Non-Invasive Ventilation for Adult Acute Respiratory Failure. Part II

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ABSTRACT
Objective: To discuss the clinical indications and complications of non-invasive ventilation.

Data sources: A review of articles published in peer-reviewed journals from 1966 to 1998 and identified through a MEDLINE search on non-invasive ventilation.

Summary of review: Non-invasive ventilation (NIV) has been used in patients with respiratory failure caused by cardiogenic pulmonary oedema, acute respiratory distress syndrome, acute asthma and chronic obstructive pulmonary disease. However, in patients with acute respiratory failure, it appears that acute cardiogenic pulmonary oedema and acute respiratory failure associated with Pneumocystis carinii pneumonia are the only disorders in which significant benefits have been associated with the use of the NIV mode of CPAP. The potential clinical benefit of CPAP in acute asthma and blunt chest trauma remains unclear. Pressure support ventilation is beneficial in patients with hypercapnic acute respiratory failure (ARF) secondary to respiratory muscle insufficiency, high inspiratory work loads, or reduced alveolar ventilation. It appears also to be associated with an improved outcome in COPD patients with hypercapnic ARF.

Conclusions: Non-invasive ventilation using the modes of CPAP, PSV, BiPAP and NIPPV should be considered in patients with respiratory disorders who remain in acute respiratory failure despite conventional therapy, before considering invasive mechanical ventilation.

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Key Words: Non-invasive ventilation, work of breathing, minute ventilation, ventilation circuits

Non-invasive ventilation and acute respiratory failure
Non-invasive ventilation has been used for many diseases causing acute respiratory failure although pulmonary oedema (cardiogenic and non-cardiogenic), chronic obstructive pulmonary disease, and asthma are diseases in which non-invasive ventilation has been used most successfully (Table 1).

Cardiogenic pulmonary oedema.
Acute cardiogenic pulmonary oedema is characterised by an elevated pulmonary capillary hydrostatic pressure due to the presence of acute left ventricular (LV) diastolic dysfunction. Interstitial and alveolar flooding ensues, reducing pulmonary compliance and increasing work of breathing (Wb). Bronchospasm or oedema may increase air flow resistance (Wres). Hypoxic and (in severe cases), hypercapnic acute respiratory failure (ARF) frequently supervenes. Efforts to maintain the mean arterial pressure include sympathetic-induced tachycardia and systemic vasoconstriction. The latter, together with large negative intrathoracic pressures from inspiratory effort will increase LV afterload. Myocardial ischaemia is exacerbated by the increased LV work, by arterial hypoxia, and by coronary hypoperfusion.

The potential benefits of NIV in acute cardiogenic pulmonary oedema (APO) are, 1) a reversal of hypoxia, 2) reduction in flow resistance, 3) a reduction in Wb, 4) a reduction in LV afterload.
and, 5) the reversal of adverse chronotropic and lusitropic effects of myocardial ischaemia.

The first report of mask-CPAP in the treatment of cardiogenic APO was in 1936.13 Since then many reports14-18 have lent support to its therapeutic efficacy. Nearly fifty years after Poulton's report, Rasen published the first randomised controlled study of mask-CPAP (at 10 cm.H2O) in 40 patients with acute cardiogenic pulmonary oedema and hypoxic ARF, but without hypercapnia or acidosis.7 They found significant improvements in heart rate, respiratory rate and oxygenation, and a trend towards a reduction in the intubation rate with mask-CPAP.

In a larger randomised controlled study of 100 patients with acute cardiogenic pulmonary oedema without acidosis (i.e. pH = 7.38 ± 0.08) similar results were found.5 A significant reduction in pulmonary shunt fraction and the need for intubation (16% vs. 36%) was demonstrated in the mask-CPAP (at 2.5 - 12.5cm.H2O) group. This work was repeated by Bersten, et al., in a group of 39 severe acute cardiogenic pulmonary oedema patients with mixed metabolic and respiratory acidosis, who were randomised to receive mask-CPAP (10 cm.H2O, n = 19) or high-flow oxygen (control group, n = 20).6 Both groups received conventional pharmacological therapy for APO and had a similar degree of hypoxia, hypercapnia (PaCO2 58 ± 8 vs. 64 ± 17mmHg) and acidosis (pH 7.18 ± 0.08 vs. 7.15 ± 0.011). A more rapid improvement in vital signs (i.e. respiratory and heart rates), respiratory acidosis, and oxygenation was found in the CPAP group. They also identified a significant reduction in intubation rate (0 vs 7), length of stay in intensive care (1.2 vs. 2.7 days) and a trend (which did not reach significance) towards a reduction in mortality (2 vs. 4).

Further work based on this data demonstrated the cost-effectiveness of NIV and intensive care admission for all patients with acute severe cardiogenic pulmonary oedema, not just those requiring mechanical ventilation.17 Statistical analysis of the combined results from these three controlled trials (n = 179) demonstrates that, in this group of APO patients, withholding mask-CPAP increased the risk of intubation by 3.61 (95% CI = 1.8 - 7.39). The outcome figures reported in two of the studies suggest that mask-CPAP was associated with a lower in-hospital mortality (8.7% vs. 14.3%) but this difference was not statistically significant.5,6 No other major complications of NIV were reported.

The optimal level of CPAP in APO remains unclear, although 10 cmH2O appears to be safe and effective from the above studies. It is possible, using invasive techniques, to determine ‘optimal CPAP’ according to oxygen-related criteria such as mixed venous saturation21,19 and shunt fraction.5 However these end-points may simply reflect the response of PaO2 and cardiac function to an increase in inspired oxygen concentration (FiO2) rather than a response to CPAP.

If it is necessary to define an ‘optimal CPAP’ level then it may be more appropriate to use end-points which reflect Wb and are less influenced by FiO2. Measurement of Wb requires invasive monitoring such as gastric and oesophageal pressures. If clinical indicators, such as respiratory rate and visual-analogue scores of breathlessness, were found to correlate with WB, they may be more practical even though they are less accurate.

In summary, current evidence supports the routine use of mask-CPAP in acute cardiogenic pulmonary oedema, both as an adjunct to standard therapy and as the first-line option for respiratory support. Clinical experience supported by this research has resulted in the widespread use of mask-CPAP for cardiogenic APO in most critical care areas including the Emergency Department.20

Issues that remain to be resolved by further investigation include:

- What is the optimal level of CPAP?
- Is there a role for prolonged use of mask-CPAP after clinical recovery?21
- Is there a role for mask-CPAP in the pre-hospital management of acute cardiogenic pulmonary oedema?
- Is there a role for domiciliary use of mask-CPAP for patients with recurrent APO?
- Is mask-CPAP per se more efficacious than conventional pharmacological treatment for APO?

Acute lung injury

The high success rate of mask-CPAP in APO suggests that it should also be beneficial in non-cardiogenic pulmonary oedema and acute lung injury (ALI). ALI is associated with an increased alveolar-capillary permeability resulting in interstitial and alveolar oedema, alveolar collapse, reduced lung compliance, increased pulmonary shunt, and severe hypoxia. The work required to overcome pulmonary elastic recoil (Wb) and to a less extent the work required to overcome airway resistance (Wres) are increased.

CPAP has been used in the treatment of infants with idiopathic respiratory distress syndrome for over 30 years.21 Positive end expiratory pressure (PEEP)22-24 and CPAP25,26 have also been used in the treatment of in adults with the acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Despite some early reports of success using CPAP in ALI27 the failure
rate remains high.\textsuperscript{15,28} This may relate to differences in pathophysiology, in the severity of pulmonary dysfunction, or in the duration of ARF.

There are successful case reports of NIV in the management of ARF secondary to community-acquired bacterial pneumonia\textsuperscript{15,26,29,30} viral pneumonia,\textsuperscript{31-33} and in immunocompromised patients with opportunistic infections such as \textit{Pneumocystis carinii} pneumonia (PCP).\textsuperscript{34,39} Although PCP often responds to appropriate antimicrobial agents and steroids, PCP-related ARF carries a significant morbidity and mortality.\textsuperscript{40} Mechanical ventilation is associated with a higher mortality\textsuperscript{35,41,42} presumably because such patients have more severe ARF. There are numerous series reported with the successful use of mask-CPAP in the management of PCP-related ARF\textsuperscript{35-39} in these studies (n = 86) mask-CPAP was successful in controlling ARF in 68\% of patients, although the 12-month mortality was high. The average duration of NIV was 4.5 days. Failure of NIV and the decision to provide MV was associated with a high in-hospital mortality.

There are no randomised controlled trials of NIV in (any form of) ALI to substantiate its exact role, if any. Based on current data there is little to suggest a benefit from NIV, except in specific circumstances (such PCP in immunocompromised patients) where the disease is reversible and where MV carries an unacceptably high mortality.

Issues that remain to be resolved include:

- Does NIV have a role in subgroups of patients with ALI?
- Does NIV have any prophylactic role in ALI?
- Would PSV be a more successful mode of NIV in ALI?
- Is it justified to use NIV as a form of ‘limited’ ventilatory support for ALI patients unsuitable for intensive care admission or mechanical ventilation?

\textit{Post-operative respiratory failure}  
Abdominal and thoracic surgery are associated with significant changes in post-operative lung volumes and respiratory mechanics. A 30-60\% fall in functional residual capacity (FRC) and vital capacity (VC) has been reported.\textsuperscript{43-44} A reduced end-expiratory lung volume (EELV) decreases lung compliance and increases $W_{av}$ at a time when increased alveolar ventilation may be required. Pulmonary collapse increases intra-pulmonary shunt and $F_{O_2}$ requirements. Post-operative depression of central respiratory drive\textsuperscript{45} and airway reflexes, together with the decrease in VC, may cause retention of respiratory secretions and increase the risk of basal collapse, nosocomial pneumonia and ARF.\textsuperscript{44} Other risk factors for postoperative respiratory failure include pre-existing pulmonary or cardiac disease, smoking, increasing age, and fluid overload.\textsuperscript{45}

Since 1958, there have been many reports of attempts to use CPAP to prevent post-operative ARF.\textsuperscript{46} They revealed consistent improvements in EELV,\textsuperscript{47-50} shunt fraction, and oxygenation.\textsuperscript{51,54} However these effects wane rapidly following cessation of therapy.\textsuperscript{50,52} There are also numerous uncontrolled reports of mask-CPAP producing an apparent reduction in post-operative pulmonary complications.\textsuperscript{15,25,35,56}

Unfortunately randomised controlled trials of post-operative CPAP\textsuperscript{57,58} and NIPPV\textsuperscript{59} have failed to demonstrate a significant clinical benefit in terms of pulmonary complications or outcome. Similar results have been documented in patients following cardiothoracic surgery. Although mask-CPAP appears to be well tolerated,\textsuperscript{50,52} and although it improves both oxygenation\textsuperscript{52,56-64} and respiratory rate,\textsuperscript{64} randomised controlled trials have neither demonstrated a reduction in morbidity nor an improvement in outcome.\textsuperscript{51,65}

It is possible that many of these studies suffer from a type II error because of their small sample size and the variability in end-points chosen (e.g. clinical and radiological assessment). Failure to demonstrate a benefit with NIV may also be influenced by factors such as the duration of use,\textsuperscript{50,52} or the mode. PSV + CPAP may be more beneficial than CPAP alone, as a number of these patients are likely to have high inspiratory $W_b$ and reduced alveolar ventilation. Given the number of controlled trials with these findings, there is no evidence for the routine use of mask-CPAP in the prevention or treatment of post-operative ARF.

\textit{Post-traumatic respiratory failure}  
Blunt chest trauma may cause immediate or delayed ARF. Factors influencing the risk of ARF\textsuperscript{66,67} include, 1) pre-existing cardiac or respiratory disease, increasing age, and cigarette smoking, 2) a high injury severity score, abdominal injury, and neurotrauma, and, 3) fat embolism, surgery and anaesthesia, inadequate or excessive analgesia, and nosocomial infection. Early MV is often required for severe chest trauma, although successful conservative management has also been reported.\textsuperscript{68-70} The physiological benefits of NIV, such as increased compliance, improved oxygenation and decreased $W_b$, may be advantageous in treating ARF following blunt chest trauma. CPAP may also stabilise chest wall mechanics, such as the paradoxical movement of a flail segment.

There are a number of clinical reports of the successful use of CPAP in blunt chest trauma.\textsuperscript{15,51,72} In 1982 Linton, et al, published a small retrospective
analysis of chest trauma management. Their data suggested that mask-CPAP plus thoracic epidural analgesia produced a lower pulmonary complication rate and length of stay in the intensive care unit when compared to elective MV. In 1990 Bolliger, et al., performed a similar comparison in a prospective randomised trial. Patients were randomised to receive either mask-CPAP with thoracic epidural analgesia (n = 36) or elective mechanical ventilation and narcotic analgesia (n = 33). Both groups were matched for age, pre-existing lung disease, and severity of injury. The thoracic epidural group experienced a lower incidence of clinical ‘pneumonia’ and shorter (intensive care unit and hospital) length of stay. Two subjects in the control group died but the mortality difference was not statistically significant.

In the management of blunt chest trauma there is reasonable evidence to support the benefit of conservative, non-ventilatory treatment, and the benefit of regional analgesia. In the studies mentioned above it is therefore difficult to distinguish the benefits of regional analgesia and other aspects of intense but conservative therapy, from the possible benefits of NIV alone.

NIV may be contraindicated in the presence of other injuries particularly neurotrauma as CPAP may increase intracranial pressure. A depressed conscious state may also increase the risk of aspiration pneumonia, and pneumocephalus has been reported in a patient with a base of skull fracture. Abdominal injury is not necessarily a contraindication to NIV unless diaphragmatic splitting from inadequate analgesia or abdominal distension are present. Mask-CPAP can be safely used in the presence of a recent pneumothorax if effective intercostal drainage has been achieved.

Issues that remain to be resolved by further investigation include:

- Is there a role for NIV in the management of blunt chest trauma?
- What is the most effective mode of NIV?
- Does NIV add to therapy in the presence of effective regional analgesia?
- Does NIV reduce the risks of ARF and intubation?

**Acute asthma**

Airway obstruction in acute asthma (due to bronchospasm, acute inflammation and mucus production) results in an increase in W_{\text{res}}. Prolongation of expiratory time results in an increase in EELV due to dynamic hyperinflation, which in turn creates work required to overcome an inspiratory threshold (W_{\text{ITL}}) and shifts the pressure:volume relationship to the right increasing elastic work (W_{\text{el}}). Minute ventilation (V_{\text{E}}) increases at an early stage, possibly in an attempt to reduce EELV, and this causes hypocarbia. Acute dyspnoea and anxiety are symptoms of the rise in W_{\text{B}} and V_{\text{E}}. Expiratory W_{\text{B}} is exacerbated by airway collapse (increasing expiratory W_{\text{res}}) and by persistent inspiratory muscle activity. This high W_{\text{B}} may cause respiratory muscle insufficiency and a sudden fall in alveolar ventilation.

Hypoxia is a rare significant problem until this point.

Since CPAP has beneficial effects in the presence of W_{\text{ITL}} and an elevated W_{\text{res}} it may be useful in acute asthma. On the other hand, for intubated patients with airways obstruction, CPAP may further increase EELV and PEEP, and exacerbate dynamic hyperinflation and barotrauma. These concerns have led to the view that in acute asthma, 1) MV is best avoided, 2) PEEP is contraindicated, and 3) the preferred mode of MV is controlled hypventilation with permissive hypercapnia. This mode appears to be associated with a fall in ventilator-associated morbidity and mortality.

Against this background are a small number of laboratory and clinical reports which document an improvement, in asthma-induced breathlessness and W_{\text{B}}, with mask-CPAP. In addition, data from COPD patients (see below) has demonstrated the safety and efficacy of mask-CPAP in subjects with chronic airflow limitation and dynamic hyperinflation.

In 1982, Martin, et al., reported that mask-CPAP (12 ± 0.9 cm.H_{2}O) applied to 8 asthmatics with histamine-induced bronchospasm resulted in a 30% reduction in W_{\text{B}} (transdiaphragmatic pressure-time product, or Pdi/dt). Similarly, Loughed, et al., reported that the beneficial effects of mask-CPAP in a group of 12 asthmatics with metacholine-induced bronchospasm CPAP levels were titrated to achieve maximal subjective improvement. This ‘optimal’ CPAP level (5.3 ± 0.6 cm.H_{2}O) was similar to the measured threshold load (P_{\text{ITL}} = 6.9 ± 1.0 cm.H_{2}O) and mask-CPAP was found to reduce breathlessness, dynamic hyperinflation (EELV) and PEEP, CPAP reduced inspiratory muscle tension-time index by 27% and W_{\text{B}} (Pdi/dt) by 14%.

Shivaram, et al., in 1987 reported that mask-CPAP (5.3 ± 2.8cm.H_{2}O) reduced inspiratory time and breathlessness. Six years later, the same group reported clinical benefit from mask-CPAP (5 - 7.5cm.H_{2}O) in a series of 21 acute asthmatics (peak expiratory flow rate = 144 ± 7 L/min, RR = 22 ± 1) in whom bronchodilators were withheld. Significant clinical improvements in respiratory rate and dyspnoea occurred in all but two patients, both of whom experienced increasing dyspnoea which improved with bronchodilators. No other complications, such as hypotension, occurred.
It is interesting to note that in Poulton’s original article he described the successful use of his ‘pulmonary plus pressure machine’ in 8 out of 11 asthmatics, with ‘good results’ in 3 patients. There are other anecdotal reports of mask-CPAP to treat acute asthma\textsuperscript{90, 91} and to prevent nocturnal asthma.\textsuperscript{92-94}

NIPPV-delivery of bronchodilators has been described as more effective than delivery by spontaneous breathing.\textsuperscript{95, 96} however these authors did not consider the possibility of an independent benefit from NIV. Bronchodilators can be effectively delivered to spontaneously breathing subjects via a high-flow CPAP circuit.\textsuperscript{97}

Whilst this limited data supports a possible therapeutic role for mask-CPAP in acute asthma, its exact status is yet to be determined. Laboratory subjects are generally well motivated, co-operative and tolerant of unpleasant procedures - the same cannot be said of acute asthmatic patients. The current data supports the need for controlled clinical trials. Since the intubation rate in acute asthma is quite low, a large multicentre trial would be required to reliably demonstrate a clinically significant difference.

Issues that remain to be resolved by further investigation include:

- Is there a role for NIV in the treatment of acute asthma?
- If so, would it be safe to use in the pre-hospital phase?
- Is there a role for domiciliary mask-CPAP in the prevention of bronchospasm in brittle asthmatics?\textsuperscript{94}

**COPD and hypercapnic respiratory failure**

ARF with COPD\textsuperscript{98, 99} may be precipitated by a variety of factors which include pulmonary infection, bronchospasm, left ventricular failure, centrally-depressant drugs, trauma, surgery, and pulmonary embolus, etc. Many such patients require admission to an intensive care unit. They often require prolonged mechanical ventilation, may be difficult to wean, carry a high morbidity, and thus consume a considerable proportion of hospital resources.

Patients with severe COPD have an elevated $W_B$\textsuperscript{98, 100} due to a combination of an increase in lung elastance, an increase in airways resistance ($W_{re}$), the presence of PEEP, and $W_{ITL}$,\textsuperscript{101} and an increase in $V_t$ requirements to maintain normocapnoea (due to loss of alveoli and an increase in physiological dead space). Hypoxia becomes a problem if alveolar loss is extensive or if alveolar collapse (e.g. from APO or infection), supervenes. The later conditions may further increase $W_{et}$. Each of these mechanical deficiencies may potentially respond to NIV.

Interest in the use of NIV for COPD patients arose out of, 1) the efficacy of CPAP and PSV in intubated COPD patients weaning from mechanical ventilation,\textsuperscript{102-105} 2) laboratory studies of CPAP in COPD subjects,\textsuperscript{96-110} 3) the clinical experience with NIV in other forms of ARF, and, 4) case reports of clinical success. PEEP has been considered a potentially harmful modality in intubated COPD patients,\textsuperscript{98,111,112} since it may exacerbate dynamic hyperinflation and lead to barotrauma. Paradoxically low levels of PEEP may be beneficial for intubated COPD patients by reducing the circuit impedance ($W_{el}$) and threshold work ($W_{ITL}$) required to trigger assisted ventilation.\textsuperscript{103,111,112} Petrof et al, have demonstrated that 5 - 15 cmH$_2$O CPAP reduced spontaneous $W_B$ ($P_{d/dt}$) by 40-50% in intubated COPD subjects.\textsuperscript{109} Both the inspiratory and the expiratory $P_{max}$ components of mask-CPAP appear to be beneficial in reducing the dyspnoea of COPD patients.\textsuperscript{110} Although expiratory positive airway pressure (EPAP) increased dyspnoea, inspiratory positive airway pressure (IPAP) had the opposite effect and the combination of the two (i.e. CPAP) had the greatest benefit. Other authors have also documented less dyspnoea with NIV in COPD.\textsuperscript{109,110,113}

It would appear that CPAP unloads the threshold load ($W_{ITL}$) produced by dynamic hyperinflation and PEEP.\textsuperscript{103,111,112} This reduces the inspiratory muscle work\textsuperscript{112} required during the inspiration, and induces phasic relaxation during the expiration.\textsuperscript{81} A number of investigators have confirmed that both mask-CPAP\textsuperscript{106,107} and mask-PSV\textsuperscript{108} reduce $W_B$ in COPD subjects. Mask-CPAP (7.5 - 10cmH$_2$O) applied to exercising COPD subjects has been shown to reduce $W_B$ ($P_{d/dt}$) by 43%,\textsuperscript{107} but the combination of PSV + CPAP results in a greater reduction.\textsuperscript{106,108}

Since 1990 there have been numerous uncontrolled reports involving over 350 COPD patients with hypercapnic ARF\textsuperscript{115-128} supporting the clinical efficacy of NIV. Many of these authors have documented that NIV in hypercapnic ARF results in an improvement in vital signs, oxygenation and correction of the acute respiratory acidosis.\textsuperscript{113,115,129} The failure rate (i.e. intubation rate) in these reports ranged from 0 - 58% (mean = 26.5 ± 17%). Some investigators suggested that lack of a clinical response to NIV within the first 2 hours correlated with a higher failure rate.\textsuperscript{115,122,129}

A variety of mask and ventilatory modes were successfully trialed in these reports and most authors reported high compliance rates. The incidence of side-effects and complications was low,\textsuperscript{90, 104, 113, 116, 120, 130, 131} but not adequately documented by some.\textsuperscript{99, 107, 132, 133} It is worth pointing out two authors\textsuperscript{119,128} admitted to patient intolerance of the mask, considerable nursing workload, and low success rates, associated with NIV. Bedside
workload has been measured by others \(^{90,113}\) and found to be no greater than the workload required for a mechanically ventilated patient - both groups of patients requiring considerable 'direct' care during the first eight hours.\(^{90}\)

Since 1992 there have been six reports of randomised controlled trials of NIV in COPD, although only three have been published in full.\(^{90,113,129,134}\) A number of different NIV modes were utilised: PSV, PSV + CPAP, BiPAP, and NIPPV. These trials had sufficient similarities (in design and entry and exit criteria) to support a meta-analysis.\(^{134}\) All investigators reported improved outcome in the NIV group, with a significantly lower rate of intubation (24% vs 69%) and mortality (8.9% vs 31.2%). In these COPD patients with hypercapnic ARF conventional treatment without NIV increased the risk of intubation by 7.2 (95% CI, 3.3 - 15.5) and increased the risk of death by 4.7 (95% CI, 1.8 - 11.6). Mean duration of NIV was 4 ± 2 days. There was no difference in length of stay which may have been attributable to the higher mortality in the control groups. It should be noted that NIV trials cannot be blinded and all these trials differed somewhat in entry criteria, definition of ARF, control therapy and mode of NIV. In addition a high proportion of potentially eligible COPD patients were excluded.

Success rates for NIV in COPD patients with hypercapnic ARF are lower than those reported in cardiogenic APO.\(^{117,130}\) This probably reflects, at least in part, the differences in pathophysiology and natural history of COPD-related ARF. At present there are few predictive markers of the subgroup of COPD patients likely to avoid intubation. In a recent report\(^{117}\) of 90 COPD patients (with ARF and treated with NIV) a number of factors such as age, severity of respiratory failure, and precipitating condition were noted to be predictive of a 'physiological response' to NIV. Even though they found the intubation rate was higher in ARF due to pneumonia (41%) and congestive cardiac failure (46%) than for ARF with other causes (18%), they were unable to define any variables that were predictive of failure (i.e. intubation). A number of authors have observed that an early fall in PaCO\(_2\) (within 1-2 hours) appears to be associated with a greater success rate and avoidance of MV.\(^{28,114,117}\) To date there are have been no prospective studies to test this hypothesis.

All modes of NIV have been shown to be beneficial in COPD patients with hypercapnic ARF.\(^{134}\) Whilst they all improve PaO\(_2\) and PaCO\(_2\),\(^{135}\) there are no controlled clinical trials which have addressed the question of which mode is best. Most clinical reports have described using PSV + CPAP\(^{28,99,115,116,129}\) and there is some laboratory data to support this combination,\(^{106,110}\) NIPPV,\(^{117,118,119,122,124,126,128}\) and BiPAP\(^{28,120,121}\) also appear effective.

Patients with predominant hypoxia, bronchospasm or increase in threshold work are likely to respond to CPAP. Those with reduced alveolar ventilation, hypercapnia, or respiratory muscle insufficiency are more likely to respond to PSV, NIPPV, or BiPAP (Table 1). Optimal pressure levels remain to be defined, but the range reported for PSV is 5 - 10 cmH\(_2\)O and a CPAP level of 0 - 5 cmH\(_2\)O. There is evidence that the optimal level of CPAP is less than the level of PEEP,\(^{80,106}\) but the measurement of PEEP, requires invasive monitoring.

On the basis of NIV physiology it would appear that the PSV level should be titrated to achieve an adequate \(V_\text{E}\) and PaCO\(_2\), whilst the CPAP level should be titrated to achieve the minimum inspiratory effort required to overcome any threshold load (W\text{TRL}) and trigger PSV. The \(F_\text{O}_2\) can safely be adjusted to treat hypoxia since there is evidence that the reversal of hypoxia in COPD does not significantly reduce central respiratory drive.\(^{136-138}\)

Issues that remain to be resolved by further investigation include:

- What is the cost-benefit ratio in this group of patients?
- Is there a subgroup of COPD patients in whom NIV has a higher success rate?
- What is the optimal pressure level(s) and mode of NIV for COPD-related ARF?
- Should NIV be used as a form of 'limited' ventilatory support for COPD patients unsuitable for intensive care admission or mechanical ventilation?\(^{122}\)
- In such patients is it ethical to withhold mechanical ventilation in the event that NIV fails?

**Safety of non-invasive ventilation**

Like all therapeutic agents, NIV is not without potential complications. In general NIV appears safe, well tolerated and carries a low side-effect profile.\(^{117,129,130,139}\) Much of this may be attributed to the use of NIV in critical care environments where close monitoring and expert personnel are readily available. The most significant complication of NIV is failure to reverse the ARF. Thus it is imperative that patients receiving NIV should be in an environment where appropriate monitoring, equipment, and personnel are available.
The most frequent problems encountered during NIV are patient intolerance and other complications of the mask. Nasal bridge necrosis can occur from prolonged use. Drying of nasal mucosa, epistaxis, and conjunctivitis have all been reported. Bacterial contamination of the circuit is rare. Positive intrathoracic pressure may cause hypotension in preload-sensitive subjects, atrial arrhythmia, raised intra-cranial pressure and raised intra-ocular pressure in glaucoma sufferers. Pneumothorax and pneumopericardium have been reported in infants, and there is also a case-report of pneumocephalus occurring in an adult with an undiagnosed fractured base of skull. Aerophagy, gastric distension, and gastro-oesophageal reflux are potential concerns and although they have been demonstrated in infants, they rarely occur in adults. Thus routine nasogastric intubation is not necessary. Although a number of contraindications to NIV have been previously suggested the only absolute contraindication to its use is in the unconscious patient because of the presence of an unprotected airway. Care should be taken in patients who fail to respond within the 1-2 hours and also in pulmonary conditions where there is little evidence to support its use.

Conclusion

NIV is a form of ventilatory support which has been demonstrated to have physiological and clinical benefit in patients with certain types of ARF. CPAP is advantageous when ARF is associated with hypoxia, poor lung compliance, increased airways resistance, or the absence of threshold work. CPAP may also improve cardiac function in the presence of ischaemia and/or afterload sensitivity. Current data supports the routine use of mask-CPAP as the first-line ventilatory mode in patients with cardiogenic APO. For immunocompromised patients with ALI (e.g. PCP) although there are no controlled trials of NIV, the weight of current evidence supports NIV as the preferred form of ventilatory assistance. At present there is insufficient data to support the routine use of NIV in other forms of ALI, including post-traumatic ARF. For the prevention of post-operative ARF there are a number of controlled trials that have failed to demonstrate an overall benefit from CPAP.

Whilst CPAP does have the potential to benefit patients with bronchospasm, its routine use in acute asthma must await controlled clinical trials. Even though there is evidence of benefit in COPD patients, CPAP appears to be less effective than PSV as the sole ventilatory support mode. PSV is advantageous for hypercapnic ARF secondary to respiratory muscle insufficiency, high inspiratory work loads, or reduced alveolar ventilation. It appears to be associated with an improved outcome in COPD patients with hypercapnic ARF. PSV + CPAP should therefore be considered as

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### Table 1. Pathophysiology of acute respiratory failure subgroups and response to non-invasive ventilation.

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<td><strong>Cardiac disorder</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preload sensitive</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Afterload sensitive</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Lusitropy</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Optimal mode of NIV: CPAP, CPAP±PSV, CPAP, PSV±CPAP, NIPPV, BiPAP

\[+' = \text{severity, } '-' = \text{absent, APO = acute pulmonary injury, ALI = acute lung injury, COPD = chronic obstructive pulmonary disease }\]

\[P_AO_2 = \text{Alveolar partial pressure of oxygen, }\]

\[P(A-a)O_2 = \text{Alveolar - arterial oxygen tension difference, }\]

\[W_{el} = \text{work required to overcome elastic recoil, }\]

\[W_{res} = \text{work required to overcome airway resistance, }\]

\[W_{ITL} = \text{work required to overcome an inspiratory threshold load, }\]

\[V_E = \text{minute ventilation, NIV = non-invasive ventilation, CPAP = continuous positive airway pressure, PSV = pressure support ventilation, NIPPV = non-invasive positive pressure ventilation, BiPAP = bilevel positive airway pressure.}\]
the first-line ventilatory support mode in these patients.

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