REVIEW SERIES

Chronic obstructive pulmonary disease • 9: Management of ventilatory failure in COPD

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The management of respiratory failure during acute exacerbations of COPD and during chronic stable COPD is reviewed and the role of non-invasive and invasive mechanical ventilation is discussed.

MANAGEMENT OF RESPIRATORY FAILURE DURING ACUTE EXACERBATIONS OF COPD

The purpose of managing respiratory failure/supporting ventilation in acute exacerbations of chronic obstructive pulmonary disease (COPD) is to prevent tissue hypoxia and control acidosis and hypercapnia while medical treatment works to maximise lung function and reverse the precipitating cause of the exacerbation. There are four strategies to consider:

- oxygen therapy;
- respiratory stimulants;
- non-invasive ventilation; and
- invasive mechanical ventilation.

They should be considered as adjuncts to optimum medical treatment which will usually include bronchodilators, systemic steroids, and antibiotics. Their use will depend on availability, but also on the severity of the respiratory failure.

pH as a marker of severity

In acute exacerbations of COPD, pH is the best marker of severity and reflects an acute deterioration in alveolar hypoventilation compared with the chronic stable state.[1 2] Regardless of the chronic level of arterial carbon dioxide tension ($Paco_2$), an acute rise in $Paco_2$ due to worsening alveolar hypoventilation is associated with a fall in pH. Warren *et al*[3] retrospectively reviewed 157 admissions with COPD and found that death was associated with increasing age and a low pH, a pH of <7.26 being associated with a particularly poor prognosis. In 1992 this group also reported a prospective study of 139 episodes of respiratory failure in 95 patients with COPD.[4] Death occurred in 10 of the 39 episodes in which $[H]^+$ rose above 55 mmol/l (that is, pH <7.26). Hypoxia and hypercapnia were not different between the survivors and those who died. Similarly, in a 1 year period prevalence study of patients admitted to hospital with COPD, the mortality in patients with a normal pH was 6.9%, rising to 13.8 % in those who were acidotic (pH <7.35) after initial medical treatment.[5] Moreover, studies of non-invasive ventilation (NIV) have also found pH to be predictive of the need for intubation and in-hospital mortality.[6–11]

These data support the theoretical view that it is not the absolute level of $Paco_2$ that is important but the magnitude and speed of any change, which is reflected by pH. COPD patients with acidosis account for 20% of all COPD admissions.[5]

Oxygen therapy

Since the 1960s it has been known that uncontrolled oxygen therapy can produce respiratory acidosis and CO_2 narcosis, requiring invasive mechanical ventilation.[12] Similarly, there is concern that leaving patients profoundly hypoxic is potentially life threatening[13]—for example, due to arrhythmia. The mechanism by which oxygen is responsible for the deterioration in arterial blood gases is ill understood. However, the main mechanism appears to be an increase in Vd/Vt with a small component due to a reduction in respiratory drive.[14–16]

At present the BTS guidelines[17] recommend that Pao_2 should be maintained at >6.6 kPa without a fall in pH below 7.26, or >7.5 kPa if the pH is satisfactory. Controlled oxygen therapy is recommended—that is, fixed percentage Venturi masks or low flow nasal cannulae. The latter are associated with more variable Fio_2.[18] However, there are no good quality data on the proportion of patients at risk because these studies are very difficult to perform. Studies in patients with stable COPD are unlikely to be generalisable to the unstable state, so acute studies are necessary. There are some epidemiological data to suggest that all hypercapnic patients are susceptible to oxygen therapy and these account for 47% of COPD admissions.[5] There is also some evidence that maintaining Spo_2 between 85% and 92% (equivalent to 7.3–10 kPa) minimises the risk of acidosis[5] and that a Pao_2 of >10 kPa is associated with acidosis in 33–50% of hypercapnic COPD patients.[19 20] Jubran and Tobin[21] studied invasively ventilated patients and found that targeting an Spo_2 of 92% provided a satisfactory level of oxygenation, but that oximetry was less reliable in black patients. Taking into account the shape of the oxygen dissociation curve and that patients with COPD are usually acclimatised to a degree of hypoxia, delivering oxygen to maintain an Spo_2 of 85–92% may be safer and more appropriate than recommending a particular concentration of oxygen. In a small study Moloney *et al*[22] found that only three of 24 patients developed clinically important CO_2 retention (defined as a rise in $Paco_2$ of >1 kPa) with oxygen therapy administered to maintain the oxygen saturation at 91–92%. However, Agusti *et al* [91] found that delivering oxygen at the lowest concentration to achieve an Spo_2 >90% was associated with significant periods during

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Table 1 Effectiveness of non-invasive ventilation (NIV) in patients with COPD in the ICU, on the ward, and in A&E departments

	Setting	Baseline data pH	ETI or "surrogate"	Mortality	Mode plus settings (cm H_2O) and use on day 1 (when stated)
ICU studies					
Brochard *et al*[28]	ICU	7.28 *v* 7.27	11/43 *v* 31/42	4/43 *v* 12/42	PSV 20 for at least 6 hours/day
Celikel *et al*[30]	ICU	7.27 *v* 7.28	1/16 *v* 6/15	0/15 *v* 1/15	PSV 15.4 for mean of 26.7 hours
Kramer *et al*[29]	ICU	7.29 *v* 7.27	9% *v* 67%		IPAP 11.3, EPAP 2.6 for 20.1 hours
Martin *et al*[31]	ICU	7.27 *v* 7.28	25% *v* 45%; 5.26 *v* 15.6/100 ICU days	8% *v* 9%	IPAP 11, EPAP 5.7
Ward studies					
Angus *et al*[33]	Ward	7.31 *v* 7.30	0/9 *v* 5/8	0/9 *v* 3/8	IPAP 14–18
Bardi *et al*[35]	Ward	7.36 *v* 7.39	1/15 *v* 2/15	0/15 *v* 1/15	IPAP 13, EPAP 3
Bott *et al*[32]	Ward	7.35	0/30 *v* 5/30	3/30 *v* 9/30	Volume cycled ventilators for 7.63 hours
Plant *et al*[34]	Ward	7.32 *v* 7.31	15% *v* 27%	10% *v* 20%	IPAP 10–20, EPAP 5 for median of 8 hours
A&E studies					
Barbe *et al*[36]	A&E and ward	7.33	0/12 *v* 0/12	0/12 *v* 0/12	IPAP 14.8, EPAP 5 for 2 × 3 hour sessions per day
Wood *et al*[37]	A&E	7.35 *v* 7.34	See text	See text	Subgroup COPD (n=6 of which 2 NIV, 4 control)

ETI=endotracheal intubation; PSV=pressure support ventilation.

the 24 hours when Spo_2 was <90%, but that this was less with Venturi masks than with nasal cannulae (5.4 *v* 3.7 hours, p<0.05). However, there were no episodes of worsening hypercapnia or acidosis in the patients under study. There are no definitive data to inform the correct use of supplemental oxygen in acute exacerbations of COPD, but individual titration with regular monitoring of pulse oximetry and arterial blood gas tensions should be performed. There is evidence that oxygen therapy is more effective with the use of a prescription chart.[23]

Respiratory stimulants

Doxapram is the most widely used respiratory stimulant. Its effectiveness has been the subject of a Cochrane systematic review,[24] the conclusions of which were that doxapram is the most effective respiratory stimulant but is only able to provide minor short term improvement in blood gas tensions.[25–27] One randomised controlled trial has compared the effectiveness of doxapram with NIV.[25] Seventeen patients were randomised to receive either NIV (n=9) or conventional therapy plus doxapram (n=8). In the doxapram group an improvement in Pao_2 was seen at 1 hour compared with baseline, but by 4 hours no difference was seen in either Pao_2 or $Paco_2$. In the NIV group Pao_2 and $Paco_2$ improved and was maintained. There was a statistically non-significant trend to improved survival in the NIV group with 3/8 dying with conventional care and 9/9 surviving with NIV. With the increasing use of NIV, doxapram should be confined to patients who are awaiting initiation of NIV, when it is not available or poorly tolerated, or for those who have reduced drive—for example, due to sedatives and anaesthetic agents.

Non-invasive ventilation

NIV can be used in the intensive care unit, in the ward, or in the accident and emergency department. A number of randomised controlled trials have looked at the effectiveness of NIV in these locations (table 1), with most including patients with an acute exacerbation of COPD, a raised respiratory rate, and a pH <7.35 with a $Paco_2$ of >6 kPa.[28–37] Patients deemed to warrant immediate intubation were excluded from all studies.

The rates of intubation and mortality are generally higher in the ICU studies despite similar arterial blood gas criteria.[30 38–40] Patients in the emergency department who are acidotic will have had little time to respond to medical treatment and hence those allocated to medical treatment will generally do well, avoiding intubation and mortality.[36] By comparison, individuals in the ICU remain acidotic despite much medical treatment and, for them, being allocated to medical treatment will be associated with a higher risk of intubation or mortality.

By pooling the ICU studies (mean pH 7.28), the risk of intubation is 63% (95% CI ±9.4%) with a 66% reduction in risk with NIV to 21% (±7.7%).[28–30 40] Similarly, NIV reduces mortality from 25% (± 8.4%) to 9% (± 5.6%), a risk reduction of 64%. Hence, in the ICU the numbers needed to treat (NNT) are 2.4 to prevent one intubation and 6.3 to prevent one death. In health economic terms Keenan *et al*[41] have also shown, using decision tree analysis, that NIV in the ICU results in improved clinical outcomes but also reduced costs from the hospital's perspective.

In the ward setting 16% of all patients admitted with COPD remain acidotic.[34] For a typical district general hospital, this equates to 72 patients per year.[5] It is not possible in the UK for all these patients to be managed on the ICU and ward based NIV has to be considered. However, the technique is likely to be less effective in this setting with a lower nurse to patient ratio, limited monitoring facilities, and less experience of ventilatory support.

In the largest ward trial, simple protocol driven NIV reduced the need for intubation on objective criteria from 27% to 11%, real intubation rates from 11% to 6%, and mortality from 20% to 10%. A risk reduction for all three end points of 45–50% and NNT of 8.3 for objective criteria for intubation, 20 for real intubation, and 10 for mortality was achieved.[34] NIV could be established in 93% of patients and only consumed an additional 26 minutes of qualified nursing time. For patients with an initial pH of <7.30 the outcome with this strategy was less good than expected from the ICU studies. This may reflect the fact that 11 of 14 centres were new to the technique. It may also reflect the limitations of the simple ventilator and protocol rather than limitations of the setting alone.

Within the A&E there is little evidence to support the routine use of NIV in all acidotic patients as the study by Barbe *et al* showed that no patients in the conventional arm required endotracheal intubation or died.[36] Moreover, it is known that 20% of all acidotic patients in the A&E correct their pH by the time they reach the ward, and the study by Barbe *et al* with only 12 patients in each limb was underpowered to pick up a difference in outcome.[5 36]

Monitoring of patients on NIV and managing the failing patient

One study in the ward environment has shown a potential disadvantage of NIV. Wood *et al*[37] randomised 27 patients with acute respiratory distress to receive conventional treatment or NIV in the emergency department. Intubation rates were similar (7/16 *v* 5/11), but there was a non-significant trend

Table 2 Controlled clinical trials of non-invasive ventilation (NIV) versus conventional therapy: 1 year survival

	n	Conventional	NIV
Plant[11]	118	54%	62%
Bardi[35]	15	53%	87%
Confalonieri[49]	24	50%	71%
Vitacca[48]	27/30	37%*	70%

*All intubated in the conventional control group.

towards increased mortality in those given NIV (4/16 *v* 0/11, p=0.123). The authors attributed the excess mortality to a delay in intubation as conventional patients requiring invasive ventilation were intubated after a mean of 4.8 hours compared with 26 hours in those on NIV (p=0.055). It is difficult to draw many conclusions from this study about the place of NIV in acute exacerbations of COPD, given its small size; only six patients had COPD and they were not severely ill on pH criteria (mean pH at entry 7.35). The groups were also poorly matched with more cases of pneumonia in the NIV group. However, it does highlight the need to monitor patients, offer NIV in a location with trained nurses, and to ensure that endotracheal intubation is promptly available when needed.

The time at which NIV should be abandoned in favour of invasive mechanical ventilation (IMV) is unclear. However, improvement in pH, a fall in $Paco_2$, and a fall in the respiratory rate over the first 1–4 hours are consistently associated with success in both controlled and uncontrolled trials.[4–6 11 28 30 32 42–45]

Failure later in the course of the admission after a period of successful NIV—that is, beyond 48 hours—is associated with a poorer prognosis. Moretti *et al*[46] studied 137 patients admitted with COPD and acute hypercapnic respiratory failure, initially treated successfully with NIV, of which 23% deteriorated after 48 hours of NIV. These so called "late failures" were then assigned (non-randomly) to either an increased number of hours of NIV or IMV, depending on the wishes of the patient and/or relatives. Patients assigned to increased NIV did significantly worse with a mortality of 92% compared with 53% in those invasively ventilated, but there was a substantial difference in the mean pH at the time of "late failure" between the groups.[47] Regardless of this, failure of NIV late after initial successful NIV carries a poor prognosis.

Invasive mechanical ventilation (IMV)

The place of IMV in patients with COPD needs to be re-evaluated in the light of the increasing availability of NIV. The reported outcome after intubation tends to be worse than for patients treated with NIV alone (table 2),[11 35 48 49] but is not sufficiently poor to render IMV inappropriate for the COPD population as a whole with 1 year survival rates after IMV of 44–66%.[50–55] In assessing the appropriateness for IMV and the associated ICU admission, the severity of the underlying disease, the reversibility of the precipitating cause, the quality of life of the patient, and the presence of severe co-morbidities should be considered.[17] NIV may have a role in patients who have been intubated from the outset or after a failed trial of NIV. Nava *et al*[56] found that extubation onto NIV after a failed T-piece trial at 48 hours was associated with a shorter duration of ventilatory support (10.2 days *v* 16.6 days), a shorter ITU stay (15.1 days *v* 24 days), less nosocomial pneumonia (0/25 *v* 7/25), and improved 60 day survival (92% *v* 72%) compared with continued invasive ventilation. However, in a similar study Girault *et al*[57] did not find any difference in outcome with a similar approach.

MANAGEMENT OF RESPIRATORY FAILURE IN CHRONIC STABLE COPD

The aim of pharmacological therapy in COPD is to alleviate symptoms by reversing correctable abnormalities, but in many patients the changes are largely irreversible. In time, patients develop respiratory failure, pulmonary hypertension, and peripheral oedema. Once peripheral oedema supervenes, the prognosis is poor with a 5 year mortality of 70–100%.[58] Various therapeutic strategies have been developed to treat the consequences of chronic airway obstruction in an attempt to improve survival and reduce symptoms. These include:

- long term oxygen therapy (LTOT);
- respiratory stimulant drugs; and
- mechanically assisted ventilation.

Long term oxygen therapy (LTOT)

LTOT is one of only two interventions shown to improve survival in patients with COPD, the other being smoking cessation. Two large studies in the 1970s showed at least a doubling in survival when oxygen was used for at least 15 hours per day in patients hypoxaemic due to COPD,[59 60] although survival improved even further with more daily use.[59] The mechanism by which LTOT improves survival remains unknown. Severity of airflow limitation as measured by FEV_1 is a major predictor of survival,[61] and this remains true even in oxygen treated patients.[62] It is currently recommended if the Pao_2 falls below 7.3 kPa when the patient is clinically stable, and should be used for at least 15 hours per day. There are no data to support the use of LTOT in patients with predominantly nocturnal hypoxia.[63] In one study patients who did not fulfil the daytime arterial blood gas criteria for LTOT but who did have evidence of nocturnal hypoxia (mean nocturnal Sao_2 88%) were randomised to overnight oxygen or standard therapy. They found no difference in survival, evolution of pulmonary hypertension, or the time at which LTOT became necessary.

Drug treatment of chronic ventilatory failure

The use of drugs to improve arterial blood gas tensions has not found widespread acceptance, but a number of drugs have been evaluated including medroxyprogesterone,[64 65] acetazolamide,[66] protriptyline,[67 68] and almitrine bismesylate.[69]

Protriptyline, a non-sedating tricyclic antidepressant, has been shown to improve diurnal blood gas tensions in patients with COPD, increasing Pao_2 by approximately 1 kPa.[67 68] It is thought that the changes are mediated through a reduction in the amount of time spent in rapid eye movement (REM) sleep. Protriptyline has now been withdrawn in the UK, but other non-sedating REM suppressants such as fluoxetine have been shown to have an effect on REM related sleep disordered breathing[70] and probably warrant further evaluation. Four short term controlled studies of the use of acetazolamide in patients with chronic COPD have been reported[71] and discussed in a recent Cochrane review.[72] All showed a similar direction and size of effect; acetazolamide caused a metabolic acidosis and produced a non-significant fall in $Paco_2$ (weighted mean difference (WMD) –0.41 kPa; 95% CI –0.91 to 0.09) and a significant rise in Pao_2 (WMD 1.54 kPa; 95% CI 0.97 to 2.11). One study reported an improvement in sleep but there were no data concerning outcomes such as health status, symptoms, exacerbation rate, hospital admissions, or deaths. Side effects were reported infrequently. The reviewers concluded that the drug did have an effect but larger longer term studies were needed. Almitrine bismesylate is a pharmacologically unique respiratory stimulant which has the advantages of oral activity and prolonged duration of action. It has been shown to improve arterial blood gas tensions, particularly Pao_2; in one large study[69] Pao_2 increased after 1 year by an average of 2.1 kPa in one third of patients and in 55% Pao_2

increased by a least 1.6 kPa compared with placebo. A smaller proportion of patients taking almitrine were admitted to hospital and there were fewer episodes of right heart failure. However, its usefulness is limited by side effects, particularly peripheral neuropathy,[73] and there is a concern that it may cause worsening pulmonary hypertension[74 75]; it is not licensed for use in the UK.

The role of respiratory stimulants probably warrants revisiting as even small changes in Pa_{O_2} may result in patients moving above the threshold at which LTOT would be started. It remains to be seen, however, whether this translates into improved survival and patient quality of life.

Non-invasive ventilation

A number of studies have shown that NIV is feasible at home during sleep in patients with COPD,[76–82] and that abnormal physiology can be corrected using NIV. However, there have been few controlled trials and most of these had small numbers of patients followed over a short period of time.[83–86] They have generally been characterised by no significant advantage from NIV,[83–85] poor tolerance,[83] and worse sleep efficiency.[85] However, Meecham Jones *et al*[84] showed improvements in daytime arterial blood gas tensions, sleep quality, and quality of life during the pressure support (PSV) limb of a crossover study comparing PSV and oxygen with oxygen alone. This was the only study in which the overnight control of nocturnal hypoventilation was confirmed, and the improvement in daytime Pa_{CO_2} correlated with a reduction in overnight transcutaneous CO_2. Possible explanations for the failure of NIV in other studies include: patients not hypercapnic, insufficient inflation pressures to achieve effective ventilation, and inadequate patient acclimatisation to the technique. Case series of patients with COPD[80 87] suggest survival comparable to that seen in the oxygen treated patients in the MRC and NOTT studies.[59 60 88] These patients were often those who had "failed" (not rigorously defined) despite LTOT.

Preliminary results from two multicentre European trials comparing NIV with LTOT in COPD suggest that NIV does not improve survival but may reduce the need for hospitalisation.[89 90] Until further data are available, a trial of NIV can only be justified in patients who have symptoms of nocturnal hypoventilation (morning headaches, daytime sleepiness) despite maximal bronchodilator therapy or cannot tolerate LTOT even with careful administration. It should also be considered in patients with repeated admissions to hospital with acute hypercapnic ventilatory failure. Most studies suggest that it is patients with more severe hypercapnia who are likely to benefit and there is no place for nocturnal NIV at present in those without sustained daytime hypercapnia. Adequate control of nocturnal hypoventilation should be confirmed since this has been a feature of the studies in which benefit has been seen.[77 84]

CONCLUSIONS

In acute exacerbations of COPD the purpose of oxygen therapy and ventilatory support is to prevent tissue hypoxia and hypercapnia while medical treatment optimises lung function and reverses the precipitating cause. For most hypercapnic COPD patients, maintaining Sp_{O_2} at 85–92% (7.3–10 kPa) with controlled oxygen balances the risks of oxygen induced hypercapnia and tissue hypoxia. A low pH is an indicator of a severe and acute deterioration and such individuals benefit from receiving NIV in a location with trained staff, monitoring, and access to prompt intubation. As this group accounts for 16% of all patients with COPD, this requires ward based provision in the UK which may best be provided in respiratory care units analogous to coronary care units. A proportion of patients will still require IMV, including those who are unconscious on admission and those who fail with NIV in the first few days. NIV should be considered again after 48 hours of IMV as a weaning method. In patients with chronic respiratory failure LTOT remains the gold standard treatment but, in certain highly selected patients, drugs or NIV may have a role; further studies are needed.

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LUNG ALERT

Peroxisome proliferator-activated receptor ligands for airway diseases?

▲ Patel HJ, Belvisi MG, Bishop-Bailey D, *et al*. Activation of peroxisome proliferator-activated receptors in human airway smooth muscle cells has a superior anti-inflammatory profile to corticosteroids: relevance for chronic obstructive pulmonary disease therapy. *J Immunol* 2003;**170**:2663–9

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors belonging to the hormone receptor family. The alpha and gamma subtypes are predominantly expressed in liver, muscle, and adipose tissues where, when activated by ligands such as glitazones, they regulate lipid metabolism. Using RT-PCR, Western blot analysis, and confocal microscopy, Patel and colleagues have shown, for the first time, the expresssion of these receptors on cultured human airway smooth muscle cells. In addition, activation of the gamma subtype by ciglitazone decreased the synthesis of GM-CSF (an eosinophil survival factor) and G-CSF (a neutrophil survival factor) by stimulated airway smooth muscle cells, demonstrating a potential anti-inflammatory role for this class of drugs in the airway. They also inhibited smooth muscle growth and promoted their apoptosis more potently than dexamethasone.

Since smooth muscle cells have a significant role in airway diseases such as asthma and COPD, PPAR gamma ligands may prove to be effective in regulating their function, particularly in the process of airway remodelling. Their role in regulating airway smooth muscle migration and controlling steroid insensitive airway inflammation needs further study.

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