Dyspnoea: Assessment and pharmacological manipulation

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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 Lindholm [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-
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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 cmH₂O) under double-blind conditions, with randomization of the order and

![Experimental Protocol](image)
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 be 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.
Sensitivity

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
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 H₁ 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 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 (Ve) 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 prostano­
ids might be postulated.

In a double-blind randomized study, the effects of ac­
ute and chronic administration of indomethacin were 
pared with placebo in breathless patients with 
diffuse parenchymal disease of the lung [22]. 
Indomethacin had no effect on the breath­
lessness/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, particu­
larly 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 reproduc­
ibility and of sensitivity, whereas in the patient study 
[22], only reproducibility was assessed. An effect in 
patients might therefore have been missed for metho­
dologica 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 gener­
ally 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, sup­
pressed 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 alveoli 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 ex­
cise 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 stimu­
ation 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 cromogly­
cate 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 aer­
sol with a mass median diameter of 1.7 µm (geomet­
ric 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% ligno­
caine (MMD 2.5 µm; GSD 1.7 µm) to dyspnoeic 
patients with diffuse alveolar disease or chronic 
airflow obstruction. No dramatic benefit on dysp­
noea or walking distance was apparent although the 
interpretation was hindered by a small reduction in 
forced expiratory volume in one second (FEV₁) 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 adminis­
tered 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 lungs 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. While 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

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