Introduction

Breathlessness is a common and distressing symptom in a number of disease states, yet the basic underlying mechanisms for the sensation remain incompletely understood and treatment (unless the responsible condition can be treated) is non-specific and often unsatisfactory. There is no precise borderline between the 'pathological' breathlessness of disease and the 'physiological' breathlessness of normal subjects during heavy exercise; with progressive respiratory impairment, for example, breathlessness occurs at decreasing levels of exercise and finally even with minimal exertion.

A major problem in unravelling the mechanisms of breathlessness has been the difficulty of quantifying the sensation in a reliable and reproducible way. In recent years, techniques for scaling sensations have been applied to breathlessness and this has allowed important experiments to be undertaken, shedding new light on mechanisms. A second problem relates to the definition of breathlessness, as distinct from other respiratory sensations. Some conflicting results between experimenters can be partly explained by differences in their understanding of the term breathlessness. Despite these problems, an improved understanding of the mechanisms of breathlessness is emerging. As yet, this has not led to any therapeutic advances but there is hope for the future.

Definition of breathlessness

Most people have experienced breathlessness and intuitively know what is meant by the term, although they would be at pains to describe the sensation in words. A working definition is needed when attempting experiments to quantify the sensation. Comroe has described it as 'difficult, laboured, uncomfortable breathing; it is an unpleasant type of breathing, though it is not painful in the usual sense of the word'.

In our own work with patients and normal subjects being asked to scale their breathlessness we describe it as 'the common experience of that feeling of an uncomfortable need to breathe'.

Patients generally say, if asked, that the breathlessness they experience currently is qualitatively similar to the breathlessness with heavy exercise they experienced before their illness; the only difference is that they now have the sensation with relatively minor exercise, or at rest. This is important because much experimental work on breathlessness has involved inducing the sensation in normal subjects; extrapolating this to the breathlessness experienced in disease states may or may not be valid.

Breathlessness in disease states

Before discussing basic mechanisms of breathlessness, it is worth considering what is known about its aetiology in different disease states. The conditions associated with the symptom of breathlessness can be grouped into three main categories, which are not mutually exclusive.

1. Conditions with an increased chemical or neurological drive to breathe

A neurological drive to breathe can result from diseases involving the lung interstitium such as pulmonary embolism, pulmonary oedema, pulmonary fibrosis and pneumonia. These may also be associated with hypoxia, giving an additional chemical drive to breathe. There is typically a high respiratory frequency and a low arterial PCO₂. Anaemia and acidosis are associated with a chemical drive to breathe. In the case of acidosis associated with diabetic keto-acidosis, the increased ventilation may not be associated with
breathlessness because of the impaired level of consciousness.

2. Conditions with an increased work of breathing

Obstructive airways disease (reversible or irreversible) increases the resistive work of breathing and is an important cause of breathlessness. Other conditions that produce an increase in the work of breathing include pulmonary infiltrations or congestion. In these conditions, an increased drive to breathe is required to overcome the hindrance to breathing.

3. Conditions of decreased neuromuscular power

These include conditions of the skeleton such as kyphoscoliosis and ankylosing spondylitis, those of the respiratory muscles such as the muscular dystrophies and those involving neural output to the respiratory muscles from the spinal cord such as poliomyelitis, polyneuritis and myasthenia gravis. Again, an increased drive to functioning muscles will be necessary to maintain adequate ventilation in these conditions both at rest and on exercise.

In all the conditions described, there is likely to be an increased drive to breathe (i.e. increased motor output to the respiratory muscles) whether or not this produces an actual increase in ventilation. With a normal respiratory apparatus, an increase in ventilation occurs (as in group 1 conditions). In conditions such as airways obstruction or neuromuscular disease (groups 2 and 3), an increased drive to breathe may not produce an appropriate increase in ventilation but is nevertheless associated with breathlessness.

Measurement of breathlessness

Until recently, breathlessness has been assessed by indirect methods which are too crude and unreliable to use in experimental situations, though can be useful in the clinical setting. The classical method is to grade breathlessness according to the limitations it places on exercise capacity, first described by Fletcher. The grades are wide and can only measure large changes in breathlessness. Another indirect method is to assess exercise tolerance, assuming that exercise is limited by breathlessness and at a similar intensity during each test. Classical incremental exercise tests on treadmill or bicycle are very difficult for disabled patients and rarely produce useful data. The simple 12 minute walking test gives a useful and repeatable index of the patient's everyday exercise tolerance. The test has recently been adapted as a self-paced walk on a treadmill which has the advantage that other relevant physiological variables can be measured and the patient can directly scale breathlessness (see below) during the exercise.

Over the past two decades a number of workers have employed psychophysical techniques to study the mechanisms of respiratory sensations, including breathlessness. These techniques involve subjective assessment of the presence and/or intensity of sensations. The most quantitative of such techniques do, however, depend on establishing a relationship between a sensory stimulus intensity and the perceived sensation. Attention has been focused on the relationship between actual and perceived changes in respiratory volumes and on the ability of individuals to identify resistive and elastic loads applied to the respiratory system both in terms of their detection thresholds and on magnitude. While these experiments have provided useful information about the neural pathways involved in the perception of these respiratory sensations, there is no particular reason to assume that these experimentally-induced sensory phenomena are related to the sensory experience of breathlessness. The fact remains that the stimulus for breathlessness is unknown and probably multifactorial so that psychophysical techniques are of limited use in its study.

A 100 mm visual analogue scale for quantifying sensations produced by resistive loading was described by Aitken in 1969. In subsequent years this technique has been validated (in terms of both reproducibility and sensitivity) for the direct quantification of breathlessness induced by ventilatory stimulation both in normal subjects and in patients with respiratory disease. It is now used in both clinical 'therapeutic' and in studies of the physiological mechanisms underlying the sensation. There are wide but consistent differences between normal subjects in their scaling of breathlessness for equivalent degrees of ventilatory stimulation, however produced. This is consistent with inter-subject differences in the scaling of other sensory modalities. Judgemental, cognitive and other non-sensory factors probably play a role in this variation between individuals.

An important factor in the use of the visual analogue scale is the labelling of the extremes and the instructions given to the subject. The low extreme is labelled 'not at all breathless'. The top extreme can either be labelled 'extremely breathless' or 'worst imaginable breathlessness' which would hopefully at least be consistent over time in an individual, or 'fixed' by reference to a severe level of breathlessness actually induced. The latter approach is only suitable for short term studies where the 'standard' can be remembered.

Mechanisms of breathlessness

The origin of the sensation of breathlessness remains
unknown but recent experimental evidence, taken together with previous work, has allowed a working concept to be developed. While this fits most of the known facts, it still leaves important questions unanswered and would be disputed by some workers in the field. The working hypothesis is that breathlessness arises when drives to breathe exist which are abnormal, either qualitatively or quantitatively, and which are translated at medullary level into a motor command. The 'motor command' would be the sum of all the nervous traffic to all of the muscles involved in the act of breathing. It may or may not result in an actual increase in ventilation but is associated with the sensation of breathlessness in either case. The evidence for this hypothesis is partly positive and partly negative, against alternative possibilities for the origin of the sensation of breathlessness.

Evidence for involvement of motor output from the respiratory 'centre' in the medulla comes from both anecdotes and careful experiments. Patients with disease of the medulla, such as poliomyelitis or glioma, involving the respiratory 'centre' area usually do not feel breathless, even though ventilatory drives of hypoxia, hypercapnia and lung deflation are all present; there is no increased motor output to the respiratory muscles, no ventilatory response. In one such patient being maintained on a ventilator it has been reported that the addition of CO₂ to the inspirate caused drowsiness but not breathlessness; in a similar patient breathlessness has been reported, however, and presumably the exact site of the medullary lesion is crucial.

The voluntary control of breathing, presumably originating in the cortex, has a descending pathway to the phrenic and intercostal anterior horn cells that is separate from the 'automatic' respiratory centre descending pathway. Adams and co-workers have shown, in both normal subjects and respiratory patients, that breathlessness is greatly diminished or absent during voluntary isocapnic hyperventilation compared with ventilation at the same level stimulated by exogenous CO₂. This finding has recently been confirmed in normal subjects, comparing voluntary isocapnic hyperventilation during exercise with the same total ventilation stimulated entirely by exercise. Additional work has shown that the voluntary and stimulated ventilation are the same in terms of pattern and mechanical work done. Thus the activation of respiratory muscle anterior horn cells in the spinal cord in the same manner, by the voluntary as by reflex pathways, has the same results as far as the development of respiratory muscle tension and shortening is concerned, but quite different results for breathlessness. This suggests that respiratory muscle afferent discharge (the same in the two cases) is unlikely to be relevant in the genesis of breathlessness; and that the respiratory centre in the medulla, by-passed in the voluntary pathway, may be an important site in its genesis.

A major theory for the mechanism of breathlessness has been that of 'length-tension inappropriateness'. This postulates that breathlessness arises in situations where the ventilation achieved is inappropriately small in relation to the neural drive to the respiratory muscles; the major sources of the sensation are thought to be the respiratory muscle spindles. There is a body of evidence in favour of the importance of respiratory muscle afferent information in sensing lung volume, change of volume and respiratory load (elastic or resistive). However, these sensations are not the same as breathlessness; there is preliminary evidence that normal subjects can distinguish the sensation of breathlessness from that of loaded breathing during the same experiment (L. Adams, personal communication).

There is other evidence against the origin of breathlessness being in afferent sensations from the respiratory apparatus. Many years ago it was reported that breathlessness could be experienced by subjects during respiratory muscle paralysis induced by curare, although later workers reported a reduction in the sensation of breathlessness and an increased breath-holding time after curarisation. Patients with complete transections of the spinal cord as high as C5/6 become breathless with lobar collapse, pulmonary embolus or pneumonia. Chest wall afferents therefore cannot be crucial to the sensation.

Another possibility is that chemical (hypoxia, hypercapnia, acidosis) or neurological (lung afferents) drives to breathe via the IXth and Xth cranial nerves may themselves be felt as breathlessness. This seems not to be the case unless a motor output to the respiratory muscles results. In a recent study, the synchronous discharge of non-myelinated afferents in the alveolar walls of normal man was elicited by the injection of the pepper alkaloid capsaicin into the right atrium; there was no ventilatory response and no breathlessness, but there was a raw burning sensation in the chest.

Coming to chemical drives to breathe, there is now evidence, in both normals made hypoxic during exercise and in patients whose oxygen desaturation during exercise is reversed, that hypoxia is a stimulus to breathlessness and this can be disassociated from its effect as a ventilatory stimulus. Nevertheless, for both hypoxia and hypercapnia it appears to the resulting motor output to the respiratory muscles that is more closely linked to the sensation of breathlessness. This has been shown in an experiment with an oscillating hypoxic or hypercapnic stimulus; both the ventilatory response and the sensation of breathlessness were reduced when the frequency of oscillation was increased, although the peak stimulus intensities were the same.
While abnormal drives to breathe, either chemical or neurological, are probably not the source of the sensation of breathlessness, without their accompanying respiratory motor output, there is no doubt that removing an abnormal drive to breathe usually has a beneficial effect on breathlessness and concomitantly reduces the associated breathing. Examples are relief of hypoxia, carotid body resection and vagal blockade or section.  

If it is accepted that breathlessness is likely to arise when an abnormal drive to breathe is translated into a motor command at medullary level, this still leaves important questions unanswered. What combination of receptors need to be activated to give rise to the sensation and what is their anatomical location? What part of the cerebral cortex is involved in the experience of breathlessness, assuming that cortical involvement is essential for a conscious sensation?

**Conclusion**

Recent experimental work using subjective scaling of the sensation of breathlessness has added to our understanding of this distressing symptom. A mechanism underlying all the situations in which breathlessness arises can now be proposed and has evidence to support it. So far, however, this increased understanding has not led to the development of specific treatments for the symptom and treatment must still rely on treating the underlying disease or, if this is not possible, on reducing the abnormal drive to breathe and/or generally obtunding conscious sensations.

**References**


Breathlessness.

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