

Ventilatory failure on acute take

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This conference was held at the Royal College of Physicians on 6 July 2005

Clin Med 2005;5:620-4

Respiratory disease comprises a significant burden of acute admissions on a medical take, and patients in acute ventilatory failure are among the most challenging faced by a variety of healthcare professionals.¹ Ventilatory failure is defined as the inability of the respiratory system to function effectively as a pump, resulting in hypoxaemia ($\text{PaO}_2 < 8.9 \text{ kpa}/60 \text{ mmHg}$) and hypercapnia ($\text{PaCO}_2 > 6.7 \text{ kpa}/50 \text{ mmHg}$). The hallmark of life-threatening ventilatory failure in the decompensated form is characterised by the presence of respiratory acidosis when arterial pH falls below 7.35 in addition to the gas exchange abnormalities mentioned above. Up to 20% of patients admitted to hospital with exacerbation of chronic obstructive pulmonary disease (COPD) present with a respiratory acidosis.² A nationwide audit of acute COPD exacerbations in 2003 revealed an inpatient mortality rate of 7.5%, a 90-day mortality of 15% and a readmission rate of 31%.³

This multidisciplinary conference, held jointly with the British Thoracic Society, discussed state-of-the-art management as well as controversial issues regarding ventilatory failure on the acute medical take.

Initial assessment and management of the patient in acute ventilatory failure

Identifying clinically the presence of ventilatory failure in a patient may not always be straightforward, and often such assessments are performed by general practitioners (GPs), ambulance staff or others in primary care. The use of pulse oximetry in the community and primary care settings may be helpful with a heightened diagnostic suspicion if the oxygen saturations fall below 92%. The importance of adequate initial assessment, continuous monitoring of oxygen saturations and the administration of titrated oxygen therapy during ambulance transport was stressed.⁴ Although high-flow oxygen therapy is appropriate in the majority of patients, particular care must be taken in patients with a diagnosis of COPD, where uncontrolled oxygen therapy resulting in hypercapnia and respiratory acidosis has been shown to lead to increased mortality.^{2,4} In general, maintenance of oxygen saturations at 90–92% will be adequate for the majority of patients.

The importance of clear prescription of oxygen

therapy (including concentration, duration and method of administration) was stressed. A simple facemask and reservoir bag should be used in respiratory failure complicating asthma, pneumonia, pulmonary embolism or cardiogenic pulmonary oedema. A Venturi system mask is useful when careful titration of oxygen therapy is desired, eg in decompensated COPD or when the patient's condition is deemed clinically stable. The use of nasal cannulae in the acute setting as a means of oxygen delivery should be discouraged. Adequate monitoring of patients following oxygen prescription, such as monitoring saturations and arterial blood gases, is similarly important. On wards, many trusts use early warning scores to identify potentially critically ill patients. However, frequently these lack emphasis on monitoring oxygen saturation, and this needs to be addressed.

Although decompensated chronic lung disease most commonly presents as acute ventilatory failure, the importance of medications resulting in respiratory depression was highlighted. The use of drugs such as opiates, benzodiazepines and antipsychotics as a cause of respiratory depression should be considered when the aetiology of ventilatory failure is being sought in addition to causes such as COPD, pulmonary oedema, and neuromuscular or chest-wall diseases. It is recognised that emergency room assessment and subsequent decision-making may be difficult, as the patient may be too unwell to give a coherent history and the patient's relatives or friends may not be present. This is heightened by the lack of immediate access to medical records or clinic letters and the fact that initial investigations such as X-rays may be of poor quality. The emerging use and importance of patient-held cards that contain details of the underlying diagnosis, medications and even treatment wishes were discussed. The implementation of such cards would require an extensive programme of patient education, discussion of treatment options and counselling during the stable state, and the role of specialist nurses in this respect was raised.

Principles of management of acute ventilatory failure

- Controlled oxygen therapy in cases of acute ventilatory failure via a Venturi mask, maintain-

ing arterial oxygen saturation between 90% and 92%, including during ambulance transport.

- Always obtain an arterial blood gas sample on admission if oxygen saturation is less than 92%.
- Consider the role of drugs, eg opiates, as a cause or precipitant in acute ventilatory failure.
- The presence of respiratory acidosis despite controlled oxygen therapy and optimal medical management should warrant urgent assessment and consideration of ventilatory support.
- The use of early warning scores incorporating oxygen saturation in order to identify critically ill patients is recommended.
- The use of patient-held cards containing details of any underlying diagnosis, medications and advanced directives is a promising area that needs wider implementation.

Non-invasive ventilation (NIV) may be initiated successfully in the accident and emergency (A&E) department. The provision of this service in A&E departments is becoming more common nationally.⁵⁻⁷ The key to establishing a successful acute NIV service lies in a locally designed integrated system with emphasis on provision of local guidelines, clinical leads, multidisciplinary staff training and interdepartmental liaison. A UK survey involving

228 hospitals conducted in 2003 showed that NIV was available in 96% of hospitals and could be initiated in A&E/medical assessment units in 55% of hospitals.⁸

Key to establishing a successful acute non-invasive ventilation service

- A locally designed integrated system with emphasis on local guidelines, staff training and clinical leads.
- The ability to initiate NIV in both A&E and ward scenarios.
- The ability to monitor patients safely when NIV is administered, including during the transfer from A&E to other areas of the hospital.
- The importance of doctors establishing a treatment plan once NIV is initiated regarding the ceiling of ventilatory support.

Clinicians must also be aware of the contraindications of NIV in the setting of facial trauma and burns, fixed upper-airway obstruction and haemodynamic instability, as well as limitations in the presence of copious respiratory secretions, altered consciousness, agitation, undrained pneumothorax and bowel obstruction.⁹ The intensive care unit (ICU) should be alerted in such circumstances if the patient is deemed a suitable candidate for invasive ventilation.

Conference programme

■ Assessing the patient, diagnosis and initial management: 'the acute physician's view'

Dr Derek Bell, The Royal Infirmary of Edinburgh

■ Assessing the patient and organising systems for the management of the ventilatory failure patient: 'the emergency physician's view'

Dr Ellen Jones, Heart of England NHS Foundation Trust

■ Management of ventilatory failure complicating acute pulmonary oedema: what to do when simple measures are insufficient

Dr Mike Grocott, University College London and Whittington Hospital, London

■ Management of the patient in ventilatory failure-getting it right: 'the intensivist's view'

Dr Andrew Bentley, Wythenshawe Hospital, Manchester

■ TUDOR EDWARDS MEMORIAL LECTURE

Management of acute ventilatory failure: past, present and future

Professor Peter Calverley, The University of Liverpool

■ What the nursing and paramedical staff need from medicine in the management of acute ventilatory failure

Mrs Vicky Furlong, University Hospital Aintree

■ Acute non-invasive ventilation beyond COPD: where is it going?

Dr Mark Elliott, St James's University Hospital, Leeds, and University of Leeds

■ Getting it right: giving an ethical context to the management of acute ventilatory failure. We know what we can do, how do we get our decision making right?

Dr John Coakley, Homerton University Hospital, London

Management of ventilatory failure complicating acute cardiogenic pulmonary oedema

The role of intravenous nitrates was highlighted, showing physiological benefits of vasodilation in an increase in cardiac output, and this should be considered as first-line therapy.^{10,11} Although diuretic therapy is not contraindicated, clinicians should be aware of the potential to decrease cardiac output by venodilation and reduction in left ventricular end diastolic pressure (LVEDP). NIV plays a key role in managing ventilatory failure complicating cardiogenic pulmonary oedema in terms of improving pulmonary compliance, reducing preload and afterload, decreasing alveolar pressure and reducing work of breathing. These benefits are translated clinically in improved oxygenation and reduced need for endotracheal intubation.¹²⁻¹⁵ Early use of NIV should be encouraged, although continuous positive airway pressure (CPAP) has been demonstrated to be as effective as bilevel positive airway pressure (BiPAP) in several studies.^{16,17} The role of the ICU extends beyond simply providing invasive ventilatory support, both in this and in other conditions. The importance of cardiac monitoring, particularly in the ICU, was also raised, as was the titration of therapy such as inotropes according to haemodynamic parameters such as pulmonary wedge pressure and cardiac output.

Management of ventilatory failure during acute exacerbations of chronic obstructive pulmonary disease

Ventilatory failure is a common manifestation of COPD exacerbations requiring hospital admission. Treatment options broadly involve medical management and the provision of assisted ventilation such as NIV or invasive positive pressure ventilation (IPPV). Of central importance to the clinician is the arterial blood pH, in terms of identifying those patients with a respiratory acidosis who require assisted ventilatory support as well as serving as a prognostic marker. This underlies the importance of performing arterial blood gas analysis in exacerbations of COPD requiring emergency admission. A pH of less than 7.3 implies a worse outcome and consideration of NIV/assisted ventilation at an earlier stage.

Medical therapy involves the prescription of controlled oxygen therapy (maintenance of oxygen saturations at 90–92%), bronchodilators, oral corticosteroids and antibiotics if appropriate. The use of intravenous aminophylline is less clear, with recent studies showing no significant overall improvement in FEV1 (forced expiratory volume in 1 s) or clinical outcomes and a potential for adverse effects.^{18–20}

NIV has been demonstrated to reduce mortality, the need for intubation and length of hospital stay. It is indicated in the presence of respiratory acidosis (pH <7.35 and hypercapnia). Clinical predictors of success included an improvement in the pH, PaCO₂ and respiratory rate 1 h after initiation of NIV.^{21,22} Failure is more likely in the presence of a lower baseline pH (<7.25), radiological consolidation, copious secretions, poor nutritional status, significant comorbidity, confusion and edentulous state.^{21,23} Simultaneous liaison with the ICU is recommended under such circumstances, as IPPV may then be initiated quickly if NIV fails. Although a depressed level of consciousness has been considered a contraindication for NIV, this has been challenged by a recent study evaluating the use of NIV in hypercapnic coma.²⁴ The panel was keen to stress the importance of defining a 'ceiling' of treatment (deciding whether IPPV should be administered if NIV failed) relatively early on, particularly at the time of commencing NIV, and senior input from chest physicians and intensivists should be sought in addition to exploring the views of the patient and her/his relatives. As the baseline pH is an important factor in determining success of NIV, it is thus important that NIV is delivered early during an admission complicated by acidotic ventilatory failure.

The role of respiratory stimulants such as doxapram during acute COPD exacerbations was also debated. Although doxapram has a role, particularly in patients intolerant to NIV, NIV was demonstrated to be superior in terms of gas exchange.²⁵ Misconceptions regarding lengthened periods of ventilation, multiple unsuccessful attempts at weaning and universal mortality following the initiation of IPPV in acute COPD exacerbations have been challenged by several studies.^{26–28} In a study of 74 patients admitted to ICU, 63 (85.1%) underwent IPPV, with an in-hospital mortality of 20.3%. The median durations of IPPV and ICU stay were 2 and 3 days, respectively.²⁶

This and other studies concluded that the need for mechanical ventilation did not predict short- and long-term mortality.

Roles of nursing and paramedical staff in treating acute ventilatory failure

An important message from the conference lies in the multidisciplinary nature of managing acute ventilatory failure at the coalface. In many hospitals, the task of establishing the patient on NIV in the acute setting often lies with physiotherapists or trained nursing staff once a decision has been made. A survey in 1997 showed that NIV was set up by nurses in 15%, doctors in 33%, physiotherapists in 9% and a combination in 41% of centres.²⁹ Often, specialist nurses play an invaluable role in exploring the patient's treatment wishes and liaising with relatives, and this may be applicable both in the chronic stable state and acutely. In addition, specialist nurses are also involved in the education of junior doctors regarding practical issues concerning NIV in acute respiratory failure.

However, there are also challenges that need to be addressed. Medical staff must effectively fulfil their roles in terms of adequate 'gatekeeping' of acute ventilatory failure units in order to prevent inappropriate admissions and subsequently incorrect treatment. Doctors must also state clearly a management plan early on during every admission, which also involves defining a ceiling of treatment and making decisions regarding cardiopulmonary resuscitation. Protocols must also be established in every unit. Such actions will be of great assistance to paramedical staff when managing patients with acute ventilatory failure. Medical staff must decide on the suitability of NIV for each individual case as well as deciding the location at which NIV should be administered, eg ICU or respiratory ward, thus acting as gatekeepers at the coalface of acute medicine.

The intensive care unit perspective and the role of acute non-invasive ventilation beyond chronic obstructive pulmonary disease

Optimal management of a patient admitted to the ICU with acute ventilatory failure begins before such a patient reaches the stage of receiving critical care. Often, patients are admitted to the ICU late during the clinical course of their illness and signs of clinical deterioration have been missed or their importance not recognised.³⁰ Adequate monitoring of patients on the ward, the early identification of deteriorating patients, subsequent liaison with the ICU, and optimal management in terms of oxygen therapy, airway, breathing and circulation may result in decreased mortality and morbidity during ICU stay or may even avoid ICU admission. Education of medical and paramedical staff in this area is fundamental, and there are both regional and national courses dealing with the recognition and management of critically ill patients. The importance of adequate handover and preserving continuity of care in view of the shortening of junior doctors' hours as a result of the European Working Time Directive was also stressed. The structure and process of delivering acute care in general requires re-evaluation and further

debate. In one study, the ICU outcome of admissions with acute respiratory failure was more dependent on dysfunction of other vital organs than on the physiological derangement of gas exchange.³¹

The role of NIV in treating acute respiratory failure outside exacerbations of COPD is increasing. Reductions in endotracheal intubation and mortality rates have been observed in the treatment of neuromuscular diseases, chest-wall diseases and obesity-hypoventilation syndrome complicated by acute ventilatory failure.^{32–34} Respiratory manifestations of morbid obesity are becoming increasingly recognised, and this includes the development of daytime ventilatory failure, which may decompensate, leading to emergency admission.^{35,36} Evidence to support the use of NIV in the treatment of immunocompromised patients with pulmonary infiltrates as well as in acute asthma and pneumonia is emerging, but it must be stressed that NIV should be administered in the ICU under such circumstances.^{37–40}

Non-invasive ventilation in acute ventilatory failure

- The use of NIV during respiratory acidosis complicating acute exacerbations of COPD has been shown to lead to a reduction in intubation rates and improved short- and longer-term survival.
- NIV may also be used in the management of acute ventilatory failure complicating cardiogenic pulmonary oedema, but intubation and mechanical ventilation should be instituted in the absence of early improvement.
- NIV may be beneficial in other causes of acute ventilatory failure, eg obesity-hypoventilation syndrome, immunocompromised patients with infiltrates, etc, but in such circumstances it should be administered in an ICU environment with ready access to invasive ventilation.
- Before initiating NIV, think: Is NIV the appropriate form of ventilatory support? Where should the patient receive NIV? What is the treatment plan in the event of failure of NIV?
- Patients showing an improvement in terms of arterial blood gases and respiratory rate in the first hour following initiation are more likely to succeed during a trial of NIV.

Ethical issues in the management of acute ventilatory failure

The frank discussion of treatment wishes regarding ICU/invasive ventilation between healthcare professionals, patients and carers needs greater emphasis. This could be carried out on an outpatient basis when the patient is stable enough to actively participate rather than during the admission itself. Regarding the role of invasive ventilation, recent studies have highlighted the considerable variation that exists between intensivists on deciding whether to admit COPD patients to the ICU as well as in predicting prognosis. Involvement of senior ICU doctors in such stable-state discussions with patients may improve such inconsistencies.⁴¹ Patients and their relatives and carers must

also be informed in a balanced manner of the potential benefits and risks of ICU admission and receiving IPPV.

Awareness and implementation of advanced directives of care are currently low in the UK, and this area warrants further detailed research.

Summary

The optimal management of acute ventilatory failure lies in a multidisciplinary approach focusing on doing simple things correctly, close liaison between healthcare professionals and adequate communication with patients and carers. The use of NIV support is increasing in a variety of conditions, both inside and outside the ICU.

References

- 1 Chung F, Barnes N, Allen M, Angus R *et al*. Assessing the burden of respiratory disease in the UK. *Respir Med* 2002;96:963–75.
- 2 Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000;55:550–4.
- 3 Royal College of Physicians and British Thoracic Society. *Report of the 2003 national COPD audit*. London: RCP and British Thoracic Society, 2004.
- 4 Denniston AK, O'Brien C, Stableforth D. The use of oxygen in acute exacerbations of chronic obstructive pulmonary disease: a prospective audit of pre-hospital and hospital emergency management. *Clin Med* 2002;2:449–51.
- 5 Crane SD, Gray AJ, Elliott MW. The role of non-invasive ventilation in the emergency department. *Emerg Med J* 2001;18:413–14.
- 6 Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. *Eur Respir J* 2002;20:545–55.
- 7 Vanpee D, Delaunoy L, Lheureux P, Thys F *et al*. Survey of non-invasive ventilation for acute exacerbation of chronic obstructive pulmonary disease patients in emergency departments in Belgium. *Eur J Emerg Med* 2002;9:217–24.
- 8 Sulaiman MI, Rodger KA, Hawkins M. A survey of the use of non-invasive positive pressure ventilation in critical care units in the United Kingdom. *Am J Respir Crit Care Med* 2004;169:A522.
- 9 Non-invasive ventilation in acute respiratory failure. *Thorax* 2002;57:192–211.
- 10 Nelson GI, Silke B, Ahuja RC, Hussain M, Taylor SH. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart-failure following myocardial infarction. *Lancet* 1983;1:730–3.
- 11 Bussmann WD, Schupp D. Effect of sublingual nitroglycerin in emergency treatment of severe pulmonary edema. *Am J Cardiol* 1978;41:931–6.
- 12 Mehta S, Jay GD, Woolard RH, Hipona RA *et al*. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit Care Med* 1997;25:620–28.
- 13 Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *N Engl J Med* 1991;325:1825–30.
- 14 Lin M, Yang YF, Chiang HT, Chang MS *et al*. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema: short-term results and long-term follow-up. *Chest* 1995;107:1379–86.
- 15 Rasanen J, Heikkila J, Downs J, Nikki P *et al*. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Am J Cardiol* 1985;55:296–300.

- 16 Bellone A, Vettorello M, Monari A, Cortellaro F, Coen D. Noninvasive pressure support ventilation vs. continuous positive airway pressure in acute hypercapnic pulmonary edema. *Intensive Care Med* 2005;31:807–11.
- 17 Park M, Sangean MC, Volpe Mde S, Feltrim MI *et al.* Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Crit Care Med* 2004;32:2407–15.
- 18 Duffy N, Walker P, Diamantea F, Calverley PM, Davies L. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Thorax* 2005;60:713–17.
- 19 Barr RG, Rowe BH, Camargo CA. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003;2:CD002168.
- 20 Barr RG, Rowe BH, Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. *BMJ* 2003;327:643.
- 21 Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. *Thorax* 2001;56:708–12.
- 22 Brochard L, Mancebo J, Wysocki M, Lofaso M *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817–22.
- 23 Scala R, Bartolucci S, Naldi M, Rossi M, Elliott MW. Co-morbidity and acute decompensations of COPD requiring non-invasive positive-pressure ventilation. *Intensive Care Med* 2004;30:1747–54.
- 24 Diaz GG, Alcaraz AC, Talavera JC, Perez PJ *et al.* Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. *Chest* 2005;127:952–60.
- 25 Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax* 1996;51:1048–50.
- 26 Breen D, Churches T, Hawker F, Torzillo PJ. Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: a long term follow up study. *Thorax* 2002;57:29–33.
- 27 Nevins ML, Epstein SK. Predictors of outcome for patients with COPD requiring invasive mechanical ventilation. *Chest* 2001;119:1840–9.
- 28 Ai-Ping C, Lee KH, Lim TK. In-hospital and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD: a retrospective study. *Chest* 2005;128:518–24.
- 29 Doherty MJ, Greenstone MA. Survey of non-invasive ventilation (NIPPV) in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) in the UK. *Thorax* 1998;53:863–6.
- 30 McQuillan P, Pilkington S, Allan A, Taylor B *et al.* Confidential inquiry into quality of care before admission to intensive care. *BMJ* 1998;316:1853–8.
- 31 Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995;274:1852–7.
- 32 Perez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A *et al.* Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005;128:587–94.
- 33 Rabinstein A, Wijdicks EF. BiPAP in acute respiratory failure due to myasthenic crisis may prevent intubation. *Neurology* 2002;59:1647–9.
- 34 Elliott MW, Steven MH, Phillips GD, Branthwaite MA. Non-invasive mechanical ventilation for acute respiratory failure. *BMJ* 1990;300:358–60.
- 35 Gibson GJ. Obesity, respiratory function and breathlessness. *Thorax* 2000;55(Suppl 1):41–4.
- 36 Nowbar S, Burkart KM, Gonzales R, Fedorowicz A *et al.* Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004;116:1–7.
- 37 Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest* 2003;123:1018–25.
- 38 Hilbert G, Gruson D, Vargas F, Valentino R *et al.* Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481–7.
- 39 Confalonieri M, Calderini E, Terraciano S, Chidini G *et al.* Noninvasive ventilation for treating acute respiratory failure in AIDS patients with *Pneumocystis carinii* pneumonia. *Intensive Care Med* 2002;28:1233–8.
- 40 Confalonieri M, Potena A, Carbone G, Porta RD *et al.* Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999;160:1585–91.
- 41 Wildman MJ, O'Dea J, Kostopoulou O, Tindall M *et al.* Variation in intubation decisions for patients with chronic obstructive pulmonary disease in one critical care network. *Q J Med* 2003;96:583–91.