Breathlessness in advanced disease

Claire N MacDermott

Sam Hjelmeland Ahmedzai

Abstract

Breathlessness is a distressing symptom that arises in many diseases. It has several pathophysiological causes involving peripheral and central receptors and modulated by cortical processing. Older people and patients with cachexia are more susceptible to breathlessness on exertion. Most patients can be assessed by physical examination, and simple investigations including haemoglobin concentration, oxygen saturation, electrocardiography and imaging (X-ray, ultrasound). Research has shown that careful use of opioids can reduce the sensation of breathlessness without compromising ventilatory control. Benzodiazepines also help, probably by their anxiolytic and sedative actions. The combination of an opioid and short-acting benzodiazepine is especially useful. Nebulized furosemide is a new approach that requires further research. Oxygen is indicated if oxygen saturation falls, but increased airflow around the face (e.g. with a fan) can also help. The combination of helium and oxygen can be more effective than oxygen alone. Non-invasive ventilation can be necessary in severe cases, such as neuromuscular disease. Non-medical approaches, including breathing training and relaxation, can also help. Infusions of carefully titrated opioid and midazolam can be used in the dying patient, together with an anticholinergic agent if there are noisy upper airways secretions ('death rattle').

Keywords benzodiazepines; breathlessness; cancer; chronic obstructive pulmonary disease; dyspnoea; exercise; motor neurone disease; opioids; oxygen

Definition

Breathlessness is defined as the subjective experience of breathing discomfort. It arises from physiological, psychological, social and environmental factors, and significantly affects daily activities. The term 'dyspnoea' is derived from the Greek for 'bad breathing' and in this article will be used interchangeably with 'breathlessness'.

Patient experience

Breathless is a frightening experience; in severe episodes, patients report feeling fear and panic with thoughts of dying. When they are breathless, patients may feel as if they are drowning or choking to death.

Claire N MacDermott ***BMed Sci (Hons) MBChB (Hons) MRCP*** *is Specialist Registrar in Palliative Medicine at Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. Competing interests: none declared.*

Sam Hjelmeland Ahmedzai ***BSc MBChB FRCP*** *is Emeritus Professor at the Department of Oncology at the University of Sheffield and Consultant Physician, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. Competing interests: none declared.*

Three elements contribute to the sensation of breathlessness:

- air hunger (an unpleasant sensation of the need to breathe, while being unable to increase ventilation)
- effort of breathing (discomfort and tiredness)
- chest tightness (feeling of constriction).

Patients whose episodes of shortness of breath have triggers will avoid these.[1] If the trigger is activity, avoidance leads to inactivity, further deconditioning and a vicious cycle of increased dyspnoea and social isolation.[2] Carers' experience of looking after a patient with advanced disease and dyspnoea is often negative, with high levels of anxiety and poor sleep that increase with the severity of the patient's dyspnoea.[3]

Epidemiology

Breathlessness is common in advanced diseases including chronic obstructive pulmonary disease (COPD), heart failure, motor neurone disease (MND) and cancer. In one study, the terminal stage of COPD was associated with dyspnoea in 56% of patients, compared with 32% of a comparable lung cancer group[4]; a British retrospective survey gave equivalent figures of 76% and 60%.[5] In patients with cancer, dyspnoea is not only associated with primary lung cancer: another study of 923 cancer outpatients found that 46% reported breathlessness but only 4% had lung cancer and 5.4% had lung metastases.[6] Cancers in which at least 50% of patients reported breathlessness included lung, head and neck, genitourinary, breast and lymphoma.[6]

In many chronic conditions, dyspnoea becomes increasingly prevalent and refractory to treatment with disease progression. It is a poor prognostic factor in the hospice setting.

Pathology and pathogenesis

The common pathophysiological changes that lead to breathlessness are described in Table 1. The main causes of dyspnoea are:

- increased chemical or neurological drive to breathe (e.g. by stimulation of chemoreceptors)
- increased work of breathing (e.g. cardiac failure, pleural effusion, pulmonary fibrosis)
- decreased neuromuscular power (e.g. MND, cachexia).

Chemical and neurological drives

Dyspnoea can be thought of as arising from a mismatch between incoming afferent impulses from sensory receptors and outgoing central motor activity to the thoracic wall muscles and diaphragm.

The chemical drivers controlling normal respiration are the response to hypercapnia and hypoxia:

- hypercapnia exerts its effect via increased $PaCO_2$, which is detected primarily in the medullary chemoreceptors (and partly in the carotid bodies)
- hypoxia is detected in the carotid bodies.

Central receptors: in healthy people, the drive in response to hypercapnia is more sensitive than that to hypoxia. However, hypercapnic drive can be blunted in patients with long-standing ventilatory failure, due to advanced COPD or MND.

Recent neurovascular imaging techniques have shed light on how the ventilatory drive is processed in conscious and

Causes of breathlessness in advanced disease

System	Example of pathology	Example of disease
Pulmonary	Airflow obstruction	COPD, asthma, cancer
	Reduced lung compliance	Pulmonary fibrosis, emphysema, pulmonary consolidation
	Pleural effusion	Cancer, heart failure
	Chest wall restriction	Neuromuscular disease, mesothelioma
	Diaphragmatic restriction	Ascites
	Ventilation–perfusion mismatching	Pulmonary embolism
	Cachexia affecting the respiratory musculature	Cancer, COPD, heart failure
Cardiovascular	Pump failure	Acute or chronic heart failure
	Pericardial effusion	Cancer
	Hypovolaemia	Bleeding, too rapid drainage of ascites
Systemic	Anaemia	Chronic disease, cancer
	Biological effects of ageing	• Decrease in lung elasticity • Decrease in respiratory muscle strength • Reduction in forced vital capacity and peak flow rate • Increased air-trapping • Deterioration in gas exchange • Reduction in ventilatory response to hypoxia and hypercapnia • Increased ventilatory response to exercise • Effects of co-morbid disease (e.g. heart failure)

COPD, chronic obstructive pulmonary disease.

Table 1

subconscious parts of the brain.[7] Air hunger is correlated with increased blood flow in the mesencephalic and hypothalamic areas, limbic and paralimbic areas (amygdala), motor areas and insula.

Opioid receptors in some of these areas are probably involved in the sensation of dyspnoea, as well as the regulation of normal breathing. There is evidence that endogenous opioids such as β-endorphin may be involved in the response to exercise in patients with COPD, as naloxone causes an increase in exercise-related dyspnoea.[8] Many opioid drugs initially cause a dose-related depression of ventilatory frequency and minute volume. When opioids are carefully titrated against the level of dyspnoea, there is no significant ventilatory compromise even when respiratory rate falls.[9] The danger arises when opioids are given in excessive doses relative to the patient's needs; there is then a risk that reduced ventilation in the presence of a blunted hypercapnic ventilatory drive will lead to acute hypercapnic respiratory failure.

Peripheral receptors: peripheral carotid body receptors respond primarily to decreased PaO_2 but are also sensitive to decreased arterial pH, respiratory oscillations of $PaCO_2$, increased blood temperature and chemical stimulants. Hypoxaemia results in the activation of peripheral chemoreceptors that send afferent impulses to the brainstem respiratory centres.

The peripheral receptors that are important for the regulation of breathing and the pathogenesis of dyspnoea also include the mechanical stretch receptors in the chest wall and diaphragm muscles, stretch receptors in the airways and J-receptors in the lung parenchyma. These send afferent signals to the brain about whether the respiratory pump and lungs are able to provide the necessary ventilation for the current level of activity.[10] In COPD, there is hyperinflation and reduced compliance of the lungs, which contribute to the reduced exercise tolerance and dyspnoea on exertion.[11] The J-receptors are stimulated by increased pulmonary pressure and fluid, for example in patients with pulmonary embolism or heart failure.

A further set of receptors – the ergoreceptors (or metaboreceptors) – has recently been found to be relevant in chronic dyspnoea.[10] These detect lactate and other metabolic by-products and can provoke breathlessness on minimal exertion, especially in the presence of muscular deconditioning.

Other factors: there is a clear relation between breathlessness and anxiety: for some patients, the sensory and affective dimensions, and triggers, of dyspnoea can as be important as the physical disease.[11] Ageing is associated with anatomical and functional changes that predispose to dyspnoea.

Diagnosis

Breathlessness is readily apparent when it is severe and the patient is panicking. However, it is important to distinguish breathlessness from other types of abnormal breathing pattern, especially: