled 'not at all breathless' at one end and 'very breathless' at the other. The VAS are administered by computer and displayed on a television screen suspended in front of the subject as he walks on a treadmill. At intervals of one minute, the subject records the intensity of his breathlessness on the VAS by means of finger controls and the information is stored in the computer [10, 11].

This method is simple but its weakness is the unavoidable subjectivity. Various procedures were adopted, in an attempt to enhance the reliability of the test. Rather than relying on a single VAS, multiple VAS were used during the period of study to monitor changes in the sensations during and immediately after exercise. In this laboratory, it has been policy to fix or 'anchor' the upper end of the VAS and figure 1 shows the protocol which was followed. At the start of each study day, subjects undertook a short period of strenuous exercise which raised heart rate to about 150–160 beats per min, and as soon as the exercise ceased, the subject was told that the intensity of the breathlessness he was feeling was represented by the maximum point on the VAS. Identical exercise could be undertaken on other days of the study to provide a constant reference point. Thus, the VAS was 'calibrated' both with respect to the quantity and the quality of the sensation of breathlessness. Other laboratories have not followed this practice and may have compromised on the high level of reproducibility which it probably achieves.

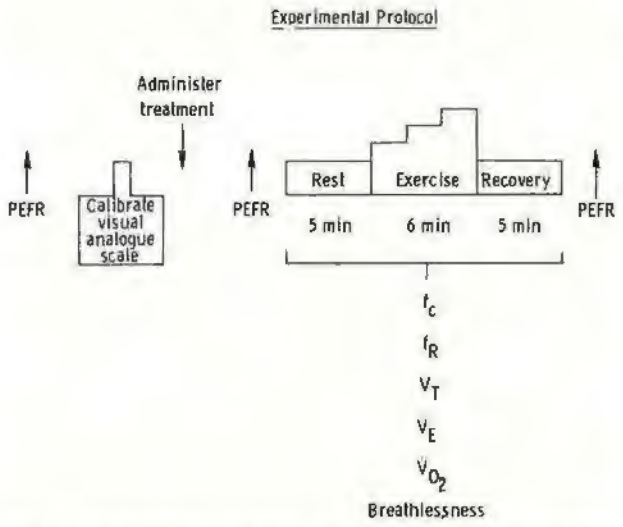

Fig. 1. Experimental protocol for studies on breathlessness. PEFR: peak expiratory flow rate; fc: heart rate; fR: respiratory frequency; VT: tidal volume; $\dot{V}_E$: minute ventilation; $\dot{V}_{O_2}$: oxygen uptake.

Other measurements and experimental design

During these studies, standard techniques were used to measure ventilation and its components, oxygen uptake, carbon dioxide production and heart rate. A constant environment was maintained throughout the study and the same personnel attended the subject [10].

In view of the subjective nature of the assessment of breathlessness, it was important to avoid bias in the design of the experiments, especially when drugs were studied. It was also important to reduce variation in the experimental results, wherever possible, in order to increase precision. Subjects were 'naive' and became familiar with the test and the VAS during preliminary sessions. Validations on the use of the VAS were performed in each subject. Treatments were compared on a within-subject basis under double-blind conditions and after randomization of the treatment order [10, 12, 13].

Validation in healthy subjects

Detailed results have been presented previously [10]. During submaximal graded exercise, ventilation and breathlessness increased and when exercise stopped, both returned towards the baseline. The relationship of breathlessness to ventilation or to oxygen uptake provided a convenient means of summarizing the response of subjects (fig. 2). The relationships between breathlessness and either tidal volume (VT) or respiratory frequency (fR) were more complex.

Validation of the methods with respect to reproducibility and sensitivity was regarded as essential. However, demonstration that the VAS was reliable in one group of subjects carried no guarantee that other groups of subjects would also use the VAS with reliability. For this reason, validation has been performed in each study. Occasional subjects did not show consistency and in accordance with the protocol, were excluded from studies during the preliminary phase.

Reproducibility was tested by comparing the response of subjects to identical periods of exercise performed one or two weeks apart. In general, individual subjects showed high levels of reproducibility [10, 13, 14]. Figure 2 shows mean relationships between breathlessness and ventilation which were highly consistent between the two tests. Between-subject variations, however, were considerable [10] and this has implications for using VAS to compare responses in **different** groups of subjects. Long-term reproducibility has less relevance to drug studies, most of which are conducted over short periods of time.

The ability of the VAS to detect real changes in breathlessness is termed the sensitivity of the test. In normal subjects this was tested by comparing exercise tests in the presence and absence of a low value inspiratory resistance (0.7 cmH_2O) under double-blind conditions, with randomization of the order and

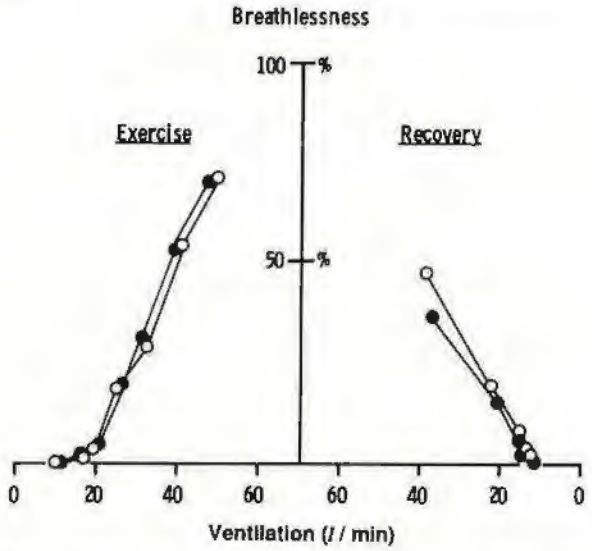

Fig. 2. Mean relationships between breathlessness and ventilation for six healthy subjects during identical periods of submaximal graded exercise. Increasing breathlessness during exercise is shown in the panel on the left, and decreasing breathlessness during recovery is shown on the right [13].

after 'anchoring' of the VAS [13, 15, 16]. It has been a consistent finding that the resistance is not detected at rest but the VAS shows greater breathlessness at the highest levels of ventilation during exercise. Adams presented data, at the Antwerp Meeting (1987), to show that his subjects did not indicate on the VAS an effect from a higher inspiratory resistance; this discrepancy may relate to the experimental design.

It is concluded that the relationship between breathlessness and ventilation is reproducible, and also sensitive to change, and therefore should be capable of detecting effects from active pharmacological agents. A final question concerns the specificity of the test *i.e.* is the VAS truly recording breathlessness. In this laboratory breathlessness has been induced by exercise to calibrate the VAS, while other investigators have used verbal descriptions of the sensation. Therefore, there may be differences between the sensations studied in different laboratories.

Sensations not related to exercise

Breathlessness has been assessed with VAS during exposure to raised levels of carbon dioxide and validations have been performed [17]. It was interesting to find that breathlessness in relation to ventilation was greater during hypercapnia than during exercise [10, 18, 19]. Similar findings have now been reported by several other groups. Measurement of breath-holding time provides an additional opportunity to assess whether drugs affect respiratory sensations [13].

Validation in patients

The test used in healthy subjects has been modified to assess dyspnoea in patients [20, 21]. The exercise loads were less and the reference point for the VAS was an activity in the patient's daily life known to induce marked breathlessness. Patients generally require more careful explanation of the VAS than young subjects working in a general scientific environment. Measurement of ventilation is also more difficult in patients especially in those with moderately severe respiratory impairment.

Reproducibility has been studied in a group of patients with chronic obstructive pulmonary disease [21]. Whilst some of the patients demonstrated a highly reproducible response to the same graded exercise, others showed considerable variability in the scores for breathlessness. It is concluded that the assessment of breathlessness in patients can be precise and reliable but a proportion of patients appear unable to use the VAS in a meaningful way. It is recommended, therefore, that clinical studies should incorporate tests of validation to determine how well the VAS is used in the study group.

The sensitivity of the test can be estimated without great difficulty in asthmatic patients, since bronchodilatation can be induced and would be expected to reduce breathlessness during exercise. In a group of asthmatic subjects, salbutamol increased peak expiratory flow rate (PEFR) by a mean value of 33% above values on placebo [21]. Three of the five patients indicated lower VAS scores for dyspnoea at given levels of ventilation after salbutamol. One patient increased his PEFR from 435–515 *l*/min and commented that he was less breathless after salbutamol but the VAS suggested greater breathlessness (fig. 3, patient 3). The conclusion must be, that some patients, even after careful explanation of the VAS and familiarization with the test, cannot use the VAS reliably. Clinical studies on mechanisms or treatment of dyspnoea probably should exclude prospectively such subjects in spite of the risk of statistical bias.

A more recent study, on the effects of indomethacin on dyspnoea in patients with diffuse parenchymal disease of the lung, has demonstrated the feasibility of including tests of validation within the study design [22].

Can the VAS be used to make comparisons between different subjects?

It has consistently been found that normal subjects use VAS to assess breathlessness in a personal and individual way [10]. Similarly, breathlessness in relation to standard ventilation is significantly different between patients [22]. The validity of using the VAS to compare different patients or groups of patients must therefore he questioned.

A more acceptable approach may be to compare the changes in VAS caused by a known intervention. For example, one patient may score breathlessness increasing from 2 to 8 units after walking 100 m while another shows a change from 4 to 5 units. Regardless of the baseline values, the first patient would appear to be indicating greater breathlessness because of the extent of the change.

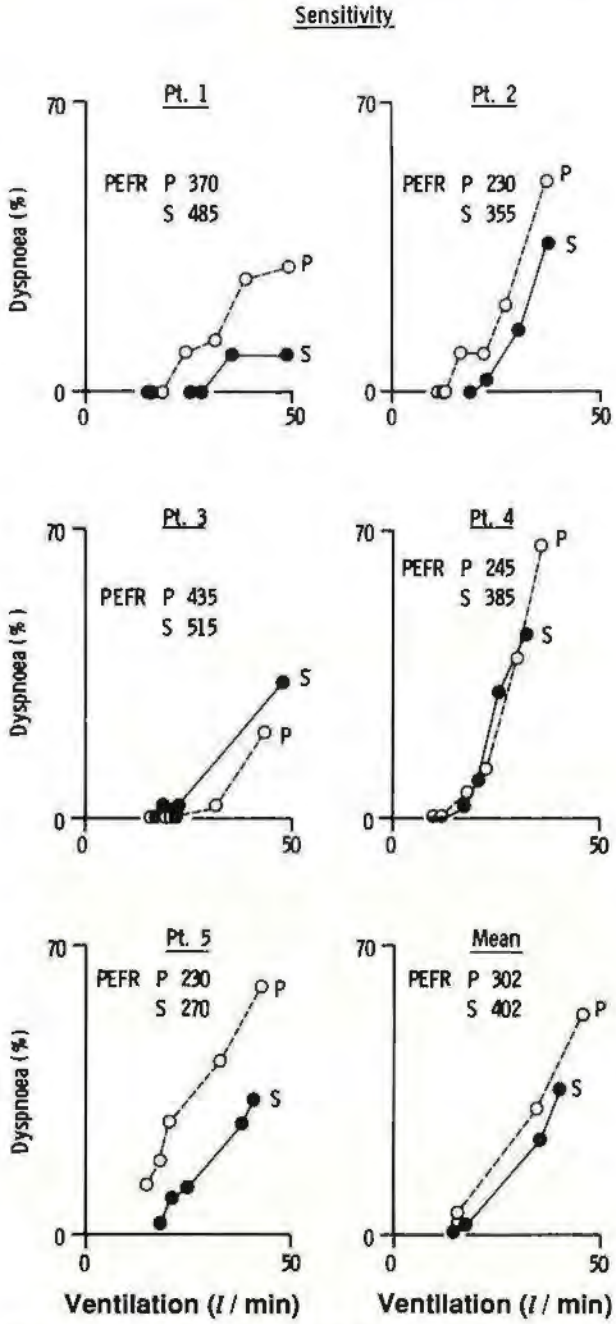

Fig. 3. Effects of salbutamol on the relationship between breathlessness and ventilation in five patients with asthma. Peak expiratory flow rates (PEFR) after placebo (P) or after salbutamol (S) aerosols are also shown [21].

Alternatively, the intervention might be a treatment and the change during therapy would provide a measure of its effect.

An example of this approach relates to multicentred studies on xamoterol, an agent for the treatment of mild or moderate heart failure [23]. Breathlessness experienced in daily life was assessed on VAS before and after three months of treatment with xamoterol or placebo. The study was double-blind in parallel groups of patients and involved random allocation of treatment. The trial population exceeded 900 patients. The mean change in VAS was from 44.8 ± 2.2 to 40.8 ± 2.1 (difference 4.0) on placebo and from 47.2 ± 1.4 to 33.0 ± 1.3 (difference 14.2) on xamoterol. The difference was highly significant ($p = 0.0001$).

In conclusion, there is now experience of the use of VAS to compare different groups of patients but the focus has been on changes during treatment rather than on single responses. The experimental design and the size of the population are important considerations.

Quality of dyspnoea

So far, I have described efforts to quantify dyspnoea. Attempts to discover differences in quality of the sensation have been less successful. Early studies, in which normal subjects shaded a silhouette to show the location of the sensation, suggested that breathlessness after exercise was localized to the sternum, whereas during hypercapnia it was located around the lower rib margin. More formal studies failed to confirm these findings [10]. Questionnaires have been used to study the quality of dyspnoea in various patient groups and have shown the presence of discomfort, particularly during inspiration, in patients with chronic obstructive disease of the airways [24].

Pharmacological manipulation

General

Two possible patterns of drug effect on dyspnoea have been described [25] and these are illustrated in figure 4. The first type of response includes reductions in ventilation and in breathlessness. Thus, in comparison with placebo, there is a regression down the line of relationship between breathlessness and ventilation. The second type of response consists of a change in this relationship so that breathlessness is reduced but ventilation is unchanged. Thus, the line of relationship moves towards the ventilation axis. In most circumstances, the second profile is more attractive for a therapeutic agent since it avoids disturbance of the control of breathing.

At this stage, a considerable number of known therapeutic agents have been assessed with the precise methods now available. It was unlikely that large effects would be discovered since these would have been apparent already in everyday clinical usage. An effect of the size demonstrated with salbutamol in asthmatic patients (see before) probably would be of some clinical interest.

Type I: Opioid

Morphine is known to be beneficial in left ventricular failure though the mode of action is not clear. Morphine has been used also in 'pink puffers' in the late stages of the disease and amelioration of dyspnoea appears to occur. Codeine at a single oral

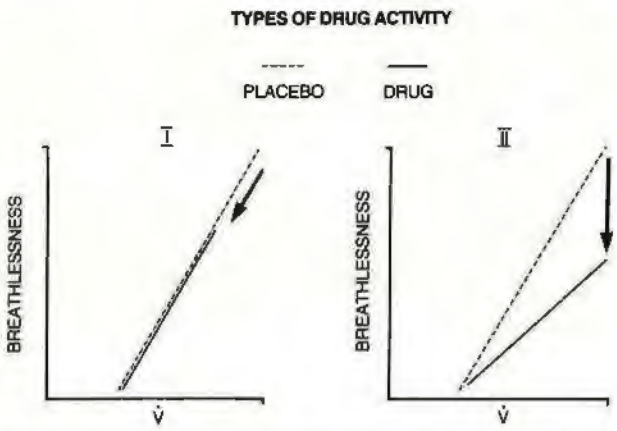

Fig. 4. Potential patterns of drug effects on breathlessness. In Type I breathlessness and ventilation both decrease and the line of relationship does not change. In Type II, ventilation is unchanged and breathlessness alone decreases.

dose of 60 mg was assessed in healthy subjects. Only small effects occurred but both breathlessness and ventilation during exercise decreased significantly [13]. Such changes were consistent with the Type I profile (fig. 4). Codeine did not prevent detection of an inspiratory resistance but permitted higher levels of carbon dioxide to be tolerated during breath-holding.

WOODCOCK *et al.* [26] studied dihydrocodeine in patients with the 'pink puffer' syndrome and, although they did not present the results in the form of breathlessness/ventilation plots, it would appear that proportionally breathlessness was more affected than ventilation. Such findings would not be consistent with a Type I effect, and in view of the contrast to codeine, further study would seem to be appropriate.

Type II: Centrally acting agents

Although there were claims that chronic administration of diazepam at doses of about 25 mg/day reduced dyspnoea in 'pink puffers' [27], the findings were not confirmed in a later study [28]. In normal subjects diazepam did not change breathlessness during exercise or hypercapnia and breath-holding was unaffected.

A small and statistically significant reduction in dyspnoea occurred after promethazine in 'pink puffers' [28] but no significant effects could be demonstrated in healthy subjects [16]. Efforts were made to look more closely at the components of promethazine's pharmacological activity by comparing mebhydrolin, a specific H_1 receptor antagonist with minimal sedative properties, and chlorpromazine, the archetypal phenothiazine [16]. Mebhydrolin was without effect but chlorpromazine depressed the relationship between breathlessness and ventilation (Type II; fig. 5). The mean reduction in breathlessness at the standardized ventilation was almost 20% and this was achieved without measurable sedation. This effect of chlorpromazine is the greatest seen in healthy subjects and similar in size to the effects of salbutamol in patients

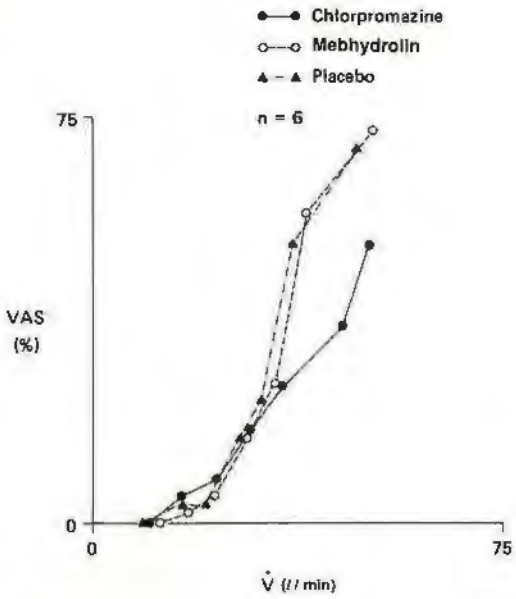

Fig. 5. Mean relationships between breathlessness (VAS) and ventilation (V̇) for six healthy subjects after placebo (▲), mebhydrolin (○) or chlorpromazine (●) [16].

with asthma. A definitive study of chlorpromazine in patients would be of considerable interest.

Bronchodilator agents

Reference was made earlier to the secondary effects on breathlessness which follow bronchodilatation in asthma. Salbutamol decreased the VAS score without changing ventilation [21]. In contrast, salbutamol in normal subjects affected neither ventilation nor breathlessness and similar findings occurred with ipratropium bromide [14].

Agents affecting prostanoids

The widespread occurrence of prostanoids raises the possibility that they might have modulating effects at a peripheral site of origin for the sensation of dyspnoea. In a double-blind study indomethacin, a widely used inhibitor of cyclooxygenase, was given at an oral dose of 50 mg and compared with placebo on a within-subject basis [15]. Minute ventilation ($\dot{V}E$) and the pattern of breathing were not significantly affected by indomethacin but breathlessness in relation to ventilation was significantly reduced (Type II profile). The size of the change was not large but might have indicated a possible role for prostanoids in normal subjects.

The next step was a study of patients in whom active inflammation may have been present in the lung. It was expected that the role of prostanoids would be exaggerated in this situation. Although the aetiology of breathlessness is not established in such patients, GUZ *et al.* [29] provided evidence that block of the vagus nerves caused a slower, deeper pattern of breathing and a reduction in dyspnoea in a proportion of patients with decreased lung compliance. A

neural mechanism involving stimulation by prostanoids might be postulated.

In a double-blind randomized study, the effects of acute and chronic administration of indomethacin were compared with placebo in breathless patients with diffuse parenchymal disease of the lung [22]. Indomethacin had no effect on the breathlessness/ventilation relationship or on the distance walked in 6 min.

The discrepancy between the findings in normal subjects and in patients is of some interest, particularly since it was contrary to expectation. Hypoxia during exercise occurred to a similar extent after placebo and after indomethacin treatment; patients in whom least desaturation occurred, showed no greater response to indomethacin. An increased hypoxic drive to respiration therefore, does not provide an easy explanation for the lack of effect in patients. The VAS is probably a less sensitive test in patients than in young, healthy subjects. In the study of normal volunteers [15] validation included tests of reproducibility and of sensitivity, whereas in the patient study [22], only reproducibility was assessed. An effect in patients might therefore have been missed for methodological reasons but the absence of effect on the walking distance provides further evidence that indomethacin genuinely lacked an effect.

Interventions affecting respiratory drives: role of the vagus

In healthy subjects, local anaesthesia of the vagus nerves at the base of the skull prolonged breath-holding and removed the associated sensation but did not alter the resting pattern of breathing [30, 31]. In certain patients, blocking the vagus nerves either by local anaesthesia or by surgical section, reduced the sensation of dyspnoea [32]. Effects were seen in patients with pulmonary infiltrations as well as in a proportion of patients with emphysema, and generally this was accompanied by a reduction in the frequency of breathing.

Administration of local anaesthetic agents by aerosol to patients with various pulmonary disorders, including chronic obstructive airways disease, suppressed cough but did not modify dyspnoea [33]. This suggests that sensory receptors in the large airways are not major contributors in the generation of dyspnoea. The aerosol had particles mainly in the size range 5–20 μm and therefore would have little effect on the unmyelinated vagal afferents which arise in the vicinity of the alveolus and pulmonary capillary at the J receptors described first by PAINTAL [34]. Thus, it is possible that activity of these receptors could explain the beneficial effects of vagal block on dyspnoea, which is consistent with the speculation that J receptors mediate dyspnoea in diseases associated with diseases of the alveoli or pulmonary circulation [35].

Some support for a role for J receptors being involved in breathlessness during exercise in normal subjects emerged from a study of β-adrenoceptors. An antagonist increased breathlessness during exercise and this could not be attributed to a change in bronchomotor tone [12]. It is possible, that a reduction in cardiac contractility caused a rise in pulmonary capillary pressure with associated stimulation of J receptor activity.

To test the J receptor hypothesis, it is necessary to interrupt the activity of the unmyelinated vagal fibres at their source close to the alveoli of the lung. There is experimental evidence from dogs suggesting that disodium cromoglycate given intravenously reduced the activity of J receptors in response to capsaicin [36]. When given by Spinhaler, disodium cromoglycate had no effect on breathlessness in healthy subjects, although this aerosol may not have achieved deposition in the relevant areas [14].

An alternative approach to testing the role of J receptors involves administering local anaesthetic by a specially designed aerosol producing particles small enough for alveolar deposition. Using a modified jet nebulizer, 2% lignocaine solution produced an aerosol with a mass median diameter of 1.7 μm (geometric standard deviation = 1.2 μm) determined by the Particle Measuring Systems Inc. laser system [37]. This aerosol, given to rats made tachypnoeic by pulmonary microemboli, reversed the tachypnoea but a similar quantity of lignocaine given by Wright's nebulizer (MMD 11.2 μm) did not have this effect. Since the tachypnoea was probably mediated by pulmonary 'C' fibres, these results provided support for the conclusion that the aerosol was achieving deposition at alveolar level in animals. A similar aerosol generator administered 5% lignocaine (MMD 2.5 μm; GSD 1.7 μm) to dyspnoeic patients with diffuse alveolar disease or chronic airflow obstruction. No dramatic benefit on dyspnoea or walking distance was apparent although the interpretation was hindered by a small reduction in forced expiratory volume in one second (FEV_1) after lignocaine.

In normal subjects, small particle local anaesthetic aerosols did not modify the ventilatory response to hypercapnia, but a small, nonsignificant reduction in breathlessness was reported [38]. On the other hand, the physiological responses to maximal exercise were unaffected by bupivacaine depositing at alveolar level and breathlessness was unchanged [39].

Even when small particle aerosols are administered for extended periods, doubts remain on whether sufficient amounts of drug are deposited in the alveoli to achieve a pharmacological effect. The output of these aerosol generators is low and the alveolar surface area is large. In studies on patients, the regions of the lung with the most advanced pathology may be least accessible to the aerosol. Thus, there are considerable experimental difficulties in assessing the role of J receptors in clinical dyspnoea but at this stage it has to be concluded that there is no dramatic evidence in support of a major role for them.

Conclusions

This review contains abundant evidence that VAS can be helpful in the assessment of breathlessness and a degree of precision is now possible that was unachievable only ten years ago. It is unfortunate that this precision for quantifying respiratory sensations was not available in time for the classical studies of Guz, Noble, Widdicombe, Campbell and others on curarization and nerve blocks during breath-holding, hypercapnia and loaded breathing.

Methodological advances have been accompanied by a clearer understanding of the limitations of the VAS. Casual use in uncontrolled studies is unlikely to yield useful data and the elements of experimental design merit close attention. Validation of the VAS has received consideration for good reasons and should continue as an ongoing process. The specificity of the test is now being discussed and the question arises whether different investigators are assessing exactly the same sensation. A psychological input to the study of perception may be valuable but the 'clinical' approach, taken so far, is closely identified with the ultimate goal, which is to develop treatments to benefit quality of life for the patient.

In the short-term, drugs are being used as pharmacological tools in the hope that they may disclose the mechanisms responsible for dyspnoea. Whilst it is indisputable that patients with disease giving rise to dyspnoea are of the greatest relevance, there seems to be a place for determining the pharmacology in normal subjects uncomplicated by disease. Discrepancies between health and disease have been seen with indomethacin, where a small benefit occurred in normal subjects but not in patients in spite of the expectation that prostanoids might have an augmented role in patients with parenchymal disease. Chlorpromazine reduced breathlessness in healthy subjects and the effect was probably of a magnitude which was of clinical significance. A study in patients would help determine whether there is a central effect of interest in the discovery of mechanisms or whether the step from health to disease is again doubtful.

Several therapeutic agents, have a primary effect on other systems and the effect on dyspnoea secondary. Included in this category are the bronchodilators such as salbutamol and agents improving cardiac performance such as xamoterol. For dyspnoea research, such agents may provide the means of testing how well symptomatic benefit can be measured.

In the early part of this decade, there was a surge of interest in dyspnoea but there are indications already that the pace has not been maintained. The clinical problem remains, however, and patients will surely welcome the therapeutic advance which may follow deeper understanding of the mechanisms at work in dyspnoea.

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References

1. Respiratory Diseases Study Group of RCGP. – Chronic bronchitis in Great Britain. *Br Med J*, 1961, 2, 973–979.
2. Fletcher CM. – The clinical diagnosis of pulmonary emphysema on experimental study. *Proc Roy Soc Med*, 1952, 45, 577–584.
3. Cotes JE. – *In*: Lung Function. 4th edition, Blackwell, Oxford, 1979, p. 265.
4. McGavin CR, Artvinli M, Naoe H, McHardy GJR. – Dyspnoea, disability, and distance walked, comparison of estimates of exercise performance in respiratory disease. *Br Med J*, 1978, 2, 241–243.
5. McGavin CR, Gupta SP, McHardy GJR. – Twelve-minute walking test for assessing disability in chronic bronchitis. *Br Med J*, 1976, 1, 822–823.
6. Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. – Two, six and 12 -minute walking tests in respiratory disease. *Br Med J*, 1982, 2, 1607–1608.
7. Borg G, Linderholm H. – Exercise performance and perceived exertion in patients with coronary insufficiency, arterial hypertension and vasoregulatory aesthenia. *Acta Med Scand*, 1970, 187, 17–26.
8. Aitken RCB. – Measurement of feelings using visual analogue scales. *Proc Roy Soc Med*, 1969, 62, 989–993.
9. Stark RD, Gambles SA. – A new system for assessing the effects of drugs on breathlessness. *J Clin Respir Physiol*, 1980, 16, 244P.
10. Stark RD, Gambles SA, Lewis JA. – 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. *Clin Sci*, 1981, 61, 429–439.
11. Morton PB, O'Neill PA, Stark RD, Stretton TB. – A demonstration of methods for studying breathlessness. *J Physiol*, 1983, 342, 8P–9P.
12. O'Neill PA, Morton PB, Sharman P, Marlow HF, Stark RD. – The effects of ICI 118, 587 and atenolol on the responses to exercise in healthy subjects. *Br J Clin Pharmacol*, 1984, 17, 37–41.
13. Stark RD, Morton PB, Sharman P, Percival PG, Lewis JA. – Effects of codeine on the respiratory responses to exercise in healthy subjects. *Br J Clin Pharmacol*, 1983, 15, 355–359.
14. Stark RD, Gambles SA. – Effects of salbutamol, ipratropium bromide and disodium cromoglycate on breathlessness induced by exercise in normal subjects. *Br J Clin Pharmacol*, 1981, 12, 497–501.
15. O'Neill PA, Stark RD, Morton PB. – Do prostaglandins have a role in breathlessness? *Am Rev Respir Dis*, 1985, 132, 22–24.
16. O'Neill PA, Morton PB, Stark RD. – Chlorpromazine – a specific effect on breathlessness? *Br J Clin Pharmacol*, 1985, 19, 793–797.
17. O'Neill PA, Morton PB, Sharman P, Percival PG, Stark RD. – Validation of hypercapnia as a model of breathlessness. *Clin Sci*, 1983, 64, 10P–11P.
18. Gambles SA, Stark RD. – Breathlessness during exercise and during rebreathing carbon dioxide. *J Physiol*, 1981, 316, 29P.
19. Stark RD, Gambles SA. – Effects of diazepam and promethazine on breathlessness induced by exercise or raised CO_2 in healthy subjects. *J Clin Respir Physiol*, 1980, 16, 220P–221P.
20. Stark RD, Chatterjee SS. – A new exercise test for clinical dyspnoea. *Pract Cardiol*, 1983, 9, 86–95.
21. Stark RD, Gambles SA, Chatterjee SS. – An exercise test to assess clinical dyspnoea; estimation of reproducibility and sensitivity. *Br J Dis Chest*, 1982, 76, 269–278.
22. O'Neill PA, Stretton TB, Stark RD, Ellis SH. – The effect of indomethacin on breathlessness in patients with diffuse parenchymal disease of the lung. *Br J Dis Chest*, 1986, 80, 72–79.
23. Franciosa JA. – Beta adrenergic modulation for heart failure. *Heart Failure*, 1987, 3, 135–136.
24. Stark RD, Lewis JA. – Asthma – expiratory dyspnoea? *Br Med J*, 1981, 2, 1121–1122.

25. Stark RD, O'Neill PA. – Dihydrocodeine for breathlessness in 'pink puffers'. *Br Med J*, 1983, 286, 1280–1281.
26. Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. – Effects of dihydrocodeine, alcohol and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Eng J Med*, 1981, 305, 1611–1616.
27. Mitchell-Heggs P, Murphy K, Minty K, Guz A, Patterson SC, Minty PSB, Rosser RM. – Diazepam in the treatment of dyspnoea in the 'pink puffer' syndrome. *Q J Med*, 1980, 49, 9–20.
28. Woodcock AA, Gross ER, Geddes DM. – Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in 'pink puffers'. *Br Med J*, 1981, 2, 343–346.
29. Guz A, Noble MIM, Eisele JH, Trenchard D. – Experimental results of vagal block in cardiopulmonary disease. *In*: Breathing, Hering-Breuer Centenary Symposium, R. Porter ed. Churchill, London, 1970, 315–328.
30. Guz A. – Effects of blocking the vagus nerves in man. *In*: Breathlessness, J.B.L. Howell and E.J.M. Campbell eds. Blackwell, Oxford, 1966.
31. Noble MIM, Eisele JH, Trenchard D, Guz A. – Effect of selective peripheral nerve blocks on respiratory sensations. *In*: Breathing, Hering-Breuer Centenary Symposium, R. Porter ed. Churchill, London, 1970, 233–246.
32. Stark RD, Guz A. – *In*: Dyspnoea, Symptoms. A Continuing Monograph Series. J. Conway ed. Pharmaceuticals Division of ICI, Cheshire, UK, 1984.
33. Howard P, Cayton RM, Brennan SR, Anderson PB. – Lignoeaine aerosol and persistent cough. *Br J Dis Chest*, 1977, 71, 19–24.
34. Paintal AC. – Mechanisms of stimulation of type J pulmonary receptors. *J Physiol*, 1969, 203, 511–532.
35. Paintal AC. – Thoracic receptors connected with sensation. *Br Med Bull*, 1977, 33, 169–174.
36. Dixon M, Jackson DM, Richards IM. – The action of sodium cromoglycate on 'C' fibre endings in the dog lung. *Br J Pharmacol*, 1980, 70, 11–13.
37. Stark RD, O'Neill PA, Russell NJW, Heapy CG, Stretton TB. – Effects of small-particle aerosols of local anaesthetic on dyspnoea in patients with repiratory disease. *Clin Sci*, 1985, 69, 29–36.
38. Guz A, Hamilton RD, Winning AJ. – The effects of local anaesthetic aerosols of different particle size on the response to CO_2 rebreathing in man. *J Physiol*, 1985, 358, 94P.
39. Hamilton RD, Winning AJ, Guz A. – Maximal exercise in normal man – effect of inhaled local anaesthetic aerosol depositing at alveolar level. *Clin Sci*, 1985, 68, suppl. 11, 46P.