

MEETING REPORT

Recent developments in managing breathlessness

International researchers' meeting on Breathlessness in London, November 2006

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Intractable breathlessness is the most common and distressing symptom in far-advanced cardiopulmonary disease. It affects millions of people world-wide. Despite advances in research over recent years there are still many unresolved questions regarding the pathophysiology and aetiology of breathlessness as well as the best management options. At an international meeting in London, researchers discussed how to improve and extend breathlessness research. Topics ranged from qualitative through to biomedical research and included: (i) the aetiology of breathlessness in cancer and its relation to deconditioning; (ii) the personal experience of breathlessness and social effects of chronic obstructive pulmonary disease (COPD); (iii) the measurement of breathlessness; (iv) the use of grey literature; (v) the latest developments in functional brain imaging (fMRI); and (vi) the effects of a breathlessness intervention service (BIS) to help patients cope

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with their breathlessness. Various areas for further research were identified such as understanding the genesis of breathlessness, the role of pulmonary rehabilitation in cancer patients and the need for functional imaging studies in patients with breathlessness.

Keywords: *Breathlessness, COPD, fMRI, breathlessness intervention service, pulmonary rehabilitation*

Following a meeting at the Medical Research Council (MRC) in London in 2005 (1), a second international meeting on breathlessness was held in London on 23 November 2006. The meeting was organised by the Cicely Saunders International, the Department of Palliative Care, Policy & Rehabilitation at King's College London and the Addenbrooke's Palliative Care Research Group, Cambridge, and was funded by the Novartis Foundation. The group met to discuss the evidence in breathlessness in advanced disease and potential steps for further research.

The opening remarks reflected that dyspnoea is a difficult symptom to manage and lacks good evidence to guide treatment regimens. The prevalence of breathlessness in advanced disease is high, varying between 15–70% in the final year of life of cancer patients (2–4) and around 70–80% of patients with chronic obstructive pulmonary disease (COPD) (5). There is a wide range of pathophysiological conditions contributing to breathlessness in patients with advanced disease. However, the psychological impact on the patient and the subjectivity of the symptom has to be taken into account as well (6–8). Management includes both pharmacological and non-pharmacological measures.

The aims of the meeting were to:

- *facilitate liaison and multiprofessional interaction*
- *increase cohesion and foster international collaboration*
- *exchange information and to learn from each other*
- *debate methodological issues in breathlessness research in palliative care patients*
- *foster cross fertilisation of ideas.*

It is agreed that rigorous research methods and open debate are needed to carry breathlessness research forward

and improve the evidence available on which clinicians can base their treatment decisions in discussion with patients. The meeting comprised of a series of presentations and open discussion amongst the researchers and this is detailed below.

BREATHLESSNESS IN ADVANCED CANCER

Professor Deborah Dudgeon, medical oncologist and palliative care physician from Canada, reported on research carried out in collaboration with Denis O'Donnell (respiratory physician, Professor of Medicine, Canada) on the aetiology of breathlessness in advanced cancer (9). This study explored the mechanisms for unexplained dyspnoea and exercise limitation in clinically stable out-patients with cancer.

Aims

The main research questions asked were whether respiratory muscle weakness in cancer is an isolated phenomenon or part of global skeletal muscle weakness and whether there were significant differences amongst the cancer patients with and without dyspnoea and normal subjects with respect to exercise tolerance, intensity of exertional dyspnoea, exertional leg discomfort, nutritional status, levels of depression, anxiety and quality of life.

Methods

This descriptive, case-matched study compared 24 cancer patients with moderate-to-severe exertional dyspnoea, 39 cancer patients with no dyspnoea and 47 normal subjects.

Results

When compared to the healthy group, dyspneic cancer subjects, had on average:

- *reduced maximal inspiratory pressure (MIP; 20%)*
- *decreased peripheral muscle strength*
- *symptom-limited reduction in peak maximum oxygen uptake ($\dot{V}O_2$) of 30%*
- *reduction in anaerobic threshold*
- *accelerated heart rate response to exercise*
- *reduction of peak ventilation of 16 l/min*
- *increased Borg scores for shortness of breath at any given $\dot{V}E$ (up to 3 unit difference) (minute ventilation: the volume of air expired in 1 min)*
- *increased ventilation at iso- $\dot{V}O_2$ (by up to 15 l) (maximum capacity to transport and utilise oxygen)*
- *relatively rapid-shallow breathing pattern demonstrated in minute ventilation at peak exercise (l/min)*
- *accelerated reduction in inspiratory capacity.*

Conclusions

The overall increase in ventilatory demand, peripheral muscle weakness and exercise limitation were thought to indicate signs of deconditioning with:

- *increased ventilation at lower work rate*
- *decreased ventilation at peak exercise*
- *early anaerobic threshold*
- *normal $\dot{V}E/\dot{V}CO_2$ around anaerobic threshold*
- *low $\dot{V}O_2$*
- *accelerated heart rate.*

All these findings could also be explained by a metabolic myopathy which can not be ruled out. The cancer dyspnoea group also showed a reduction in ventilatory capacity with dynamic hyperinflation during exercise and dynamic inspiratory muscle weakness.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Dr Marjolein Gysels, anthropologist, London, reported on her study investigating patients' personal experience of breathlessness and the social effects of COPD which had uncovered some interesting and practical implications for the discussions that doctors have with their patients at the time of diagnosis.

Aims

The aims were to investigate how breathlessness influences patients' outlooks on the future and the impact of breathlessness on participants' quality of life.

Methods

Gysels conducted a qualitative study using in-depth interviews with topic guides, with 56 patients suffering from breathlessness from a variety of conditions and 25 carers. She focused on the findings relating to the patients with COPD. Narrative methods were used with special attention to the structure of the narratives to uncover patients' views of their illness and interactions with healthcare.

Results

Patients with COPD behave differently from the commonly described health-seeking pattern for patients with chronic disease (10). Usually, patients first notice symptoms which then have an impact on the way they live. This encourages them to seek help to find a diagnosis and get treatment. COPD has an insidious onset and is already quite advanced by the time it is diagnosed. The interviews showed that contact with healthcare services was not established at the first signs of illness, but was postponed until there was a crisis. The diagnosis did not lead to

changes in life-style which would have improved patients' health (such as stopping smoking) because they did not adequately understand what the label of 'COPD' referred to. Also, at the time of diagnosis, the nature and further course of the illness were not addressed so that patients did not realise that the condition was life-limiting. Patients only sought a doctor's advice on treatment once the symptoms had a serious impact on their life and they started to raise questions about prognosis once the disease was already advanced. Prior to this, patients did not mention the future. Poor communication added to the deterioration in the patient's quality of life.

Conclusions

The ways in which diagnosis and prognosis are conceptualised and discussed in medical interviews needs to be rethought and fitted into a specific model to suit patients with COPD. From her study, Gysels recommended integrating questions about diagnosis with prognosis. Care should also include a holistic and patient-centred approach with survival not necessarily being a high priority. A step-wise approach within a frame directed to surveillance is necessary, *i.e.* diagnosis is not a one-off event but needs to be repeatedly discussed in a long-term relationship with the health professional. Issues around uncertainty must be recognised and the focus should be on quality of life.

GREY LITERATURE

Professor David Currow, palliative care physician, Adelaide, Australia, discussed the 'grey literature as a research tool for breathlessness'. He reminded the group that most data relevant to palliative care is not in the published palliative care literature. The so called 'pink literature', *i.e.* the lay media including tabloid newspapers and magazines, may have more impact on patients than carefully worked out studies in respected journals. Much information is contained in the grey literature in forms of abstracts, theses, government and service reports and some commissioned research. Much of this literature is not peer-reviewed and not uncovered by systematic searching. It was argued that the information in the grey literature needs to be included in our work as it provides important information for formulating new studies, avoiding duplication and building on previous work. We also have to ensure that systematic reviews are as comprehensive as possible. In palliative care there is a very low conversion rate from abstracts to peer-reviewed literature (about 8%) as the threshold for accepting abstracts is low.

To support palliative care researchers to access the grey literature, Currow and colleagues developed a website, <www.caresearch.com.au>, which is mainly based on Australian information from 450 unlisted journal articles

from 12 leading palliative care journals (including abstracts), approximately 70 government reports, 50 theses and treatises and more than 1700 unpublished conference proceedings abstracts (from 1980–2005). The website provides graded evidence for various areas in palliative care, including information on breathlessness. On this subject, there are 21 citations of which 5 are from the unindexed literature (2 went on to further key work) and 16 from unpublished abstracts (9 relate directly to breathlessness). Work on the website is continuing.

MEASUREMENT OF BREATHLESSNESS

Dr Claudia Bausewein, Munich, Germany, discussed different scales for the measurement of breathlessness. Various aspects of breathlessness can be measured such as triggers of breathless episodes, the severity and intensity, the effort and sensation, and the impact on function and activity. Bausewein and colleagues conducted a systematic review on measurement scales for breathlessness (11).

Aims

The study aimed to identify and systematically review the literature for instruments regularly used to measure breathlessness in conditions such as COPD, cancer, chronic heart failure and motor neurone disease. A second aim was to relate these tools to the specific situation of patients with advanced disease and identify those measures that could be used by patients near the end of life.

Methods

A systematic literature search was performed in Medline. All studies focusing on the development or evaluation of tools for measuring breathlessness in chronic respiratory disease, cardiac disease, cancer, or motor neurone disease were identified. Their characteristics with regard to validity, reliability, appropriateness and responsiveness to change were described. The tools were then examined for their usefulness in measuring significant aspects of breathlessness in advanced disease.

Results

The review identified 33 tools available to measure breathlessness. Four were unidimensional and 29 multidimensional, of which 18 were disease-specific and 11 breathlessness-specific. The four unidimensional tools (modified Borg scale, visual analogue scale [VAS], Oxygen Cost Diagram and numerical rating scale [NRS]) measure severity of breathlessness (*e.g.* in exercise tolerance tests) and are easy to use. All are self-administered and take only seconds to complete. Clearly defined anchors are necessary for all of them. The breathlessness-specific tools cover a variety of domains such as effort, associated symptoms, and relation to activity or coping strategies.

Six are self-administered, more than half are validated in COPD and four are developed for cancer patients. The most frequently used tools in this group are the MRC dyspnoea scale and the Baseline/Transition Dyspnoea Index (BDI/TDI), which is specifically developed to capture changes in shortness of breath.

Conclusions

1. *For general clinical questions, a VAS/NRS or modified Borg scale are recommended. If the focus is more on quality of life (QoL), a multidimensional tool (e.g. Chronic Respiratory Disease Questionnaire or the Lung Cancer Symptom Scale) should be used.*
2. *Breathlessness-specific questionnaires assess both the sensation of breathlessness and its impact on function.*
3. *For research, a combination of a measure of breathlessness at a point in time (using a one-dimensional tool) and a QoL or breathlessness-specific questionnaire will give the broadest picture.*
4. *Alternatively, a mixed-methods approach can be used, e.g. a unidimensional scale and a qualitative interview for experiential and contextual factors.*

FUNCTIONAL BRAIN IMAGING

Dr Douglas Corfield, Reader in Physiology, Keele University, UK, talked about latest developments in functional brain imaging (fMRI) which are helping to explain the genesis of the sensation of breathlessness. fMRI works by determining the local changes in brain blood oxygen levels that correlate with the changes in brain activity during episodes of breathlessness. Corfield demonstrated that the perception of breathlessness is dependent on a network of limbic and para-limbic structures (12). A separate study has shown that voluntary inhibition of breathing is mediated by limbic pre-frontal and sub-cortical structures. This voluntary inhibition of rhythmic respiratory motor output from the brainstem is probably mediated via the pons. Common brain areas are activated by pre-air hunger (breath hold) and air-hunger states suggesting that the same neural network may 'monitor' breathing status in these two conditions. The perception of breathlessness may reflect a change in information flow around this network.

BREATHLESSNESS INTERVENTION SERVICE

Petrea Fagan, specialist physiotherapist, Cambridge and Dr Morag Farquhar, Research Associate, King's College London, presented their experiences in implementing and evaluating a breathlessness intervention service (BIS) in Addenbrooke's Hospital, Cambridge, UK.

Service description

This service aims to help patients suffering from breathlessness due to any diagnosis (chronic lung disease, heart failure, cancer and long-term conditions). The focus of care is on patients and their carers, offering a flexible service delivery (hospital, out-patients, or home). After initial clinical assessment, patients have, on average, 4–6 consultations including home visits, medical assessment and telephone follow-up. Each patient gets an individual plan for symptom management with a 'tool kit of breathing exercises' and a personal activity plan. Patients are referred to other services as necessary. Non-pharmacological measures include education (breathing control), reassurance and explanation, a management and emergency plan regarding breathlessness and anxiety; and introduction to the use of a cool draught of air with a hand-held fan. Regarding activity and rehabilitation, the patients get information on modifying activities of daily living, positioning, nutrition and hydration as well as on relaxation, visualisation and meditation. Medical advice is given regarding oxygen and pharmacological treatment (opioids, anxiolytics, and antidepressants).

Evaluation

As BIS is a novel, and complex intervention (*i.e.* involves several components), evaluation is necessary to assess its efficacy over and above existing services – this is being carried out following the MRC Framework for the Evaluation of Complex Interventions (2000) <www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003372>. This is a five-phased approach ranging from theory to long-term implementation underpinned by a continuum of increasing evidence.

In the pre-clinical phase (theory), a qualitative study with lung cancer and COPD patients was undertaken looking into the experiences of breathlessness (13). This study showed that breathlessness is frightening, disabling and restricting. Informal carers suffer significantly from severe anxiety and helplessness and feel powerless. The existing services were highly valued, but offered only inconsistent and sporadic support.

Following the commencement of the pilot service, a phase I (modelling) audit of the management of chronic breathlessness was undertaken in the locality, as well as a qualitative study examining users' experience of the pilot service (14). Users appreciated the service's positive, educational approach (which emphasised what was possible, not what was lost), the non-pharmacological strategies (*e.g.* the hand-held fan), the open access to advice and the flexibility of BIS. Further aspects for development that arose from the interviews were: carers' need for more support and information; the sometimes problematic location of BIS within an oncology setting; and patients' and carers' need for prior information about BIS.

Referrers valued the educational role and the second opinion that BIS offered. The results of phase I were fed back into the further development of BIS.

Currently, the evaluation process is in phase II where a pragmatic exploratory delayed intervention randomised controlled trial of the re-developed service is being undertaken. COPD patients who are using BIS are being randomised into a fast-track group which receives the service immediately or a control group which receives the service as a delayed intervention after 8 weeks. This exploratory trial will inform the design of phase III, a definitive randomised controlled trial of the service for patients with any diagnosis.

DISCUSSION

Each talk was followed by a discussion in the group regarding further directions of research. The following topics were raised:

1. *A longitudinal study in patients with breathlessness due to malignant disease with lung function tests would be useful to look at changes from the time of diagnosis to progressive disease to understand the genesis of breathlessness. Muscle biopsies from respiratory muscles and quadriceps were considered to be helpful to detect structural changes.*
2. *Pulmonary rehabilitation could be beneficial for patients with malignant disease and dyspnoea. However, the right timing for and components of this intervention is unclear.*
3. *It is also unclear whether deconditioning follows the effects of dyspnoea or whether the rise in inflammatory markers leads to deconditioning of respiratory muscles and subsequent dyspnoea. Furthermore the role of inflammatory markers, such as interleukin-6 in dyspnoea, remains unclear.*
4. *Prognostication, especially in COPD patients, is very difficult with little practical help being available from prognostic indices such as BODE which can only predict survival to an accuracy of two or more years. More importantly, it was stated that patients are more interested in the trajectory of their disease rather than the prognosis.*
5. *The models of care that we know from work on cancer patients are often unhelpful in patients with non-malignant disease. Palliative care services in patients with organ failure need to be adapted to the needs of the patients rather than a theoretical disease trajectory. However, we have to ensure that COPD patients get access to the services they need. This generates the question of how to configure these services and at what point they need to be offered to give patients with COPD the best service.*

6. *For fMRI, patient-based studies are necessary as most studies up to now have been conducted in healthy volunteers undergoing induced breathlessness states. However, various challenges must be overcome to undertake such research in breathless patients. For example, some breathless patients may find it difficult to lie flat in the scanner and others may find the scanning environment claustrophobic. Protocols that can induce breathlessness experimentally, without the use of exercise, must be developed and optimised for the relevant patient groups.*
7. *Breathlessness intervention services can help to change the experience and perception of breathlessness rather than changing the underlying pathology. Such services focus on increasing self-efficacy and mastery of the symptom. These are complex interventions and further examination of these is necessary to elucidate which component works most effectively in different conditions.*

CONCLUSIONS

Professor Irene Higginson brought the meeting to a close with a summary of the day and discussion around future research. It was concluded that more longitudinal studies are required in breathlessness research to explore both therapeutic options (such as the efficacy and safety of opioids in patients with non-malignant disease) and service delivery questions.

This would require international collaboration and pooling of data across research networks. Primary endpoints in the studies would need to include subjective and physiological measures of breathlessness. Areas for further study include models of care for breathlessness in patients with advanced disease, assessing how clinical outcomes are related to the aetiology of breathlessness and feasibility studies of therapeutic interventions in breathlessness which might need to include a mixed methods approach (using quantitative and qualitative research methodology) as well as a physiological component such as using neuro-imaging for a sub-group of patients.

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ATTENDEES

Claudia Bausewein, Sara Booth, Doug Corfield, David Currow, Deborah Dudgeon, Petrea Fagan, Morag Farquhar, Marjolein Gysels, Irene Higginson, Miriam Johnson, Caroline Jolly, Farida Malik, Shakeeb Moosavi, Graeme Rocker, Catherine Urch, Patrick White.

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