Pulmonary hypertension in COPD

# Pulmonary hypertension in patients with COPD: NO treatment?

**J Pepke-Zaba, N W Morrell**

The application of "pulsed" NO combined with LTOT may have a role in treating pulmonary hypertension secondary to COPD.

Following the identification of nitric oxide (NO) in 1986 as "endothelium derived relaxing factor", there has been an exponential growth in our understanding of the physiological role of NO culminating in the award of a Nobel Prize, and the naming of NO as "molecule of the decade".[1] Considerable research has subsequently been devoted to understanding the role of this molecule in vascular biology in general, and the pulmonary vascular system in particular.

NO is an unstable radical with a low blood gas partition coefficient. For decades NO was considered an environmental contaminant produced by bacteria and internal combustion engines. Believed to be highly toxic, it appeared an unlikely candidate for a major role as a biological mediator. However, within the last 15 years it has become clear that endogenously produced NO is ubiquitous in mammalian systems, playing an important role in both health and disease: in the regulation of blood pressure and flow, inflammatory responses, and neurotransmission. Insight into these physiological roles has led to its use as a therapeutic agent in a number of clinical settings.

There are ample data to support a major role for NO in the regulation of tone and vascular remodelling in the normal and diseased pulmonary circulation. Endothelial NO contributes significantly to the normally low pulmonary vascular tone,[2] and dysfunction of endothelial NO release has been documented in patients with chronic obstructive pulmonary disease (COPD).[3 4] Although nitro-vasodilatation (acting through the intracellular generation of NO) has been used effectively since the 1800s for systemic arterial dilatation (delivered sublingually, orally, and intravenously), the prospect of selective pulmonary nitro-vasodilatation only became evident in the early 1990s.[5] Treatment with inhaled NO has subsequently been applied in a variety of lung diseases which have in common a degree of pulmonary vascular endothelial dysfunction and/or abnormalities of gas exchange based on low ventilation/perfusion (V/Q) ratios. This includes the use of NO in patients in intensive care, neonates with persistent pulmonary hypertension, and in postoperative settings where NO is used to reduce pulmonary vascular resistance and/or improve oxygenation—for example, pulmonary thromboendarterectomy, heart and lung transplantation, acute lung injury.

In the lungs, one important molecule with which NO reacts is oxyhaemoglobin ($HbO_2$). The affinity of $HbO_2$ for NO is $10^6$ times greater than its affinity for oxygen.[6] Oxidative reactions of NO with haemoglobin largely limit the effects of inhaled NO to the lung vasculature. However, there are reports that high concentrations of inhaled NO have peripheral vascular effects when peripheral endothelial NO synthesis is blocked, suggesting that at least a portion of inhaled NO survives long enough to reach tissue remote from the lungs.[7] The major immediate breakdown products of NO in human plasma are inactive nitroxides such as nitrite ($NO_2^-$). The rate of this reaction increases exponentially with the concentration of both oxygen and NO.[8] This has several consequences. Firstly, low NO concentrations or oxygen free environments permit relatively long term persistence of NO. Secondly, the therapeutic efficacy of inhaled NO may not rise dramatically with increased doses as the more NO given, the faster it is oxidised.[9] In fact, higher doses of NO result in a relatively greater proportion of toxic products with little incremental yield of intact NO. Finally, the rapid inactivation of inhaled NO in an oxygen rich environment is what makes NO a selective pulmonary vasodilator. Inhalation delivers NO to the pulmonary resistance vessels before it is oxidised. The seconds before the inhaled NO enters the systemic circulation are enough for its breakdown by interaction with oxygen and haemoglobin.

Pulmonary hypertension secondary to COPD is probably more common than is generally appreciated. Right heart catheterisation studies suggest a prevalence of up to 40% in selected series of patients with severe COPD.[10 11] A degree of pulmonary hypertension was observed in 55% of consecutive respiratory outpatients using Doppler echocardiography.[12] The presence of pulmonary hypertension in patients with COPD is associated with increased mortality[11 13] and an increase in exacerbation rate and length of hospital stay, independent of the degree of airflow obstruction.[14] Although often inferred, the precise contribution of pulmonary hypertension to exercise limitation or quality of life in stable COPD patients is unknown. Mean pulmonary artery pressure in patients with COPD is typically mild (in the region of 25 mm Hg) at rest but can rise to abnormally high levels on exercise.

At present there are no specific treatments recommended for the reduction of pulmonary artery pressure in COPD. Although long term oxygen therapy (LTOT) improves survival in hypoxaemic patients with COPD, it has a negligible effect on pulmonary haemodynamics. Clearly, other factors in addition to alveolar hypoxia contribute to the development of pulmonary hypertension in COPD. For example, remodelling of the pulmonary vessels is present in many patients with mild COPD who are not hypoxaemic and appears to be related to cigarette smoking.[15]

There are several reports of the use of inhaled NO in patients with stable COPD.[16–19] NO inhalation alone may worsen V/Q relationships and exacerbate systemic hypoxaemia while lowering pulmonary vascular resistance. However, when NO is delivered to well ventilated alveolar units with fast time constants, the deleterious impact on gas exchange is avoided.[19] This effect can also be achieved by using "pulsed" delivery of NO where spikes of NO are added at the beginning of inspiration. The addition of oxygen to NO further prevents hypoxaemia.

The study reported in this issue of *Thorax* by Vonbank *et al*[20] shows that long term use of pulsed NO with oxygen leads to sustained improvement in pulmonary haemodynamics without worsening hypoxaemia in patients with stable COPD. Benefits of the pulsed method include the reduced formation of nitrogen dioxide and methaemoglobinaemia. A further safety issue that needs to be addressed is whether discontinuation of long term inhaled NO can lead to severe rebound pulmonary hypertension. Although the results presented by Vonbank *et al* show promise, it remains to be determined whether pulsed NO/oxygen treatment will lead to an improvement in exercise tolerance, quality of life, and survival in patients with hypoxaemic COPD. Potential disadvantages of the approach include the delivery system and monitoring systems necessary to ensure accurate dosing and safety. In addition, long term gas therapies are far



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from convenient for the patient. NO reduces pulmonary vascular resistance by increasing cyclic GMP levels in vascular smooth muscle cells. This effect can also be achieved by inhibition of the enzymes that metabolise cyclic GMP. Inhibitors of the type 5 cyclic GMP phosphodiesterase such as sildenafil may have some selectivity for the pulmonary circulation, and it remains to be seen whether these drugs administered orally may have an effect equivalent to inhaled NO.

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Childhood asthma

# Second line treatment for severe acute childhood asthma

**M South**

The choice of treatment for a child with severe acute asthma unresponsive to high dose inhaled bronchodilators and oral or intravenous corticosteroids is still the subject of debate. Although both salbutamol and aminophylline have been around for a long time and have been the subject of many studies, it is still not possible unreservedly to recommend one of these agents over the other as second line treatment.

Most physicians would agree that first line treatment for an acute exacerbation of childhood asthma should be the administration of high dose inhaled bronchodilators[1] and corticosteroids administered either orally or intravenously,[2] but when a child with severe acute asthma is unresponsive to such treatment—what should come next? This is an important question that is faced by doctors every day in emergency departments, paediatric wards, and intensive care units the world over. Most commonly, physicians will reach next for intravenous salbutamol or intravenous aminophylline, although some will consider other treatments.

Salbutamol and aminophylline have been shown to be individually better than placebo in severe acute asthma.[3 4] Although a recent Cochrane systematic review appeared to cast doubt on this statement for salbutamol,[5] many suspect that this is a flaw caused by the inclusion of several very weak early studies of salbutamol in the analysis. A large study of aminophylline[6] and another Cochrane systematic review[7] have confirmed its efficacy in improving a number of important outcomes including the need for, and duration of, mechanical ventilation in acute childhood asthma.

A study by Roberts *et al*[8] in this edition of *Thorax* is the first to compare the two agents using a good trial design. The authors have attempted to study these second line treatments in a randomised controlled trial to compare an intravenous bolus of salbutamol with a loading dose of aminophylline followed by an intravenous infusion. They have inevitably come across two of the major obstacles faced by anyone studying acute asthma episodes in children: (1) how to study such very sick children and (2) what outcomes are both measurable and important in this context? Improvement in severity score and reduced length of hospital stay are clearly of interest but are not the main goals of treatment. Unfortunately, despite the inclusion of five hospitals in the study, their sample size is still relatively small with only 44 subjects. Although this was the required number from the calculations, it is too small to address important outcomes such as the need for intensive care admission or mechanical ventilation, and much too small to examine an impact on long term morbidity or mortality from severe asthma exacerbations. In their salbutamol group 11% of patients required intubation and ventilation, while only 4% in the aminophylline



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group required such intervention. It is a pity that the study is too small to draw any statistical inference from this difference.

The results of the study are useful but they could have been even more powerful if the investigators had chosen to use each of the agents in an optimal fashion. For the intravenous salbutamol arm, the study design would have been better if they had included either repeated bolus doses or an infusion of salbutamol. For the aminophylline arm, the loading dose given (5 mg/kg) was small and the levels achieved were probably inadequate to fully test the efficacy of the agent. Despite these limitations, the study was well conducted and the results have implications for everyday paediatric practice.

Efficacy is only one issue in choosing between treatments. For salbutamol and aminophylline cost differentials and administration practicalities are irrelevant, but differences in drug safety may be important. Aminophylline has a relatively narrow therapeutic margin, with nausea and vomiting being common even with drug levels in the therapeutic range. Severe toxicity has been reported when the drug is given in overdose.

There are a large number of children worldwide who suffer severe exacerbations of asthma each year; both salbutamol and aminophylline have been around for a long time and many studies have been conducted. It is therefore surprising that we still cannot unreservedly recommend which of these agents to choose first when faced with the scenario described above. On balance, it seems that aminophylline has advantages for efficacy but at the cost of additional adverse effects. There is also very limited evidence about the efficacy of using intravenous salbutamol and aminophylline together, although it is quite common practice for them to be used in this way.

To further complicate decision making in severe acute asthma, a number of other treatments present themselves as candidates for second line therapy. These include alternative $\beta_2$ agonists (such as adrenaline); inhalational anaesthetic agents (such as halothane); intravenous magnesium sulphate; inhaled helium-oxygen mixtures; or non-invasive mechanical respiratory support of various forms such as face mask continuous positive airway pressure (CPAP). Most of these treatments have only a theoretical basis for their use, or evidence from case reports or small studies comparing them with placebo or no treatment. There are no useful comparative studies, and it is going to become increasingly difficult to evaluate the place of the multitude of treatments available with any certainty. What is certain is that emergency treatment should not be delayed, and that any agents chosen must be used both optimally and safely.

The bad news for children with severe acute asthma is that the doctors caring for them will have to make decisions between complex treatment regimens with only limited scientific evidence to aid them. The good news, however, is that the risk of death or an adverse outcome from acute asthma is fortunately small once the child has reached a high quality health care facility.

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Critical care

# Improving the care for patients with acute severe respiratory disease

**M W Elliott**

Services to improve the care of patients with acute severe medical conditions in general, and respiratory disease in particular, need to be improved. This includes access to a non-invasive ventilation service, available 24 hours per day, in all hospitals admitting patients with acute medical conditions.

In the early 1960s the first coronary care units (CCU) were established and are now a "given" in every hospital admitting patients with acute cardiac disease. For patients admitted to hospital with physiological disturbance due to non-acute cardiac medical conditions, the only options are usually either admission to an intensive care unit (ICU) or to a general medical ward. Inevitably, given the differences in staffing and facilities with one nurse looking after one patient with comprehensive physiological monitoring on the ICU compared with perhaps only two or three nurses looking after 30 patients at night with minimal continuous monitoring on a general medical ward, some patients will be admitted to the ICU who could be managed elsewhere. This is economically disadvantageous. Alternatively, patients may be looked after in an area in which proper care is not possible. This is an issue of standards of care and clinical governance. In the UK there are a number of drivers towards improving the acute care for medical patients including two recent reports—one from the Royal College of Physicians of London[1] and the other from the NHS Modernisation Agency.[2] Patients with respiratory failure constitute a significant proportion of medical admissions and the development of appropriate services for these patients is important from both the clinical governance and the economic perspectives. The provision of appropriate facilities for patients with acute severe respiratory disease is not just an issue in the UK.[3]



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## CLINICAL GOVERNANCE

The report by the Royal College of Physicians (RCP) Working Party looked at the interface between acute medicine and critical care and highlighted the fact that the standard of care received by acutely ill inpatients in the UK has been shown to be suboptimal in a number of recent surveys and publications.[1] In a confidential inquiry into quality of care before admission to the ICU,[4] two external reviewers assessed the quality of care—especially recognition, investigation, monitoring, and management of abnormalities of airway, breathing and circulation, oxygen therapy and monitoring—in 100 consecutive admissions to two UK ICUs. Twenty patients were deemed by both to have been well managed and 54 to have received suboptimal management, with disagreement about the remainder. Case mix and severity were similar between the groups, but ICU mortality was worse in those who both reviewers agreed received suboptimal care. Admission to the ICU was considered late in 37 patients in the suboptimal group. Overall, a minimum of 4.5% and a maximum of 41% of admissions were considered potentially avoidable. Suboptimal care contributed to morbidity or mortality in most instances. The main causes were failure of organisation, lack of knowledge, failure to appreciate clinical urgency, lack of supervision, and failure to seek advice.

In another UK study[5] of patients either dying unexpectedly on a general ward or requiring admission to the ICU during a 6 month period, 317 of the 477 hospital deaths occurred on the general wards of which 20 (6%) followed failed attempts at resuscitation. Thirteen of these unexpected deaths were considered potentially avoidable: gradual deterioration was observed in physiological and/or biochemical variables, but appropriate action was not taken. During the same period 86 hospital inpatients were admitted on 98 occasions to the ICU, 31 of whom received suboptimal care before the ICU admission either because of non-recognition of (the severity of) the problem or inappropriate treatment. Mortality rates were significantly higher in these patients than in well managed patients in both the ICU (52% *v* 35%) and hospital (65% *v* 42%), $p<0.0001$. The authors concluded that patients with obvious clinical indicators of acute deterioration can be overlooked or poorly managed on the ward.

In a study from the USA[6] the records of consecutive inpatients who had a cardiac arrest over a 20 month period were reviewed. There were 150 cardiac arrests on the medical wards with a hospital mortality rate of 91%. In 99 cases a nurse or physician had documented deterioration in the patient's condition within 6 hours of the cardiac arrest. Common findings included failure of the nurse to notify a physician of a deterioration in the patient's mental status or failure of the physician to obtain or interpret an arterial blood gas measurement in the setting of respiratory distress. Cardiac arrests were more common in patients discharged from the ICU. Schein *et al*[7] reported a similar picture with 84% of inpatient cardiac arrests having documented deterioration within 8 hours of the event. There is therefore a clear need to improve the quality of care afforded to patients with acute non-cardiac medical conditions.

There are a number of solutions,[8] including better education of medical and nursing staff and more senior input into the assessment of patients at an early stage in the admission. ICU outreach teams are strongly recommended to avert admissions by identifying patients who are deteriorating and either helping to prevent admission or ensuring that admission to a critical care bed happens in a timely manner to ensure best outcome.[9] This presupposes that such patients are brought to the attention of the team and this can be helped by the use of early warning scores.[10] The team needs to be available 24 hours per day. The RCP Working Party recommended that appropriate facilities for provision of level 2 care (see box 1) to medical patients be available. Ideally this should be in close proximity to the level 3 facility and suggests the need for a unit for medical patients, of whom a significant proportion will be those with respiratory disease.

## NON-INVASIVE VENTILATION

There is now a robust evidence base[11 12] for the use of non-invasive ventilation (NIV) in patients with mild (pH 7.31–7.35),[13] moderate (pH 7.25–7.30),[14–17] and severe (pH <7.25)[18] acidotic exacerbations of chronic obstructive pulmonary disease (COPD).[11] It is best instituted "early" before ventilatory support is definitely needed but, even when the patient appears to warrant intubation and mechanical ventilation, there is much to be gained and little to be lost by a trial of NIV.[18] NIV has also been used in patients with hypoxaemic respiratory failure resulting from a variety of different conditions.[19–22] It has been shown to be both more effective and cheaper than intubation and ventilation on the ICU[23] and conventional treatment on general wards.[24] It is certainly feasible outside the ICU.[13]

**Box 1 Levels of care as defined by the Department of Health[9]**

Level 0: Patients whose needs can be met through normal ward care in an acute hospital.
Level 1: Patients at risk of their condition deteriorating, or those recently relocated from higher levels of care whose needs can be met on an acute ward with additional advice and support from the critical care team.
Level 2: Patients requiring more detailed observation or intervention including support for a single failing organ system or postoperative care and those "stepping down" from higher levels of care.
Level 3: Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multiorgan failure.

A review of adult critical care services in the UK published by the Department of Health[9] recognised that NIV was one of a number of clinical areas impacting upon the level of critical care provision that required additional evaluation. In response the NHS Modernisation Agency Critical Care Team assembled a multiprofessional working group to discuss the issues relating to current practice and the resources needed to deliver a service. Their report and an Executive Summary were published in April 2002[2] and are available at www.criticalcare.nhs.uk. A key recommendation was that "an NIV service be established in each acute trust for the management of patients with acute respiratory failure . . .". A number of further recommendations were made including that NIV should be available continuously, appropriately supported by nursing and allied health professional staff, equipped to standards specified by the British Thoracic Society[25] with data collection and audit facilities and a training facility for all junior medical, nursing, and allied health professional staff.

Acute NIV has grown out of home ventilation and the technology necessary to deliver it is easily portable. It could therefore be argued that it is easy to take the equipment to the patient and there is no need to have a specialist unit with NIV being possible for all patients in any clinical area. However, the evidence does not support this approach for the generality of patients needing NIV. In a study by Plant *et al*,[13] while it was clear that NIV was feasible on a standard general ward with the usual staffing complement, subgroup analysis suggested that the outcome for those with a pH of <7.30 using a simple ventilator according to protocol was not as good as the results seen in patients with similar illness severity managed in a higher dependency setting. There is much more to NIV than the provision of the necessary hardware and there are many advantages to concentrating the NIV service in one location. Foremost among these is the development of the appropriate expertise, particularly among the



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nursing staff. Whether nurses are the primary deliverers of NIV or whether another professional group such as physiotherapists or technicians takes the main role, the nurses must be familiar with it because they are the only healthcare professionals who are with the patient 24 hours per day. They must be both confident about the technique and recognise when there are problems, particularly of a technical nature. Continued use of skills once learnt is important in maintaining them, and this will be facilitated by concentrating all the NIV in one area. Plant *et al*[26] showed that if all patients needing NIV shortly after admission to an average district hospital with an acute exacerbation of COPD were managed in two areas, the staff would treat ⩽1 patients per month 20% of the time, whereas if it was all delivered in one mixed sex location this reduced to 2%. NIV is used for many other conditions, but patients with an acute exacerbation of COPD are likely to remain the largest group. A single location also facilitates the purchase and use of appropriate monitoring equipment and storage of both ventilators and consumables.

One further approach to consider is that of an NIV team, perhaps led by a nurse consultant, which does indeed take the technology to the patient. This is in keeping with the philosophy behind comprehensive critical care—namely, of a service rather than a place—but it is difficult and expensive to provide such a service 24 hours per day throughout the year. Because the nurse primarily responsible for the bedside care of the patient is unlikely to be familiar with NIV or to gain much experience of it over time, a lot of "hands on" support will be required on a "one to one" basis. It may be difficult for the team if there are a number of patients receiving NIV dispersed around the hospital. In practice most of the time is needed at initiation of NIV[13 15 27] and, once patients are established, they will just need a watching brief and regular review, but help should be readily available if there are problems.

The exact model will vary from hospital to hospital, but there is now a clear requirement to provide an acute NIV service[2] in all hospitals admitting emergency medical patients and to improve the standard of care for patients with acute severe medical conditions generally.[1] These requirements may be best met by a general medical or multispecialty high dependency unit (HDU). However, in a recent survey only 26% of 190 general hospitals with an ICU had an HDU[28]; the proportion of beds allocated for medical patients was not stated. Anecdotal evidence suggests that there has been a considerable expansion in HDU facilities in the last 2–3 years, but there are no firm data on this. Most of the extra provision has been for surgical patients, driven by cancelled operations because of the lack of ICU bed and waiting list targets. Physicians as a group should certainly be pressing for more level 2 facilities for their patients. However, if these are not forthcoming, the need to improve the standard of care for patients with acute respiratory disease and to provide an NIV service could be achieved in respiratory medicine at a relatively small extra cost compared with many other critical care initiatives.

The experience of NIV in Continental European and North American ICUs suggests that a nurse to patient ratio of 1:3 or 4 is satisfactory, which compares favourably in economic terms with a classical UK HDU in which one nurse is recommended for two patients. Designating part—say, one bay—of a larger specialist ward as a mixed sex "acute respiratory care unit" would provide a focus for NIV, as well as the care of level 1 and 2 patients with acute severe respiratory disease. In such a unit staff can be used flexibly and there is no need for major and expensive building works. It is largely an administrative change, with some extra staffing resource and improved monitoring. The patients are already being cared for within the medical (usually) bed base; instead of being dispersed they are now in one location. The beds must be considered in the same light as coronary care and other higher dependency beds in terms of bed management to ensure that the patients who need acute respiratory care are managed in the right environment. It should no longer be acceptable—even at times of great pressure when medicine extends outside its bed base—for acute admissions with physiological compromise due to respiratory or any other organ failure to be managed at the end of a non-acute surgical ward.

A further advantage of such units is that they can allow earlier discharge of some patients with respiratory disease from level 3 beds. Training and education are vital,[1 2 25] and junior medical staff should spend some time in critical care areas as part of their general professional training.[1 2 25] Respiratory physicians must ensure that all junior medical and nursing staff are adequately trained in the management of acute severe respiratory disease. Some consultants who were appointed before NIV became available may need training in this specific area. In the future the training of more physicians with dual accreditation in respiratory medicine and critical care is desirable.[29 30] The requirement to provide an acute 24 hour per day NIV service is a major driver to improve the standard of care for all patients with acute severe respiratory disease. The development of acute respiratory care units, either integrated into a more general HDU or as part of an existing respiratory ward, is a logical way forward. Such units should not function in isolation and clear protocols and coordination with intensive care units are vital.

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