Breathlessness in palliative care: a practical guide

ABSTRACT

Breathlessness is a common symptom for patients with terminal illness and can be challenging to manage. Breathlessness is acknowledged to be an interaction between body and mind. There are a variety of pharmacological and non-pharmacological therapies that can be beneficial. The holistic assessment of the breathlessness patient should enable delivery of a tailored package of care focused on relief of symptoms.

We all experience becoming out of breath during our day-to-day lives. It is a normal response to physical effort, and in itself is not detrimental. For many people with long-term conditions breathlessness can become chronic, and individuals find it uncomfortable to breathe, even when not physically exerting themselves.

When considering breathlessness, it is crucial to consider not only the physical sensation, but also the individual's reaction to that sensation. The concept of breathlessness as a phenomenon originating from the CNS, with both sensory and affective components, was first suggested by Comroe (Howell and Moran Campbell, 1966), but subsequent work using neuroimaging has established the concept of breathlessness as an interaction between body and mind (Herigstad et al, 2011; Pattinson and Johnson, 2014).

Which patients are affected and how much of a problem is it?

Breathlessness is a common symptom. Approximately 1–4% of consultations in primary care are related to breathlessness (Kroenke and Mangelsdorff, 1989; Charles et al, 2005). Within the secondary care environment, it has been estimated that 25% of acute medical admissions are related to breathlessness (Pearson et al, 1981). As the populations ages breathlessness becomes more common. In a large Australian study using a whole population approach the prevalence of breathlessness was nearly three times more common in those aged 65 years or over compared to those under 35 years (6.7% *vs* 16.9%) (Currow et al, 2009). The prevalence of breathlessness among those approaching end of life is estimated to be at least 50% for individuals with end-stage cancer, AIDS, heart disease, chronic obstructive pulmonary disease, neurological conditions and renal disease (Solano et al, 2006). In patients with lung cancer most patients described the presence of breathlessness and virtually all of these patients found it 'bothersome' (Yorke et al, 2015). As a symptom breathlessness can predict prognosis more accurately than more objective measures of physiology such as forced expiratory volume in 1 second (FEV_1) in patients with chronic obstructive pulmonary disease (Nishimura et al, 2002). In advanced cancer breathlessness is often multifactorial, and in terms of severity does not relate to pulmonary function or disease stage (Booth et al, 2008).

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Do I need to investigate or optimize the underlying diagnosis?

When assessing a patient with chronic breathlessness as a result of end-stage disease it is important to undertake a holistic assessment to determine what interventions may be helpful for the patient.

Investigations for the potential cause of breathlessness need to be carefully considered depending upon the patient's clinical status, wishes and needs. Before undertaking any diagnostic tests, it is important to consider what the potential therapeutic options are going to be and how the test will influence management. For example, a blood test to look for anaemia is relatively simple and may result in intervention which will improve symptoms, whereas a computed tomography scan in a patient with advanced cancer may simply confirm the presence of disease, but yield no beneficial therapeutic options for the patient.

Optimization of the underlying disease can have an impact. Simple strategies such as reviewing inhaled medication and devices can offer improvements in breathlessness. The ability of individuals to use inhaler devices varies with time. As chronic obstructive pulmonary disease progresses to severe emphysema, patients may not be able to generate appropriate inspiratory flow for dry-powder devices and swapping to a metered-dose inhaler, or metered-dose inhaler with spacer may be advantageous (Capstick and Clifton, 2012). Patients with recurrent malignant pleural effusions can benefit from insertion of long-term pleural catheters (Ost et al, 2014). For patients with heart failure, optimization of angiotensin-blocking therapies and beta-blockade may help to improve some symptoms of breathlessness.

> Optimal therapy for patients with breathlessness requires a holistic assessment of the patient's needs and goals, and an individualized approach to treatment.

Where appropriate, look for and treat reversible conditions that may be exacerbating breathlessness, such as anaemia, infection, pleural effusion, pulmonary oedema, bronchospasm or thromboembolic disease, and optimize underlying disease.

What actually works and what should I do?

Optimal therapy for patients with breathlessness requires a holistic assessment of the patient's needs and goals, and an individualized approach to treatment. Multidisciplinary assessment can improve quality of life considerably and can involve pharmacological and non-pharmacological therapies.

Non-pharmacological therapy

A meta-analysis of non-pharmacological therapies showed that breath training, walking aids, neuro-electrical stimulation and chest wall vibration all seem to be effective for the relief of breathlessness in patients with advanced disease, with the highest level of evidence for neuro-electrical stimulation and chest wall vibration (Bausewein et al, 2008). Most patients in these studies had a diagnosis of chronic obstructive pulmonary disease, but other conditions were included in some studies. In reality, neuro-electrical stimulation and chest wall vibration are frequently unavailable outside of specialist or research settings, and often require multiple clinic visits over a period of time – so in practice may be less useful for patients with the most advanced disease.

Clinicians should ensure that all patients are assessed by physiotherapy and occupational therapy services to see whether breathing training and walking aids would be beneficial.

Handheld fans

Handheld fans are cheap, portable and safe and can provide relief from breathlessness regardless of aetiology. The mechanism of action for fans is thought to be via stimulation of receptors in the face and nasopharynx, which then reduce the perception of breathlessness. The concept has long been recognized in normal subjects (Schwartzstein et al, 1987), and has subsequently been demonstrated to be of benefit in patients with advanced disease (Galbraith et al, 2010; Luckett et al, 2017). There are few downsides to offering patients a handheld fan, and their use can easily be incorporated into a self-management plan.

Pulmonary rehabilitation

Pulmonary rehabilitation does not alter the underlying physiology of advanced respiratory diseases, but attempts to improve symptom management and functional ability. Pulmonary rehabilitation is well established for patients with chronic obstructive pulmonary disease. A meta-analysis of 65 randomized controlled trials of pulmonary rehabilitation for people with chronic obstructive pulmonary disease demonstrated a statistically and clinically important improvement in breathlessness (McCarthy et al, 2015). The evidence basis for pulmonary rehabilitation for patients with interstitial lung disease is less robust. There is still evidence of improved breathlessness and quality of life during the programmes, but it is unclear whether the effect is sustained once the programme ceases (Dowman et al, 2014). Herigstad et al (2017) demonstrated changes to the rating of breathlessness and breathlessness-anxiety over a course of pulmonary rehabilitation using functional magnetic resonance imaging. They demonstrated that the brain responses became less dependent upon learned associations, thus reducing 'over-perception' of symptoms. One downside is that patients with more advanced disease are often unable to attend pulmonary rehabilitation, although one study demonstrated improvements via 15 in-home tele-treatment sessions (Marquis et al, 2015). The authors are also aware of some local hospices offering palliative pulmonary rehabilitation to patients excluded from the traditional model, with good results (Lennard et al, 2010).

Psychological therapies

The relationship between breathlessness and anxiety is well recognized and supported by studies examining functional neuroimaging (Herigstad et al, 2017). Enhanced perception of breathlessness may be associated with more frequent exacerbations of chronic obstructive pulmonary disease (Scioscia et al, 2017). In a small pilot study of cognitive behavioural therapy no changes were evident in the perception of breathlessness, but there were meaningful improvements in exercise capacity (Williams et al, 2015). The provision of a self-help manual using cognitive behavioural therapy techniques has been associated with improvements in breathlessness, as well as a reduction in use of health-care resources in people with end-stage chronic obstructive pulmonary disease (Howard and Dupont, 2014). It is important to assess the degree to which anxiety may be driving symptoms and consider appropriate psychological interventions.

Multi-component therapies

An increasing amount of evidence is emerging to show that multi-component therapies provide meaningful improvements in breathlessness to patients. The Cambridge Breathlessness Intervention Service, which uses a variety of individualized non-pharmacological and pharmacological interventions, has demonstrated cost-effective improvements in breathlessness for patients with advanced cancer; factors important to patients, such as distress, fear and anxiety and lack of confidence in self-management, all improved (Farquhar et al, 2014). Further

analysis of this service for patients with non-malignant disease was less clear cut in terms of benefits relating to breathlessness, but some of the qualitative improvements remained (Farquhar et al, 2016).

Conversely, a breathlessness support service in London comprising a short-term, single point of access service integrating palliative care, respiratory medicine, physiotherapy and occupational therapy showed symptomatic improvements which were not diagnosis-specific (Higginson et al, 2014). Interestingly the intervention demonstrated a statistically significant survival advantage at 6 months compared to the control group, although this applied only to the patients with non-cancer diagnoses.

The Respiratory Distress Symptom Intervention used a combination of controlled breathing techniques, cough easing techniques, acupressure and an information pack. In a pilot study this demonstrated improvement in breathlessness as measured by the Dyspnoea-12 score at 12 weeks in patients with lung cancer (Yorke et al, 2015). This intervention has not been assessed yet in patients with non-malignant disease.

Pharmacological therapy

Most drugs provide only modest symptomatic benefits in treating breathlessness, and all have undesirable side effects. They should be used at the lowest effective dose, with regular review to ensure that drugs that are no longer beneficial are discontinued.

Opioids

Low dose oral opioids have been associated with a small benefit in the palliation of breathlessness (notably morphine and dihydrocodeine), but there are concerns regarding the size of the trials and the potential for side effects (Barnes et al, 2016). Clinicians often worry about respiratory depression with opioids, but the commonest side effects are drowsiness, nausea and vomiting, and constipation (Barnes et al, 2016).

A meta-analysis of 63 papers found no evidence of significant or clinically relevant respiratory adverse events resulting from opioids when used in chronic breathlessness, although small effects were noted (Verberkt et al, 2017). A further large prospective study in patients with chronic obstructive pulmonary disease on long-term oxygen therapy showed a linear relationship between opioid dose and mortality (despite attempts to correct for disease severity) after a total daily opioid equivalent dose of 30 mg per day was reached (Ekström et al, 2014).

Low dose opioids can be effective for individual patients in addition to other strategies. A typical starting dose would be 2.5–5 mg immediate release morphine (if no contraindications) or 5–10 mg sustained release morphine twice daily. In view of safety concerns, clinicians should avoid titrating doses to levels higher than 30 mg morphine equivalent per day, especially when chronic use is anticipated.

Benzodiazepines

The use of benzodiazepines for breathlessness is not associated with relief of breathlessness or prevention of episodic breathlessness events (Simon et al, 2016). There is also concern regarding increased adverse events, particularly drowsiness and somnolence. In addition, a prospective safety study of the use of benzodiazepines in patients with advanced chronic obstructive pulmonary disease showed a modest increase in mortality (Ekström et al, 2014). Owing to the nature of this study causality cannot be attributed, but this does suggest that benzodiazepines should not be used first line for the treatment of breathlessness. Clinical experience suggests that benzodiazepines are best reserved for patients in whom breathlessness is associated with significant anxiety or in patients in the last days of life where severe breathlessness is a cause of considerable distress (a group who have largely been omitted from clinical trials).

Oxygen and ventilatory support

Oxygen

Many patients and clinicians feel oxygen to be a useful treatment in all instances of breathlessness, but there are significant downsides, including restriction of activities, impairment of communication with loved ones, cumbersome equipment, fire hazard, discomfort from interface and mucosal drying. In reality, not all patients will benefit. It seems that much of the symptomatic relief relates to air flow around the nose and mouth: Abernethy et al (2010) demonstrated in non-hypoxaemic subjects (PaO_2 >7.3 kPa) that oxygen delivered by nasal cannulae conferred no additional benefit than room air. This was subsequently supported by a meta-analysis which found an inconsistent benefit from oxygen in patients with cancer and chronic obstructive pulmonary disease (Cranston et al, 2008).

The British Thoracic Society guidelines recommend that the use of oxygen in a palliative care setting is restricted to those patients where oxygen saturations are less than 90% (O'Driscoll et al, 2017). They also highlight that there is no role for routine monitoring of oxygen saturations providing the patient is comfortable in the last few days of life (O'Driscoll et al, 2017). Thought needs to be given to whether continuous oxygen is required, short burst or ambulatory (or a combination), and the practicalities of equipment given the patient's usual place of residence. A small subgroup of patients (often with interstitial lung disease) will require high flow oxygen towards the end of their life for symptom control, which may limit the potential place of care because of the practicalities of delivery.

Non-invasive ventilation

The use of positive pressure non-invasive ventilation can be of benefit in some situations for patients with breathlessness. Nava et al (2013) demonstrated that the use of non-invasive ventilation for palliation of breathlessness in patients with solid tumours was more effective than oxygen alone in terms of relief of breathlessness and need for symptomatic

KEY POINTS

- Breathlessness is very common in patients towards the end of life, regardless of their underlying diagnosis, and should be actively looked for and managed.
- Where appropriate, reversible conditions that may be exacerbating breathlessness should be sought and addressed.
- Optimal therapy for patients with breathlessness requires a holistic assessment of the patient's needs and goals, and an individualized approach to treatment.
- Multidisciplinary assessment can improve quality of life considerably and can involve pharmacological and non-pharmacological therapies.
- Drugs provide modest symptomatic benefits in treating breathlessness and should be used at the lowest effective dose, and only continued if helpful.
- Oxygen is not a panacea for all breathlessness and has significant downsides. Some patients will benefit, but others will respond to the air flow generated by a handheld fan. At the end of life symptomatic relief is more important than treating the oxygen saturations.

relief with morphine. The relief of breathlessness came at a cost in terms of discomfort from the mask, with a discontinuation rate of non-invasive ventilation of 11%. The concept that non-invasive ventilation can improve the sensation of breathlessness, but needs to be balanced against the discomfort of the mask, was also found in the 3CPO trial examining the use of non-invasive ventilation *vs* oxygen in acute pulmonary oedema (Gray et al, 2008). The use of non-invasive ventilation in patients with motor neurone disease is associated with a survival benefit, as well as improvements in dyspnoea (Bourke et al, 2006). Before initiation of therapy, it is important to consider the possibility of discontinuation or withdrawal of non-invasive ventilation at some point in the future (Association for Palliative Medicine of Great Britain and Ireland, 2015).

Conclusions

Clinicians' understanding of the sensation of breathlessness is advancing but remains imprecise, and future research should aim to address a number of key areas. Which therapeutic interventions are more likely to be of benefit in certain clinical situations needs to be determined: this may rely on the development of biomarkers or phenotypes of breathlessness. Clarification of how best to measure response to therapies is essential; for example, using mastery of breathlessness and impact on ability to undertake functional activities rather than purely intensity of symptoms. There are gaps in understanding of current pharmacological therapies: the evidence base needs to be extended to newer opioid preparations, and potentially the use of novel therapies such as low dose neuropathic agents should be studied, as these have shown benefit in chronic pain and other conditions with a significant central component. A large challenge remains overcoming the obstacles to researching breathlessness in patients in the last few days of life.

As breathlessness is such a common symptom, healthcare organizations need to take the available evidence base and ensure it is integrated into day-to-day practice as well as the development of truly multimodal holistic approaches for assessment and treatment.

The management of breathlessness in end-stage disease is complex, but should be patient centred to ensure that the therapeutic interventions are appropriate for the individual. A multidisciplinary approach ensures that disease-specific strategies, non-pharmacological and pharmacological therapies can be used effectively together and tailored to the individual needs of the patient. **BJHM**

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