

Breathlessness Research Interest Group, 8th Annual Meeting

7th November 2014

Institute of Public Health, University of Cambridge

Organised by the Cambridge Breathlessness Research Group, Drs Sara Booth & Morag Farquhar.

Breathlessness remains a challenging symptom, common to a multitude of malignant and non-malignant diseases, for which there are limited effective therapies once disease control is optimised. The American Thoracic Society statement on dyspnoea reports that:

- i) Progress in dyspnoea management has not matched progress in elucidating underlying mechanisms;
- ii) There is a critical need for interdisciplinary translational research to connect dyspnoea mechanisms with treatments;
- iii) There is a need to validate dyspnoea measures as patient-reported outcomes for clinical trials.¹

There are challenges to researching breathlessness but consensus exists regarding a rational approach to designing adequately powered interventional studies to allow comparison between these in the future.² As such, research into the many dimensions of breathlessness and its significance to patients and their carers has increased over the years.³ This meeting is convened yearly to bring together researchers across various disciplines including respiratory physicians, anaesthetics, medical humanities, engineering and palliative care, to further understanding of the symptom, discuss new techniques and advances in research, and pave the way forward for future studies and interventions.

Presentation 1

Using MEG scanning to understand refractory breathlessness

Prof Miriam Johnson

Central (neural) mechanisms of breathlessness are yet to be fully understood. Although much has been elucidated with the advent of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), mostly these have been on healthy volunteers using models of induced acute breathlessness.⁴ Magnetoencephalography (MEG) scanning is a form of functional brain imaging which detects changes in magnetic fields generated in neurones when they transmit signals. These result from variations in neurotransmitter levels which alter electrical currents. MEG therefore differs from fMRI where changes in brain activity are inferred from measured changes in blood flow due to altered metabolic activity. It has advantages in terms of better patient tolerability, such as the ability to sit upright in the machine, and it allows direct measurement of neuronal activity in response to the patient's circumstances for example, exercise which can be done simultaneously in the scanner.

Professor Johnson's team are using MEG to study patients with chronic breathlessness and their neural responses to therapeutic interventions such as cool air across the face. They hope to develop methodology for future studies and confirm whether MEG imaging will be key to exploring the mechanisms by which patients perceive breathlessness.

Presentation 2

Neuroimaging of respiratory control in the human periaqueductal gray to understand brain mechanisms in breathlessness

Dr Kyle Pattinson

The brain is the final common pathway in various sensations such as pain, fear and breathlessness. Understanding the neural pathways involved will improve our understanding of breathlessness and therapies could potentially be targeted to these central mechanisms.⁴

The periaqueductal gray (PAG) is a small structure located superiorly in the brainstem and as it sits at a junction between the cortex and brainstem, is key in the emotional and mechanical control of breathing. We know from animal models that the PAG is involved in active and passive coping strategies and through connectivity to other parts of the brain, its activity can be up- or down-regulated in response to different situations such as pain or breath-holding.⁵ Until recently, there have been difficulties with poor resolution of functional imaging of the area to elucidate PAG activity. However, Dr Pattinson's group are investigating new imaging techniques including diffusion tractography (a form of MRI) to define PAG structure and activity and therefore provide greater understanding of the neurophysiology of breathlessness.

Presentation 3

Pharmacological approaches to palliating breathlessness: what's new?

Prof David Currow

Professor Currow challenged our thinking surrounding evidence-based medicine for three pharmacological approaches to breathlessness: oxygen therapy, opioids and benzodiazepines, and nebulised opioids.

It is well known that long-term oxygen therapy provides survival benefit for hypoxaemic COPD patients, however a Cochrane systematic review by Uronis et al favoured oxygen over air for patients who were breathless but did not qualify for home oxygen.⁶ This contrasts with the commonly accepted evidence base and shows that oxygen may provide some symptomatic benefit for patients. A further small study (of 32 patients) by Campbell et al showed that although the majority of patients gained no benefit from routine oxygen, approximately 10% of patients did require oxygen to relieve distress from dyspnoea at the end of their lives so perhaps we should not hastily disregard oxygen.⁷

Opioids have long been used for breathlessness with most evidence supporting regular low dose oral morphine. Professor Currow and colleagues have studied the effect of long-acting morphine on breathlessness and found benefit in a phase 2 study up-titrating once daily sustained-release morphine.⁸ Toxicities were short-lived and the number needed to treat was 1.6 patients. Over time, breathlessness improved and further analysis showed that up-titration of doses following initial response should not occur before one week.⁹ This has been further confirmed by Oxberry et al

who have a group of patients who continued the treatment on an open-label basis as they felt it improved their symptoms.¹⁰ Finally, through evaluation of the safety of benzodiazepines and opioids in patients with very severe COPD, Ekstrom et al noted that neither benzodiazepines nor opioids were associated with increased admission rates, however benzodiazepines were associated with increased mortality with a dose response trend. Opioids at lower dose (≤ 30 mg oral morphine per day) were not associated with increased mortality but higher doses were. Concurrent benzodiazepines and low dose opioids were not associated with increased admissions or mortality.¹¹ These examples provide alternative evidence for the pharmacological management of breathlessness.

Finally Professor Currow briefly talked about nebulised morphine and its potential role as a treatment for breathlessness. In a study by Shohrati et al in patients with breathlessness secondary to mustard gas exposure, nebulised morphine was shown to improve their symptoms without any major adverse effects.¹² There is further work to be done in this particular area.

Key Note Lecture

Dyspnea: The First Vital Sign

Professor Bob Banzett

Prof Banzett talked of three flavours of dyspnoea which are described differently, manipulated independently and have different neural pathways.¹³ Dyspnoea is not a single sensation and can be thought of as comprising:

1. Air hunger,
2. Work/effort of breathing,
3. Chest tightness.

It is also important to think of dyspnoea as multidimensional with sensory components such as the above three symptoms as well as mental concentration, affective components such as the immediate unpleasantness of being breathless, and the emotional or evaluative responses which drive the accompanying feelings of fear and anxiety.¹⁴

He talked about experiments his team have done which show that patients can reliably rate their breathing discomfort and that there is good day-to-day consistency. Indeed, the American Thoracic Society emphasise that dyspnoea can only be perceived by the person experiencing it.¹ However, they each respond differently to being breathless and it has been shown that clinicians significantly underestimate dyspnoea.¹⁵ Increasing a patient's tidal volume relieves air hunger even when the ribcage and diaphragm are denervated due to cervical spine injuries.¹⁶ Experiments also show that free breathing, even with increased inspired CO₂, is less uncomfortable than limited ventilation. This supports the view that air hunger is a balance between respiratory drive and ventilation, and that hypoxia is a contributor rather than a driver of breathlessness.¹⁷

Prof Banzett also discussed the evidence that dyspnoea is a better predictor of mortality and other adverse effects than FEV1 or other objective data.^{18,19} He described a pilot study in the USA where nurses in a large teaching hospital in Boston are now recording dyspnoea in conjunction with the traditional vital signs and efforts are being made to improve the methods used to measure dyspnoea and determine the ideal frequency of measurement.²⁰ Dyspnoea is becoming recognised as a 'vital sign' which impacts on patient outcomes.

Presentation 4

A feasibility study to adapt and develop a breathlessness intervention service (BIS) for people suffering from asbestosis in India: The SHWASS project

Dr Helen Clayson

Dr Clayson talked about a community-based volunteer-led educational programme using evidence-based, low-cost, low-technology, non-pharmacological interventions to try to improve breathlessness in former asbestos industry workers with asbestosis in Mumbai. Interventions trialled include exercise, fans, breathing control, positioning techniques, social support, and they were evaluated with objective measures such as the 6-minute walk test, pulmonary function tests as well as qualitative methods such as questionnaires and interviews. The project is still in progress and full evaluation is yet to be completed however, there have been many learning points already including the importance of understanding cultural differences and how these affect research.

Presentation 5

Developing a complex non-pharmacological intervention for the respiratory symptom cluster of breathlessness, cough and fatigue in lung cancer

Dr Janelle Yorke

The respiratory symptom cluster of breathlessness, cough and fatigue has been described by Molassiotis et al with breathlessness usually being the driving symptom of the cluster.²¹ An evidence basis is developing for non-pharmacological management of single symptoms, but less has been developed for clusters and given that the symptoms are usually present together, there is an argument that interventions should be targeted towards managing them concurrently in order to improve patients' quality of life. Ellis et al have interviewed patients and results revealed that they would want flexible, practical interventions that would provide strategies to cope with specific problems and that caregivers could be taught to carry out.²² Dr Yorke's group are investigating the feasibility of a respiratory symptom cluster intervention for patients with lung cancer and assessing its effectiveness via various symptom questionnaires.

Presentation 6

The Life of Breath: A Medical Humanities approach to breathlessness.

Dr Jane McNaughton

Biomedicine is not able to encompass all aspects of breathlessness as there is a significant emotional component and many metaphors exist surrounding breathing, for example the first and last breath representing birth and death. The Life of Breath project aims to provide an interdisciplinary understanding of the experience of breathing and breathlessness by bringing together historical, philosophical, anthropological and clinical research. It will investigate the cultural significances and historical origins of attitudes towards breathing, public health relationships, explore the phenomenology of breathing and breathlessness, and non-pathological versus pathological breathlessness.

Presentation 7

Data from the Living with Breathlessness study in COPD

Dr Morag Farquhar

The trajectory of COPD is of a slow decline punctuated acute exacerbations and contrasts significantly with that of lung cancer. There is a lack of fundamental research on non-malignant disease trajectories. Dr Farquhar presented some results from the baseline data of the above mixed methods study in which longitudinal interviews have been carried out on 236 patients with advanced COPD and 118 carers. There are various trends noticeable including that patients have similar comorbidities including arthritis, cardiovascular disease, and breathlessness is a universal symptom experienced. The study identified that many patients had mental health symptoms such as anxiety or depression but had not informed a healthcare professional, and there were differences between what patients perceived as care, compared to that offered by health services. A carers questionnaire was developed which looked at their needs and preparedness for caregiving. The interviews also explored patients and carers experience of the care received by various services and how well it addressed their needs.

Presentation 8

Learning about breathlessness study

Dr Clarissa Penfold

The aim of this study was to explore the educational needs of informal carers of patients with COPD and lung cancer in order to design future randomised controlled trials of interventions to address these needs. This was carried out by way of analysis of interviews with the carers. The study identified important themes for carers and elements of an educational intervention that would be desirable. The next steps in the study include developing the intervention in conjunction with patients and carers.

Presentation 9

Brief update on breathlessness and its relationship with the HPA axis

Dr Richella Ryan

The breathlessness experience consists of the perception of breathlessness, the emotional behavioural response and the impact of breathlessness on activities of daily living. Part of the emotional and behavioural response can be an association with fear of dying which activates the stress system via the hypothalamus-pituitary-adrenal (HPA) axis. We know that anxiety and respiratory disorders coexist and it is hypothesised that repeated activation of the HPA axis in chronic breathlessness leads to HPA axis dysfunction. This could lead to a range of maladaptive behaviours and emotions contributing to further breathlessness. Measurement of salivary cortisol profiles could be a candidate biomarker for stress due to breathlessness and resulting in HPA axis activation. Interventions could be targeted to this system to improve the symptom and the success of interventions could be measured by monitoring the cortisol profiles.

Conclusion

This meeting demonstrates the wide variety of research being carried out in the field of breathlessness addressing a spectrum of issues from understanding biological mechanisms to patient and carer experiences, and attempting to disseminate the knowledge to less developed countries. Each year more areas of research are introduced and progress in managing the symptom is evident. The talks generated much vibrant discussion amongst the multidisciplinary attendees and highlighted areas where care for breathless patients could be improved. It is clear that there will be further studies and ensuing interventions on the horizon.

References:

1. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012 Feb 15;185(4): 435-52
2. Dorman S et al. Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. *Palliat Med* 2009 23:213-227
3. Gray JE, Booth S, Brage S, Yorke J, Moosavi S, Bausewein C, Molassiotis A, Johnson M, Farquhar M. Meeting report of Breathlessness Research Interest Group. *Prog Palliat Care* 2010 April; 18(2): 95-98
4. Pattinson KT, Johnson MJ. Neuroimaging of central breathlessness mechanisms. *Curr Op Support Palliat Care* 2014 Sep;8(3):225-33
5. Pattinson KT, Governo RJ, MacIntosh BJ, Russell EC, Corfield DR, Tracey I, Wise RG. Opioids depress cortical centres responsible for the volitional control of respiration. *J Neurosci* 2009 Jun; 29(25):8177- 8186
6. Uronis H, McCrory DC, Samsa G, Currow D, Abernethy A. Symptomatic oxygen for non-hypoxaemic COPD. *Cochrane Database Syst Rev* 2011 Jun 15;(6):CD006429
7. Campbell ML, Yarandi H, Dove-Meadows E. Oxygen in nonbeneficial for most patients who are near death. *J Pain Symp Manage* 2013 Mar; 45(3):517-23
8. Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P, Briffa M, Johnson MJ, Abernathy AP. Once-daily opioids for chronic dyspnoea: a dose increment and pharmacovigilance study. *J Pain Symp Manage* 2011 Sep; 42(3):388-99
9. Currow DC, Quinn S, Greene A, Bull J, Johnson MJ, Abernethy AP. The longitudinal pattern of response when morphine is used to treat chronic refractory dyspnea. *J Palliat Med* 2013 Aug; 16(8):881-6
10. Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough. *J Palliat Med* 2013 Mar; 16(3):250-5
11. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014 Jan 30;348:g445
12. Shohrati M, Ghanei M, Harandi AA, Foroghi S, Harandi AA. Effect of nebulized morphine on dyspnea of mustard gas-exposed patients: a double-blind randomised controlled clinical trial study. *Pulm med* 2012; 2012:610921

13. Gilman SA, Banzett RB. Physiologic changes and clinical correlates of advanced dyspnea. *Curr Opin Support Palliat Care* 2009 Jun; 3(2):93-7
14. Lansing, RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol* 2009 May 30; 167(1):53-60
15. Hayes AW, Philip K, Spruyt OW. Patient reporting and doctor recognition of dyspnoea in a comprehensive cancer centre. *Intern Med J* 2006 Jun; 36(6): 381-4
16. Manning HL, Shea SA, Schwartzstein RM, Lansing RW, Brown R, Banzett RB. Reduced tidal volume increase 'air hunger' at fixed PCO₂ in ventilated quadriplegics. *Respir Physiol* 1992 Oct; 90(1):19-30
 Harty HR, Mummery CJ, Adams L, Banzett RB, Wright IG, Banner NR, Yacoub MH, Guz A. Ventilatory relief of the sensation of the urge to breathe in humans: are pulmonary receptors important? *J Physiol* 1996 Feb 1; 490(Pt 3): 805-15
 Bloch-Salisbury E, Spengler CM, Brown R, Banzett RB. Self-control and external control of mechanical ventilation give equal air hunger relief. *Am J Respir Crit Care Med* 1998 Feb; 157(2):415-20
17. Banzett RB, Lansing RW, Evans KC, Shea SA. Stimulus-response characteristics of CO₂-induced air hunger in normal subjects. *Respir Physiol* 1996 Jan, 103(1):19-31
18. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002 May; 121(5):1434-40
19. Banzett RB, O'Donnell CR. Should we measure dyspnoea in everyone? *Eur Respir J* 2014 Jun; 43(6):1547-50
20. Baker K, Barsamian J, Leone D, Donovan BC, Williams D, Carnevale K, Lansing R, Banzett R. Routine dyspnea assessment on unit admission. *Am J Nurs* 2013 Nov; 113(11):42-9
21. Molassiotis A, Lowe M, Blackhall F, Lorigan P. A qualitative exploration of a respiratory distress symptom cluster in lung cancer: cough, breathlessness and fatigue. *Lung cancer* 2011 Jan; 71(1):94-102
22. Ellis J, Wagland R, Tishelman C, Williams ML, Bailey CD, Haines J, Caress A, Lorigan P, Smith JA, Booton R, Blackhall F, Molassiotis A. Considerations in developing and delivering a nonpharmacological intervention for symptom management in lung cancer: the views of patients and informal caregivers. *J Pain Symptom Manage* 2012 Dec; 44(6): 831-42