Institution: King's College London

Unit of Assessment: 1- Clinical Medicine

Title of case study: Improved patient recovery and reduced mortality through the use of non-invasive ventilation (NIV) during acute exacerbations of chronic obstructive pulmonary disease (COPD)

1. Summary of the impact

Very considerable changes worldwide, in the management of patients with chronic obstructive pulmonary disease (COPD) admitted with acute ventilatory failure, have been a major impact of the research of the King's College London (KCL) Clinical Respiratory Physiology Group. Previously, invasive ventilation to treat such COPD patients was associated with complications which could be fatal. The KCL group conducted the first randomised controlled trial in the world of treatment by non-invasive ventilation (NIV). The trial demonstrated that NIV reduces complications and death compared to invasive ventilation. The study dramatically changed the treatment of hypercapnic flare-ups (where there is too much carbon dioxide in the blood) of acute COPD worldwide. NIV has become best and routine practice, and is advocated in national and international guidelines, benefiting many thousands of COPD patients.

2. Underpinning research

KCL research demonstrating that NIV is effective: The KCL Clinical Respiratory Physiology Group, led by Professor John Moxham (KCL, 1982 - present), designed and set up the first-ever trial of NIV in patients with ventilatory failure due to flare-ups or worsening, known as 'exacerbations', of COPD (1). Supported by a grant from the British Lung Foundation, the trial involved collaboration with colleagues from Southampton General Hospital and the London Chest Hospital. NIV involves patients wearing a nasal or facial mask connected to a mechanical ventilator.

KCL longstanding research on the load on, and capacity of, the respiratory muscle pump: The foundation for work on NIV was KCL research on the respiratory muscle pump. People with COPD suffer from narrowing of the airways, which is both progressive and irreversible. Obstructed airways, difficulty in expanding the chest (due to hyperinflation of the lungs) and incomplete exhalation increase the load on the respiratory muscle pump. In parallel with the increased load on the respiratory system, there is also a fall in the capacity of the inspiratory muscles used for breathing in (2,3). This is largely due to hyperinflation, which causes the inspiratory muscles to shorten and which impairs their performance. The geometry of the chest alters and adversely affects the mechanics of the respiratory muscles, so that they are less able to lower pressure in the chest and thus allow patients to breathe in (2,3,4).

KCL research into ventilatory failure: As respiratory diseases such as COPD progress, the balance between the load on, and the capacity of, the respiratory muscle pump changes, and the brain signals an increase in neural respiratory drive (NRD) to maintain adequate ventilation (5). KCL research found that when the imbalance reaches a critical point, ventilatory failure occurs (6,7), meaning patients cannot rid their body of carbon dioxide. When this happens, the carbon dioxide level in blood in the arteries ($PaCO_2$) rises, body fluids become acid (acidosis) and enzymes sensitive to acid levels fail to function. These enzymes are also needed to keep the respiratory muscles working normally. The result is a downward spiral of breathlessness – often severe.

KCL research showing NIV buys time for treatment: An acute imbalance between load and capacity of the respiratory muscle pump can be corrected by mechanical ventilation. This temporarily relieves the load on the respiratory muscle pump whilst doctors take corrective action. The introduction of non-invasive ventilation (NIV) meant that this could be achieved more easily and with less risk of complications or death compared to invasive ventilation (as invasive ventilation involves intubating patients by inserting a tube down into the patient's windpipe and sedating and mechanically ventilating the patient). KCL research showed that NIV can unload the respiratory muscle pump, control ventilatory failure, reduce breathlessness and 'buy time' for

conventional treatment (steroids, antibiotics, bronchodilators, oxygen, etc.) for COPD exacerbations to work (6). Thereafter NIV can be discontinued.

Findings widely incorporated into clinical care: The trial reported in the Lancet in 1993 (1) demonstrated that NIV was effective in treating ventilatory failure in patients with acute exacerbations of COPD. NIV reduced the carbon dioxide level in the blood ($PaCO_2$), reduced the acidity of body fluids, reduced breathlessness and reduced mortality. In the days following admission to hospital and treatment with NIV, the standard therapy for exacerbations could then reduce the load on the respiratory muscle pump and increase the capacity of the respiratory muscles (by reducing hyperinflation). Neural respiratory drive also diminishes because the balance between load and capacity improves, and patients become less breathless (5,7). This internationally leading work by KCL on NIV improves outcomes for COPD patients admitted with ventilatory failure.

3. References to the research

1. Bott J, Carroll MP, Conway JH, Keilty SEJ, Ward EM, Brown AM, Paul EA, Elliott MW, Godfrey RC, Wedzicha JA, **Moxham J**. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;341:1555–7.
2. Polkey MI, Kyroussis D, Hamnegård C-H, Mills GH, Green M, **Moxham J**. Diaphragm strength in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 1996;154:1310–7.
3. Polkey MI, Kyroussis D, Mills GH, Hamnegård C-H, Keilty SEJ, Green M, **Moxham J**. Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD. *Am J Respir Crit Care Med*. 1996;154:1146–50.
4. Luo YM, Hart N, Mustafa N, Lyall RA, Polkey MI, **Moxham J**. Effect of diaphragm fatigue on neural respiratory drive. *J Appl Physiol.* 2001;5:1691–9.
5. Jolley CJ, Luo YM, Steier J, Reilly C, Seymour J, Lunt A, Ward K, Rafferty GF, Polkey MI, **Moxham J**. Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J*. 2009;33: 289–97.
6. Stell IM, Paul G, Lee K, Ponte, **Moxham J**. Non-invasive ventilator triggering in Chronic Obstructive Pulmonary Disease: a test-lung comparison. *Am J Respir Crit Care Med*. 2001;64:2092–7.
7. Murphy PB, Kumar A, Reilly C, Jolley C, Walterspacher S, Fedele F, Hopkinson NS, Man WDC, Polkey MI, **Moxham J**, Hart N. Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax* 2011;66:602–8.

4. Details of the impact

Significant impact on treatment of COPD exacerbations: The evidence provided by the first-ever randomised clinical trial of NIV in acute hypercapnic exacerbations of COPD (1) has had a significant impact on the management of this common critical medical condition. The trial, and subsequent research which confirmed the findings, resulted in modified guidelines for managing acute exacerbations of COPD in the UK, Europe, USA and worldwide, and an increase in the use of NIV. Thousands of patients who would have died or would have suffered complications from invasive ventilation have survived (8).

Considerable improvement in outcomes for patients with ventilatory failure in acute exacerbations of COPD: The number of patients admitted with acute exacerbations of COPD in England each year is 100,000. The mortality rate in patients with ventilatory failure (high arterial $PaCO_2$ and acidosis) at the time of admission who do not respond to conventional treatment (bronchodilators etc.) is high if they are not mechanically ventilated (9).

Across England around 7% of all COPD admissions (7,000 patients) are treated with NIV, saving 800–1,000 lives. One of the indicators in the NHS Outcomes Framework 2012/13 is “preventing people from dying prematurely”. NIV is highly effective in preventing premature deaths: NICE guidelines (12) present evidence for the benefits of NIV, including reducing deaths (p. 387-389).

The British Thoracic Society (BTS) indicates that “Non-invasive ventilation in the management of acute type II respiratory failure in COPD patients represents one of the major technical advances

in respiratory care…with a reduction in mortality of approximately 50% demonstrated in studies…" (10).

Guidelines recommend NIV: The Joint British Thoracic Society (BTS) / Royal College of Physicians / Intensive Care Society Guidelines recommend "NIV should be considered for all COPD patients with a persistent respiratory acidosis after a maximum of one hour of standard medical therapy (grade A recommendation) (10). The National Institute for Health and Care Excellence (NICE) recommends non-invasive ventilation as the treatment of choice for COPD exacerbations (12). Recognition of this clinical advance by the BTS and NICE guidelines means that more and more hospitals are now offering NIV (11).

Use of NIV to treat COPD patients rises: One of the quality indicators in the NHS Atlas of Variation in Health Care for People with Respiratory Disease 2012 (11) is "Proportion of patients admitted with COPD receiving non-invasive ventilation (NIV) by Primary Care Trust (PCT)". In England, 97% of acute care hospitals now offer NIV for COPD patients although the proportion of patients admitted with COPD treated with NIV shows a seven-fold variation between different hospitals/PCTs/boroughs. As healthcare commissioners and healthcare providers are seeking to address this variation, the use of NIV in acute COPD continues to rise. BTS indicates that "There has been a rapid expansion in the provision of NIV services with over 90% of UK admitting hospitals offering this intervention" (10).

Changes in clinical practice: National and international guidelines recommending NIV for acute COPD have had a considerable impact on clinical practice. The 2010 UK National Institute for Health and Clinical Excellence (NICE) guidelines (12) recommend: "NIV should be used as the treatment of choice for persistent ventilatory failure during exacerbations…" (p.389). The 2008 national COPD audit (13) (p.23) showed that 79% of acute NHS units fully met and 18% partially met this NICE recommendation.

The Department of Health specification on service to manage COPD exacerbations (14) states that "Facilities for NIV should be available in all acute care hospitals where people with exacerbations complicated by respiratory failure are managed" (p.15). In England, Academic Health Science Networks (AHSNs), which set out to drive best practice and the requirement for all NHS providers within AHSNs to comply with evidenced-based treatments, are further extending use of NIV for acute COPD admissions where appropriate.

Considerable reduction in costs: The use of NIV has a considerable impact on costs. NICE clinical guidelines (12) present evidence that (a) NIV is cost effective in patients with a severe exacerbation of COPD as it is more effective and less expensive, than standard therapy alone and (b) the addition of ward based NIV to standard treatment is cost effective when compared with standard treatment alone, with an incremental cost effectiveness ratio of -£645 per death avoided.

Market for NIV devices expands: Success in treating acute COPD patients with NIV and subsequent wider use has greatly expanded the market for ventilators. For example, across KCL-associated hospitals, the number of ventilators used for acute COPD has increased 10 fold. At the time of the KCL research the ventilators were large, heavy and positioned on the floor; now they are small, light and sit easily on the patient's bedside locker. The challenge of devising NIV ventilators acceptable to breathless, often distressed, COPD patients has driven innovation in ventilator technology. Technical improvements have made NIV more acceptable to patients with acute COPD and have helped extend the use of NIV to patients with cystic fibrosis and to stable COPD patients with chronic ventilatory failure.

Global reach of findings: National Institute for Health and Care Excellence (NICE) guidelines have a considerable impact on treatment in many countries across the world. The global smoking pandemic is driving up the prevalence of COPD worldwide, particularly in China and India. NICE is now collaborating with China on chronic disease, with an initial focus on COPD and stroke (15). The NICE COPD guidelines are a starting point for NICE-China discussions.

5. Sources to corroborate the impact

Treatment recommendations based on KCL group's work

8. Cochrane collaboration: non-invasive positive pressure ventilation for the treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Review). 2009. John Wiley & Sons, Ltd. "Non-invasive positive pressure ventilation (NPPV) used in patients with acute exacerbations of COPD substantially improves recovery.... NPPV…has been shown to be beneficial for such patients in reducing hospital deaths and also the number of patients going on to require tracheal intubation. NPPV has also been shown to reduce complications associated with treatment and length of hospital stay" (p.2). "Implications for practice: Published data from good quality randomised controlled trials are now convincing for NPPV to be recommended as first line intervention as an adjunct therapy to usual medical care in all suitable patients for the management of respiratory failure secondary to an acute exacerbation of COPD. A trial of NPPV should be considered early in the course of respiratory failure and before severe acidosis ensures, as a means of reducing the risk of endotracheal intubation, treatment failure and mortality" (p.14). (Discusses results of the first-ever NIV clinical trial (KCL) (1) and cites it throughout) http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004104.pub3/pdf

9. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2013. "NIV has been shown to improve acute respiratory acidosis, decrease respiratory rate, work of breathing, severity of breathlessness, complications such as ventilator associated pneumonia and length of hospital stay. More importantly mortality and intubation rates are reduced by this intervention." (Cites [1] p.43 as Evidence A) http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf

10. Joint British Thoracic Society; Royal College of Physicians; Intensive Care Society Guidelines 2008. The use of Non-Invasive Ventilation in the management of patients with chronic obstructive pulmonary disease admitted to hospital with acute type II respiratory failure. (Cites [1] p.16, p.26) http://www.brit-thoracic.org.uk/Guidelines/NIPPV-NIV-in-Acute-Respiratory-Failure-Guideline.aspx

11. NHS Atlas of Variation in Healthcare for People with Respiratory Disease 2012. http://www.rightcare.nhs.uk/index.php/atlas/respiratorydisease/

National guidelines (and evidence for take-up of recommendations)

12. National Institute for Health and Care Excellence (NICE) guidance 2010. Chronic obstructive pulmonary disease (updated) (CG101) Management of chronic obstructive pulmonary disease in adults in primary and secondary care. Full guideline. http://www.nice.org.uk/nicemedia/live/13029/49397/49397.pdf.

13. Report of The National Chronic Obstructive Pulmonary Disease Audit 2008: Resources and Organisation of Care in Acute NHS Units across the UK. http://www.rcplondon.ac.uk/sites/default/files/report-of-the-national-copd-audit-2008-resources-and-organisation-of-care-in-acute-nhs-units-across-the-uk.pdf

14. Service Specification: Service to Manage COPD Exacerbations. 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/212878/Service-Spec-Managing-Exacerbations.doc

Global reach

15. National Institute for Health and Care Excellence (NICE) signed a memorandum of understanding with the China National Health Development Research Center, Chinese Ministry of Health in October 2010. http://www.nice.org.uk/aboutnice/niceinternational/NICEInternationalChinaMoU.jsp