Breathlessness in adults: epidemiology, mechanisms and management

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AIMS

To summarise the evidence regarding the:

- epidemiology,
- mechanisms
- management of the symptom of chronic breathlessness in adults.

Greater detail can be found in the ERSMonograph on palliative care in respiratory disease due to be published September 2016 and launched at the ERS Congress 2016.

SUMMARY

Introduction

Chronic breathlessness is that which persists despite optimal management of the underlying condition, and leads to negative consequences for the person concerned, and their families, in all aspects of life: physical, psychological, social, financial and spiritual. It is common and yet breathlessness is poorly recognised by clinicians as anything other than a pointer to the underlying cause.[1] Thereafter, once the pathophysiology has been treated as well as possible, the clinician tends not to see breathlessness itself as a target for intervention. As a consequence, breathlessness may not be systematically assessed regarding the patient’s experience and impact on their lives by the clinician, and the patient in return does not see that these concerns are legitimate to discuss with the doctor.[2] However, chronic breathlessness is emerging as a clinical syndrome in its own right, with evidence based interventions targeted at the mechanisms which are being delineated for the genesis and perception of breathlessness.[3]

Epidemiology

Chronic breathlessness is common, with population prevalence ranging from 9 to 61% depending on the population studied and the definition of breathlessness.[4-9] A household survey in South Australia found a prevalence of chronic breathlessness (at least 3 months out of the last six; modified Medical Research Council [MRC] dyspnea scale >1) of 9%, with symptoms attributed by the person most commonly to lung pathology.[4] The Health Survey for England 2011 found that 15% of men and 26% of women said they had experienced breathlessness (>2 MRC dyspnea scale) at some point in the previous year.[10] A Norwegian urban population survey found 13% with ‘moderate dyspnea on exertion’ using a modified version of the British Medical Research Council’s Committee on Research into Chronic Bronchitis questionnaire.[11] Breathlessness is more commonly reported by women and older people where approximately one third are affected.[6, 12] Some subpopulation seem to have a particularly high prevalence, e.g. older Korean women who smoke (prevalence 61%).[8]

Breathlessness is common in common medical conditions and worsens in the weeks prior to death [12, 13]. Prevalence estimates for non-malignant cardiorespiratory diseases range from 60 to 88% (heart failure) and 90 to 95% (COPD).[14] In cancer, depending on the tumor site, stage of disease
and setting of the study the prevalence varies between 10 and 79%.[15] Of note, breathlessness can be experienced by cancer patients in the absence of pulmonary involvement due to a variety of mechanisms including cachexia-related loss of skeletal muscle and fatigue and low maximal inspiratory pressures with evidence of respiratory muscle weakness.[16, 17] In one study 78% of bereaved carers perceived that the person who had died from cancer had been breathless.[18]

Breathlessness is associated with health service use. Primary care studies show breathlessness as a reason for encounter to comprise 1% of all consultations.[19, 20] This may be an underestimation as encounters due to first report of breathlessness or for continued symptom could not be distinguished in the Currow paper [19] although the Frese [20] data showed just over 40% encounters were for continued problems. Again, breathlessness was reported as a reason for encounter more often by women and increased by age. The most common underlying cause of breathlessness was chronic lung disease, consistent with other literature.[21] People with breathlessness were more likely to be seen in their own home or in a care home and more likely to be referred to the emergency department (ED).[19]

In a national survey of EDs in the USA, shortness of breath was the primary reason for 2.7% of all presentations across all age groups.[22] In a single hospital study in Norway, breathlessness was the third most common reason to attend (9%).[23] In palliative care patients with advanced disease presenting to the ED, the proportion is even higher (25%) and breathlessness was the most common presentation.[24] Patients presenting with breathlessness and heart failure or COPD are more likely to be admitted to a hospital (88% with heart failure, 60% with COPD)[25, 26] and breathlessness intensity on arrival is a predictor of admission (>8/10 numerical rating scale) or discharge (<3/10).[27]

Breathlessness is a predictor of poor prognosis[5, 28, 29], both of short and long term survival. [30, 31]

**Mechanisms**

The respiratory motor areas of the brain receive information and process the information according to the ventilator requirements of the body. A ventilator “command” (neural respiratory drive [NRD]) is then generated with an accompanying corollary discharge to perceptual areas. If the NRD exceeds the capacity for ventilator response, there is a “mis-match” between the NRD as sensed via corollary discharge, and afferent feedback from mechanoreceptors of the respiratory system.[32]

**Central mechanisms**

Much of what we know about central pathways involved in breathlessness perception is from functional magnetic resonance imaging (fMRI), and adds to the work on receptors and receptor pathways.[33] It confirms that the patient sensations of intensity and unpleasantness are distinct. Most work to date has been done in models of acute induced breathlessness, however there is emerging evidence that the processing of chronic breathlessness, whilst similar, has important differences: involvement of the frontal associative cortex accessing memories and fears;[34] evidence of “vigilance” even at rest and in comfort.[35] The nature of the PET and fMRI scanning processes (confined space, the requirement to lay flat for significant lengths of time) has restricted these imaging techniques in the study of chronic breathlessness. Other techniques such as magnetoencephalography is a feasible option for further study and allows breathlessness to be induced by physical exertion. [35]

**Peripheral mechanisms**

There are many peripheral sensory afferent sources implicated in the genesis of breathlessness: blood gas status; lung and chest wall position and movement; cool airflow across the face and nasal
mucosae; and skeletal muscle.[32] These are summarised in the ATS consensus statement on dyspnea by Parshall et al, 2012.[32] There is some evidence to support the use of airflow in laboratory studies, phase 2 and 3 clinical trials, and the placebo arm of oxygen trials.[36-43]

Skeletal muscle plays an important role, probably related to inflammation, and neurohormonal changes, and begins to explain the origin of the link between muscles, increased sympathetic drive, breathlessness and inflammation. This seems to be a factor in COPD,[44] heart failure (where decreased mechanical efficiency, and an increase in glycolytic type II fibres results in enhanced lactic acid production and impaired recovery of phospho-creatine stores [45]) and cancer. Cancer cachexia syndrome results in preferential skeletal muscle loss and is associated with breathlessness even if there is no direct lung pathology.[16, 46] At least in COPD and heart failure, the oxidative capacity appears to be partly reversible with rehabilitation, and there is some emerging evidence in cancer and HF to suggest that a nutritional approach is needed as well as exercise, e.g. with diet supplementation of polyunsaturated fatty acids (PUFA) and creatine.

There is widespread distribution of mu opioid receptors throughout the central and peripheral nervous systems. Whilst there is evidence to support the role of central mu receptors in modulating chronic breathlessness,[47, 48] the role of peripheral opioids receptors has not been delineated. Serotonin receptors also appear to be important in the perception and genesis of breathlessness and serotonin seems to play a role in the control of respiration and generation/perception of breathlessness perhaps due to modulation of brain stem centres responsible for respiratory rhythm and/or of centres involved in the perception of breathlessness.[49]

Management

Breathlessness is a multi-dimensional subjective experience, with intensity and unpleasantness, emotional response and restrictive functional consequences. [50] Pulmonary rehabilitation (PR), addresses many of these domains (e.g. patient education for better self-management, cognitive support, physical conditioning and exercise, group interaction) and is standard therapy for people with COPD.[51] However, implementation is suboptimal due to poor knowledge of the intervention by both patients and clinicians; poor clinicians’ knowledge of how, when and where to refer; access difficulties for patients; and clinicians’ lack of engagement with interventions which promote exercise behaviour change.[52, 53] Complex interventions using a similar approach, but tailored to people of poorer performance status, have been developed, piloted and tested in trials.[54-61] Three adequately powered randomised controlled trials [56, 58, 60] confirmed benefit in terms of reduced breathlessness intensity,[56] reduced distress due to breathlessness [58] and improved mastery over breathlessness.[60] In lung cancer, benefit has been shown to be as good from a single session of training as from three. [59] This complex approach has been described as “Breathing, thinking and functioning” and is the frame used by the Cambridge Breathlessness Intervention Service (http://www.cuh.org.uk/breathlessness-intervention-bis). Simple cool airflow from a battery operated hand held fan seems to be a useful and inexpensive intervention. [38, 40, 62]

The best evidence in favour of a pharmacological intervention is for low dose, oral, sustained release morphine.[63-66] A response of 1 point on a numerical 0-10 rating scale is a moderate effect size rated as clinically important; smaller than that for acute breathlessness. [67] Over two thirds respond, over half of whom have done so by 10mg oral morphine in 24 hours. Over 90% of responders have done so by 20mg oral morphine per day.[64] Younger people with higher baseline breathlessness seem to be more likely to respond.[68] Low dose oral opioids appear to be safe even in people with advanced lung disease; there was no associated excess mortality or hospital admission in people with advanced COPD taking doses of ≤30mg oral morphine equivalent/day.[66] Care is needed to manage side-effects such as constipation.

There is no level 1A evidence as yet for other drugs such as benzodiazepines [69] or selective serotonin reuptake inhibitors (although there is a current phase 3 trial due to report in 2017) or nebulised furosemide. There is phase 3 trial evidence that buspirone is not effective compared to
placebo. [70]Nebulised saline may be of help in reducing breathlessness and helping with mucous clearance in people with COPD. [71]

REFERENCES

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