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

G. J. DUKE*, A. D. BERSTEN†
*Intensive Care Department, The Northern Hospital, Epping, VICTORIA
†Department of Critical Care Medicine, Flinders Medical Centre, Bedford Park, SOUTH AUSTRALIA

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.*

(**Critical Care and Resuscitation 1999; 1: 199-210**)

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.[1] Interstitial and alveolar flooding ensues, reducing pulmonary compliance and increasing work of breathing (W_B). Bronchospasm or oedema may increase air flow resistance (W_{res}).[2] 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.[3] 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,[4-7] 2) reduction in flow resistance,[8] 3) a reduction in W_B,[9] 4) a reduction in LV afterload,[10-12],

Correspondence to: Dr. G. J. Duke, Intensive Care Department, The Northern Hospital, Epping, Victoria 3076
(e-mail: gduke@tnh.vic.gov.au)

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 reports[7,14-16] have lent support to its therapeutic efficacy. Nearly fifty years after Poulton's report, Rasanen published the first randomised controlled study of mask-CPAP (at l0 cm.H_2O) 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 $\pm$ 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.H_2O) 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 (l0 cm.H_2O, 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 ($PaCO_2$ 58 $\pm$ 8 vs. 64 $\pm$ 17mmHg) and acidosis (pH 7.18 $\pm$ 0.08 vs. 7.15 $\pm$ 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 cmH_2O 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 saturation[18,19] and shunt fraction.[5] However these end-points may simply reflect the response of PaO_2 and cardiac function to an increase in inspired oxygen concentration (F_IO_2) 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 W_B and are less influenced by F_IO_2. Measurement of W_B 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?[11]
- Is there a role for mask-CPAP in the pre-hospital management of acute cardiogenic pulmonary oedema?
- Is there a role for domicillary 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 (W_{el}) and to a less extent the work required to overcome airway resistance (W_{res}) 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 CPAP[25,26] 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 ALI[27] the failure

rate remains high.[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[15,26,29,30] viral pneumonia,[31-33] and in immunocompromised patients with opportunistic infections such as *Pnuemocystis carinii* pneumonia (PCP).[34-39] Although PCP often responds to appropriate antimicrobial agents and steroids, PCP-related ARF carries a significant morbidity and mortality.[40] Mechanical ventilation is associated with a higher mortality[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.[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?

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.[43,44] A reduced end-expiratory lung volume (EELV) decreases lung compliance and increases W_{el} at a time when increased alveolar ventilation may be required. Pulmonary collapse increases intra-pulmonary shunt and F_IO_2 requirements. Post-operative depression of central respiratory drive[43] 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.[44] Other risk factors for postoperative respiratory failure include pre-existing pulmonary or cardiac disease, smoking, increasing age, and fluid overload.[45]

Since 1958, there have been many reports of attempts to use CPAP to prevent post-operative ARF.[46] They revealed consistent improvements in EELV[47-50] shunt fraction, and oxygenation.[51-54] However these effects wane rapidly following cessation of therapy.[50,52] There are also numerous uncontrolled reports of mask-CPAP producing an apparent reduction in post-operative pulmonary complications.[15,25,55,56]

Unfortunately randomised controlled trials of post-operative CPAP[57,58] and NIPPV[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,[60-62] and although it improves both oxygenation[52,62-64] and respiratory rate,[64] randomised controlled trials have neither demonstrated a reduction in morbidity nor an improvement in outcome.[61,65]

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,[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.

Post-traumatic respiratory failure

Blunt chest trauma may cause immediate or delayed ARF. Factors influencing the risk of ARF[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.[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.[15,71,72] In 1982 Linton, *et al*, published a small retrospective

analysis of chest trauma management.[73] 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.[74] 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,[69,70] and the benefit of regional analgesia.[75,76] 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.[77] A depressed conscious state may also increase the risk of aspiration pneumonitis, and pneumocephalus has been reported in a patient with a base of skull fracture.[78] Abdominal injury is not necessarily a contraindication to NIV unless diaphragmatic splinting 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 mucous production) results in an increase in W_{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_{ITL}) and shifts the pressure:volume relationship to the right[79] increasing elastic work (W_{el}). Minute ventilation (V_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_B and V_E.[79-81] Expiratory W_B is exacerbated by airway collapse (increasing expiratory W_{res}) and by persistent inspiratory muscle activity.[80] This high W_B may cause respiratory muscle insufficiency and a sudden fall in alveolar ventilation.[82,83] Hypoxia is rarely a significant problem until this point.

Since CPAP has beneficial effects in the presence of W_{ITL} and an elevated W_{res} it may be useful in acute asthma. On the other hand, for intubated patients with airways obstruction, CPAP may further increase EELV and $PEEP_i$, and exacerbate dynamic hyperinflation and barotrauma.[84] These concerns have led to the view that in acute asthma, 1) MV is best avoided, 2) PEEP is contraindicated,[85] and, 3) the preferred mode of MV is controlled hypoventilation with permissive hypercapnia.[86] This mode appears to be associated with a fall in ventilator-associated morbidity and mortality.[85,86] Against this background are a small number of laboratory and clinical reports which document an improvement, in asthma-induced breathlessness and W_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 $\pm$ 0.9 $cm.H_2O$) applied to 8 asthmatics with histamine-induced bronchospasm resulted in a 30% reduction in W_B (transdiaphragmatic pressure-time product, or Pdi/dt).[87] Similarly, Lougheed, *et al*, reported the beneficial effects of mask-CPAP in a group of 12 asthmatics with metacholine-induced bronchospasm.[80] CPAP levels were titrated to achieve maximal subjective improvement. This 'optimal' CPAP level (5.3 $\pm$ 0.6 $cm.H_2O$) was similar to the measured threshold load (P_{ITL} = 6.9 $\pm$ 1.0 $cm.H_2O$) and mask-CPAP was found to reduce breathlessness, dynamic hyperinflation (EELV) and $PEEP_i$. CPAP reduced inspiratory muscle tension-time index by 27% and W_B (Pdi/dt) by 14%.

Shivaram, *et al*, in 1987 reported that mask-CPAP (5.3 $\pm$ 2.8$cm.H_2O$) reduced inspiratory time and breathlessness.[88] Six years later, the same group reported clinical benefit from mask-CPAP (5 - 7.5$cm.H_2O$) in a series of 21 acute asthmatics (peak expiratory flow rate = 144 $\pm$ 7 L/min, RR = 22 $\pm$ 1) in whom bronchodilators were withheld.[89] 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[90,91] and to prevent nocturnal asthma.[92-94]

NIPPV-delivery of bronchodilators has been described as more effective than delivery by spontaneous breathing,[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.[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 domicillary mask-CPAP in the prevention of bronchospasm in brittle asthmatics?[94]

COPD and hypercapnic respiratory failure

ARF with COPD[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[98,100] due to a combination of an increase in lung elastance, an increase in airways resistance (W_{res}), the presence of $PEEP_i$ and W_{ITL},[101] and an increase in V_E 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_{el}. 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,[102-105] 2) laboratory studies of CPAP in COPD subjects,[106-110] 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,[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_{cir}) and threshold work (W_{ITL}) required to trigger assisted ventilation.[103,111,112] Petrof *et al*, have demonstrated that 5 - 15 cm.H_2O CPAP reduced spontaneous W_B (P_{di}/dt) by 40-50% in intubated COPD subjects.[109] Both the inspiratory and the expiratory P_{ao} components of mask-CPAP appear to be beneficial in reducing the dyspnoea of COPD patients.[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.[109,110,113]

It would appear that CPAP unloads the threshold load (W_{ITL}) produced by dynamic hyperinflation and $PEEP_i$.[109,111,114] This reduces the inspiratory muscle work[110] required during the inspiration, and induces phasic relaxation during the expiration.[81] A number of investigators have confirmed that both mask-CPAP[106,107] and mask-PSV[106] reduce W_B in COPD subjects. Mask-CPAP (7.5 - 10cm.H_2O) applied to exercising COPD subjects has been shown to reduce W_B (P_{di}/dt) by 43%,[107] but the combination of PSV + CPAP results in a greater reduction.[106,108]

Since 1990 there have been numerous uncontrolled reports involving over 350 COPD patients with hypercapnic ARF[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.[113,115,129] The failure rate (i.e. intubation rate) in these reports ranged from 0 - 58% (mean = 26.5 $\pm$ 17%). Some investigators suggested that lack of a clinical response to NIV within the first 2 hours correlated with a higher failure rate.[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[90,104,113,116,120,130,131] but not adequately documented by some.[99,107,132,133] It is worth pointing out two authors[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 $\pm$ 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 report1[17] 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,[113,118,119,122,124,126,128] 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_2O and a CPAP level of 0 - 5 cmH_2O. There is evidence that the optimal level of CPAP is less than the level of $PEEP_i$,[80,106] but the measurement of $PEEP_i$ requires invasive monitoring.

On the basis of NIV physiology it would appear that the PSV level should be titrated to achieve an adequate V_E and $PaCO_2$, whilst the CPAP level should be titrated to achieve the minimum inspiratory effort required to overcome any threshold load (W_{ITL}) and trigger PSV. The F_IO_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.

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

Diagnosis:	APO	ALI	Asthma	COPD
Respiratory disorder				
P_AO_2	++	++	+/-	+
$P(A\text{-}a)_DO_2$ gradient	++	++	+/-	+
W_{el}	++	++	+	++
W_{res}	+	+	++	++
W_{ITL}	-	-	++	++
V_E	+/-	+	+/-	++
Cardiac disorder				
Preload sensitive	+/-	+	+	-
Afterload sensitive	++	+	-	+/-
Tachycardia	++	++	++	+
Lusitropy	++	+/-	-	+/-
Optimal mode of NIV	CPAP	CPAP± PSV	CPAP	PSV± CPAP, NIPPV, BiPAP

'+'=severity, '-' = absent, APO = acute pulmonary injury, ALI = acute lung injury, COPD = chronic obstructive pulmonary disease P_AO_2 = Alveolar partial pressure of oxygen, $P(A\text{-}a)_DO_2$ gradient = Alveolar - arterial oxygen tension difference, Wel = work required to overcome elastic recoil, W_{res} = work required to overcome airway resistance, W_{ITL} = work required to overcome an inspiratory threshold load, V_E = 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 most frequent problems encountered during NIV are patient intolerance and other complications of the mask.[139] Nasal bridge necrosis can occur from prolonged use.[117] Drying of nasal mucosa,[140] epistaxis,[141] and conjunctivitis[142] have all been reported. Bacterial contamination of the circuit is rare.[143]

Positive intrathoracic pressure may cause hypotension in preload-sensitive subjects,[144,145] atrial arrhythmia,[146] raised intra-cranial pressure[147,148] and raised intra-ocular pressure in glaucoma sufferers.[149,150] Pneumothorax and pneumopericardium[151] 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.[78] Aerophagy, gastric distension, and gastro-oesophageal reflux are potential concerns and although they have been demonstrated in infants,[152] they rarely occur in adults.[117,129,153] Thus routine nasogastric intubation is not necessary. Although a number of contraindications to NIV have been previously suggested[130] 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[28,117,129] and also in pulmonary conditions where there is little evidence to support it 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 presence 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

the first-line ventilatory support mode in these patients.

Received: 19 November 1998
Accepted: 12 January 1999

REFERENCES

1. Bersten AD, Holt AW. Acute cardiogenic pulmonary oedema. Current Opinion in Critical Care 1995; 1:410-419.
2. Sharp JT, Griffith GT, Bunnell IL, et al. Ventilatory mechanics in pulmonary edema in man. J.Clin.Invest. 1957; 111-117.
3. Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT 2d, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. N Eng J Med 1979;301:453-459.
4. Schlobohm RM, Falltrick RT, Quan SF, Katz JA. Lung volumes, mechanics, and oxygenation during spontaneous positive-pressure ventilation: the advantage of CPAP over EPAP. Anesthesiology 1981;55:416-422.
5. Lin M, Yang YF, Chiang HT, Chang MS, Chiang BN, Cheitlin MD. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary oedema. Short-term results and long-term follow-up. Chest 1995;107:1379-1386.
6. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary oedema with continuous positive airway pressure delivered by face mask. N Engl J Med 1991;325:1825-1830.
7. Rasanen J, Heikkila J, Downs J, Nikki P, Vaisanen I, Viitanen A. Continuous positive airway pressure by face mask in acute pulmonary edema. Am J Cardiol 1985;55:296-300.
8. Lenique F. Habis M, Lofaso F. et al. Ventilatory and hemodynamic effects of continuous positive airway pressure in congestive heart failure. Am J Respir Crit Care Med 1994;149:A644.
9. Granton JT, Naughton MT, Benard DC, Liu PP, Goldstein RS, Bradley TD. CPAP improves respiratory muscle strength in patients with heart failure and central sleep apnoea. Am J Resp Crit Care Med 1996;153:277-287.
10. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP. Cardiac output response to continuous positive airway pressure in congestive heart failure. Am Rev Resp Dis 1992;145:377-382.
11. Naughton MT, Rahman MA, Hara K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. Circulation 1995;91:1725-1731.
12. Calvin JE, Driedger AA, Sibbald WW. Positive end-expiratory pressure does not depress left ventricular function in patients with pulmonary oedema. Am Rev Repir Dis. 1981;124:121-128.
13. Poulton EP. Left-sided heart failure with pulmonary oedema. Its treatment with the "pulmonary plus pressure" machine. Lancet 1936; 231:981-983.
14. Vaisanen IT, Rasanen J. Continuous positive airway pressure and supplemental oxygen in the treatment of cardiogenic pulmonary oedema. Chest 1987;92:481-485.
15. Suter PM, Kobel N. Treatment of acute pulmonary failure by CPAP via face mask: when can intubation be avoided. Klin Wochenschr 1981;59: 613-616.
16. Perel A, Williamson DC, Modell JH. Effectiveness of CPAP by mask for pulmonary oedema associated with hypercarbia. Intensive Care Med 1983;9:17-19.
17. Holt AW, Bersten AD, Fuller S, Piper RK, Worthley LI, Vedig A. Intensive care costing methodology: cost-benefit analysis of mask continuous positive airway pressure for severe cardiogenic pulmonary oedema. Anaesth Intensive Care 1994;22:170-174.
18. Rasanen J, Downs JB, DeHaven B. Optimum versus clinically established levels of continuous positive airway pressurein respiratory therapy. J Clin Monit 1988;4:235-239.
19. Rasanen J, Downs JB, DeHaven B. Titration of continuous positive airway pressure by real-time dual oximetry. Chest 1987;92:853-856.
20. Kambourakis A, Duke GJ. The use of continuous positive airway pressure by face-mask in the emergency department management of severe acute cardiogenic pulmonary oedema. (Abstract. 5th International Conference on Emergency Medicine. London. 1994.
21. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med. 1971; 284:1333-1340.
22. Petty TL, Ashbaugh DG. The adult respiratory distress syndrome: clinical features, factors influencing prognosis and principles of management. Chest 1971;60:233-239.
23. Tyler DC. Positive end-expiratory pressure: a review. Crit Care Med 1983; 11:300-307.
24. Shapiro BA, Cane RC, Harrison RA. Positive end-expiratory pressure therapy in adults with special reference to acute lung injury: a review of the literature and suggested clinical correlations. Crit Care Med 1984;12:127-141.
25. Schmidt GB, Bombeck CT, Bennett EJ, Kotb KM. Continuous positive airway pressure in the prophylaxis of the adult respiratory distress syndrome. Langenbecks Arch Chir 1975; S439-442.
26. Venus B, Jacobs K, Lim L. Treatment of the adult respiratory distress syndrome with continuous positive airway pressure. Chest 1979;76:257-261.
27. Greenbaum DM, Millen JE, Eross B. Continuous positive pressure without tracheal intubation in spontaneously breathing patients. Chest 1976;69:515.
28. Newton F, Bersten AD, Holt AW. ICU experience of noninvasive ventiulation in the management of acute respiratory failure. Anaesth Intens Care 1995;23:401.
29. Graham, Efficiency of chest physiotherapy and intermittent positive pressure breathing in the resolution of pneumonia. N Engl J Med 1978;299:624-627.

30. Brett A, Sinclair DG. Use of continuous positive airway pressure in the management of community acquired pneumonia. Thorax 1993;48:1280-1281.
31. Sadnovnikoff N, Varon J. CPAP mask management of varicella-induced respiratory failure. Chest 1993;103:1894-1895.
32. Pillans P. Chickenpox pneumonia. A case report. S Afr Med J 1983;28:861-862.
33. Taylor GJ, Brenner W, Summer WR. Severe viral pneumonia in young adults. Chest 1976;69:722-728.
34. Schlemmer B, Dhainaut JF, Bons J, et al. Acute pulmonary infiltrates in hematologic malignancies in aplasia. Ann Med Interne (Paris) 1982;133:174-177.
35. Gachot B, Clair B, Wolff M, Regnier B, Vachon F. Continuous positive airway pressure by face mask or mechanical ventilation in patients with human immunodeficiency virus infection and severe Pneumocystis carinii pneumonia. Intensive Care Med 1992;18:155-159.
36. Miller RF, Semple SJ. Continuous positive airway pressure ventilation for respiratory failure associated with Pneumocystis carinii pneumonia. Respir Med 1991;85:133-138.
37. Gregg RW, Friedman BC, Williams JF, McGrath BJ, Zimmerman JE. Continuous positive airway pressure by face mask in Pneumocystis carinii pneumonia. Crit Care Med 1990;18:21-24.
38. Kesten S. Rebuck AS. Nasal continuous positive airway pressure in Pneumocystitis carinii pneumonia. Lancet 1988; 17:1414-1415.
39. Boix JH, Miguel V, Aznar O, et al. Airway continuous positive pressure in acute respiratory failure caused by Pneumocystis carinii pneumonia. Rev Clin Esp 1995; 195:69-73.
40. Prevederos HP, Lee RP, Marriot D. CPAP, effective support in patients with AIDS-related Pneumocystis carinii pneumonia. Anaesth Intensive Care 1991;19:561-566.
41. Wachter RM, Russi MB, Bloch DA, Hopewell PC, Luce JM. Pnuemocystis carinii pneumonia and respiratory failure in AIDS. Improved outcomes and increased use of intensive care units. Am Rev Respir Dis 1991;143:251-256.
42. Schein RM, Fischl MA, Pitchenik AE, Sprung CL. ICU survival of patients with acquired immnodeficiency syndrome. Crit.Care Med. 1986;14:1026-1027.
43. Craig DB. Postoperative recovery of pulmonary function. Anesth Analg 1981; 60:46-52.
44. Tisi GM. State of the art. Preoperative evaluation of pulmonary function. Am Rev Respir Dis 1979;119:293-310.
45. Bishop MJ, Cheney FW. Respiratory complications of anesthesia and surgery. Seminars in Anesthesiology 1983;ii:91-99.
46. Noehren TH, Lasry JE, Legters LJ. Intermittent positive pressure breathing for the prevention and management of post-operative pulmonary complications. Surgery 1958;43:658.
47. Lindner KH, Lotz P. Ahnefeld FW. Continuous positive airway pressure effect on functional residual capacity, vital capacity and its subdivisions. Chest 1987;92:66-70.
48. Ricksten SE, Bengtsson A, Soderberg C, Thorden M, Kvist H. Effects of periodic positive airway pressure by mask on post-operative pulmonary function. Chest 1986 89:774-781.
49. Stock MC, Downs JB, Gauer PK, Alster JM, Imrey PB. Prevention of post-operative pulmonary complications with CPAP, incentive spirometry, and conservative therapy. Chest 1985;87:151-157.
50. Heitz M, Holzach P, Dittman M. Comparison of the effect of continuous positive airway pressure and blowing bottles on functional residual capacity after abdominal surgery. Respiration 1985;48:277-284.
51. Noehren TH, Lasry JE, Legters LJ. Intermittent positive pressure breathing for the prevention and management of post-operative pulmonary complications. Surgery 1958;43:658.
52. Stock MC, Downs JB, Corkran ML. Pulmonary function before and after prolonged continuous positive airway pressure by mask. Crit Care Med 1984;12:973-974.
53. Dehaven CB, Hurst JM, Branson RD. Postextubation hypoxemia treated with a continuous positive airway pressure mask. Crit Care Med 1985;13:46-48.
54. Smith RA, Kirby RR, Gooding JM, Civetta JM. Continuous positive airway pressure (CPAP) by face mask. Crit Care Med 1980;8:483-485.
55. Duncan AW, Oh TE, Hillman DR. PEEP and CPAP. Anaesth Intensive Care 1986;14:236-250.
56. Anderson WH, Dossett BE, Hamilton GL. Prevention of postoperative pulmonary complications. Use of isoproterenol and intermittent positive pressure breathing on inspiration. JAMA 1963;186:763-766.
57. Carlsson C, Sonden B. Thylen U. Can post-operative continuous positive airway pressure (CPAP) prevent pulmonary complicqations after abdominal surgery? Intensive Care Med 1981;7:225-229.
58. Andersen JB, Olesen KP, Eikard B. et al. Periodic continuous positive airway pressure, CPAP, by mask in the treatment of atelectasis. Eur J Resp Care 1980;61:20-25.
59. Ali J, Serrette C, Wood LD, Anthonisen NR. Effect of post-operative intermittent positive pressure breathing on lung function. Chest 1984;85:192-196.
60. Masouye PC, Morel DR, Neidhart P. Effect of continuous positive airway pressure applied by face mask on right ventricular function after cardiac surgery. J Cardiothorac Vasc Anesth 1993;7:551-554.
61. Ingwersen UM, Larsen KR, Bertelsen MT, et al. Three different mask physiotherapy regimens for prevention of post-operative pulmonary complications after heart and pulmonary surgery. Intensive Care Med 1993;19:294-298.
62. Pinilla JC, Oleniuk FH, Tan L, et al. Use of a nasal continuous positive airway pressure mask in the treatment of postoperative atelectasis in aortocoronary bypass surgery. Crit Care Med 1990;18:836-840.

63. Jousela I. Endotracheal tube versus face mask with and without continuous positive airway pressure (CPAP.) Acta Anesthesiol Scand 1993;37:381-385.
64. Thomas AN, Ryan JP, Doran BR, Pollard BJ. Nasal CPAP after coronary artery surgery. Anaesthesia 1992;47:316-319.
65. Jousela I, Rasanen J, Verkkala K, Lamminen A, Makelainen A, Nikki P. Continuous positive airway pressure by mask in patients after coronary surgery. Acta Anesthesiol Scand 1994;38:311-316.
66. Terry M, Cooper DJ, Scheinkestel C, et al. Factors predicting ICU admission in patients with chest trauma. Anaesth Intensive Care 1993;21:717-718.
67. Moore PG, James OF, Byth PL, Simpson IJ. Factors affecting outcome after chest injury. Anaesth Intensive Care 1985; 13:362-369.
68. Gibbons J, James O, Quail A. Management of 130 cases of chest injury with respiratory failure. Br J Anaesth. 1973 45:1130-1135.
69. Trinkle JK, Richardson JD, Franz JL, Grover FL, Arom KV, Holmstrom FM. Management of flail chest without mechanical ventilation. Ann Thorac Surg 1975;19:355-363.
70. Shackford SR, Smith DE, Zarins CK, Rice CL, Virgilio RW. The management of flail chest. A comparison of ventilatory and non-ventilatory management. J Thorac Cardiovas Surg 1976;132:759-762.
71. Hurst JM, DeHaven CB, Branson RD. Use of CPAP mask as the sole mode of ventilatory support in trauma patients with mild to moderate respiratory insufficiency. J Trauma 1985;25:1065-1068.
72. Tzelepis GE, McCool FD, Hoppin FG. Chest wall distortion in patients with flail chest. Am Rev Respir Dis 1989;140:31-37.
73. Linton DM, Potgieter PD. Conservative management of blunt chest trauma. S Afr Med J 1982;61:917-919.
74. Bolliger CT, Van Eeden SF. Treatment of multiple rib fractures. Randomised controlled trial comparing ventilatory with non-ventilatory management. Chest 1990;97:943-948.
75. Worthley LIG. Thoracic epidural in the management of chest trauma. Intensive Care Med 1985;11:312-315.
76. Dittmann M, Steenblock U, Kranzlin M, Wolff G. Epidural analgesia or mechanical ventilation for multiple rib fractures. Intensive Care Med 1982;8:89-92.
77. Hormann C, Baum M, Putensen C, Mutz NJ, Benzer H. Biphasic positive airway pressure (BIPAP) - a new mode of ventilatory support. Eur J Anesthesiol 1994; 11:37-42.
78. Klopfenstein CE, Forster A, Suter PM. Pneumocephalus. A complication of continuous positive airway pressure after trauma. Chest 1980;78:656-657.
79. Peress L, Sybrecht G. Macklem PT. The mechanism of increase in total lung capacity during actue asthma. Am J Med 1976;61:165-169
80. Lougheed MD, Webb KA, O'Donnell DE. Breathelessness during induced lung hyperinflation in asthma: the role ofthe inspiratory threshold load. Am J Respir Crit Care Med 1995;152:911-920.
81. Martin J, Powell E, Shore S, Emrich J, Engel LA. The role of respiratory muscles in the hyperinflation of bronchial asthma. Am Rev Resp Dis 1980;121:441-447.
82. Benatar SR. Fatal Asthma. N Engl J Med 1986;314:423-429.
83. Appel D, Rubenstein R, Schrager K, Williams MH Jr. Lactic acidosis in severe asthma. Am J Med 1983;75:580-584.
84. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989;140:5-9.
85. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1987;136:872-879.
86. Darioli R. Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 1984; 129:385-387.
87. Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. Am Rev Resp Dis 1982;126:812-817.
88. Shivaram U, Donath J, Khan FA, Juliano J. Effects of continuous positive airway pressure in acute asthma. Respiration 1987;52:157-162.
89. Shivaram U, Miro AM, Cash ME, Finch PJ, Heurich AE, Kamholz SL. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. J Crit Care 1993 8:87-92.
90. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized prospective trial of non-invasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995;151:1799-1806.
91. Mansel JK, Stogner SW, Norman JR. Face-mask CPAP and sodium bicarbonate infusion in acute, severe asthma and metabolic acidosis. Chest 1989;96:943-944.
92. Martin RJ, Pak J. Nasal CPAP in nonapneic nocturnal asthma. Chest 1991; 100:1024-1027.
93. Zaragoza RH, Szefler SJ, Bratton DL. Brief report: therapeutic manipulations in severe nocturnal asthma. A non-conventional approach in a severe high-risk asthmatic. J Asthma 1992; 29:281-287.
94. Guilleminault C, Quera-Salva MA, Powell N, et al. Nocturnal asthma: snoring, small pharynx and nasal CPAP. Eur Respir J 1988; 1:902-907.
95. Pollack CV, Fleisch KB, Dowsey K. Treatment of acute bronchospasm with β-adrenergic agonist aerosols delivered by nasal bilevel positive airway pressure. Ann Emerg Med 1995; 26:552-556.
96. Moore RB, Cotton EK, Pinney MA. The effect of intermittent positive pressure breathing on airway resistance in normal and asthmatic children J Allergy Clin Immunol 1972;49:137-141.
97. Parkes SN, Bersten AD. Aerosol kinetics and bronchodilator efficacy during continuous positive airway pressure delivered by face mask. Thorax 1997;52:171-175.

98. Derenne J-P, Fleury B. Pariente R. Acute respiratory failure of chronic obstructive pulmonary disease. Am Rev Respir Dis 1988;138:1006-1033.
99. Vitacca M, Clini E, Rubini F, Nava S, Foglio K, Ambrosino N. Non-invasive mechanical ventilation in severe chronic obstructive lung disease and acute respiratory failure: short- and long-term prognosis. Intensive Care Med 1996;22:94-100.
100. Fleury B, Murciano D, Talamo C, Aubier M, Pariente R, Milic-Emili J. Work of breathing in patients with chronic obstructive pulmonary disease in acute respiratory failure. Am Rev Respir Dis 1985;131:822-827.
101. Haluszka J, Chartrand DA, Grassino AE, Milic-Emili J. Intrinsic PEEP and arterial pCO_2 in stable patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;141:1194-1197.
102. Kacmarek RM. Inspiratory pressure support: does it make a clinical difference? Intensive Care Med 1989;15:337-339.
103. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 1988;65:1488-1499.
104. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care 1994;150:896-903.
105. MacIntyre NR. Respiratory function during pressure support ventilation. Chest 1986; 89:677-683.
106. Appendini L, Patessio A, Zanaboni S, et al. Physiologic effects of positive end-expiratory pressure and mask pressure support during exarcebations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:1069-1076.
107. Fessler HE, Brower RG, Permutt S. CPAP reduces inspiratory work more than dyspnea during hyperinflation with intrinsic PEEP. Chest 1995;108:432-440.
108. Keilty SE, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. Thorax 1994;49:990-994.
109. Petrof BJ, Calderini E, Gottfried SB. Effect of CPAP on respiratory effort and dyspnoea during exercise in severe COPD. J Appl Physiol 1990;69:179-188.
110. O'Donnell DE, Sanii R, Giesbrecht G, Younes M. Effect of continuous positive airway pressure on respiratory sensation in patients with chronic obstructive pulmonary disease during submaximal exercise. Am Rev Resp Dis 1988;138:1185-1191.
111. Marini JJ. Should PEEP be used in airflow obstruction. Am Rev Respir Dis1989;140:1-3.
112. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. Chest 1989;96:449-451.
113. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993; 341:1555-1557.
114. Brochard L, Isabey D, Piquet J, et al. Reversal of acute exacerbation of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 1990; 323;11523-1530.
115. Meduri GU, Conoscenti CC, Menashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest 1989;95:865-870.
116. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with hypercapnic respiratory failure. Chest 1991;100:445-454.
117. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask. First line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest. 1996;109:179-193.
118. Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. Intensive Care Med 1993;19:450-455.
119. Chevrolet JC, Jolliet P, Abajo B, Toussi A, Louis M. Nasal positive pressure ventilation in patients with acute respiratory failure. Difficult and time-consuming procedure for nurses. Chest 1991;100:775-782.
120. Pennock BE, Kaplan PD, Carlin BW, Sabangan JS, Magovern JA. Pressure support ventilation with a simplified ventilatory support system administered with a nasal mask in patients with respiratory failure. Chest 1991;100:1371-1376.
121. Amjad H. Biismar H. McLung T. Bilevel positive airway pressure (BR-PAP) during acute respiratory failure with chronic obstructive disease. Chest 1993; 104:135S.
122. Elliott MW, Steven MH, Phillips GD, Branthwaite MA. Non-invasive mechanical ventilation for acute respiratory failure. Br Med J 1990;300:358-360.
123. Parkes SN, Bersten AD, Holt AW, Vedig AE, Worthley LI. Noninvasive assisted ventilation in hypercapnic respiratory failure. Anaesth Intensive Care 1993;21:111-115
124. Benhamou D, Girault C, Faure C, Portier F, Muir JF. Nasal mask ventilation in acute respiratory failure: experience in elderly patients. Chest 1992;102:912-917.
125. Laier-Groenefeld G, Huttemann U, Criee CP. Acute ventilatory failure treated by nasal ventilation. Am Rev Respir Dis 1991;143:A689.
126. Leger P, Jennequin J. Gaussorques PH, et al. Acute respiratory failure in COPD patients treated with noninvasive intermittent mechanical ventilation (control mode) with nasal mask. Am Rev Resp Dis 1988;137:A63.
127. Fernandez R, Blanch L, Valles J, Baigorri F, Artigas A. Pressure support ventilation via face mask in acute respiratory failure in hypercapnic COPD patients. Intensive Care Med 1993;19:456-461.
128. Soo Hoo GW, Santiago S. Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease:

determinants of success and failure. Crit Care Med 1994;22:1253-1261.
129. Brochard L, Mancebo J, Wysocki M, et al. Non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333:817-822
130. Abou-Shala N, Meduri GU. Noninvasive mechanical ventilation in patients with acute respiratory failure. Crit Care Med 1996; 24:705-715.
131. Brochard L, Pluskwa F, Lemaire F. Improved efficacy of spontaneous breathing with inspiratory pressure support. Am Rev Respir Dis 1987;136:411-415.
132. Mezzanotte WS, Tangel DJ, Fox AM, Ballard RD, White DP. Nocturnal nasal continuous positive airway pressure in patients with chronic obstructive pulmonary disease. Influence on waking respiratory muscle function. Chest 1994;106:1100- 1108.
133. Marino W. Intermittent volume cycled mechanical ventilation by nasal mask in patients with respiratory failure due to COPD. Chest 1991; 99:681-684.
134. Keenan SP, Kernerman PD, Cook DJ, Martin CM, McCormack D, Sibbald WJ. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. Crit Care Med 1997;25:1685-1692.
135. Meecham-Jones DJ, Paul EA, Grahame-Clarke C, Wedzicha JA. Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease: effect of ventilator mode on arterial blood gas tensions. Thorax 1994;49:1222-1224.
136. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne JP. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1980;122:191-199.
137. Aubier M, Murciano D, Milic-Emili J, et al. Effect of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 1980; 122:747-754.
138. Hanson CW 3rd, Marshall BE, Frasch HF, Marshall C. Causes of hypercarbia with oxygen therapy in patients with chronic obstructive pulmonary disease. Crit Care Med 1996;24:23-28
139. Pepin JL, Leger P, Veale D, Langevin B, Robert D, Levy P. Side effects of nasal continuous positive airway pressure in sleep apnea syndrome. Study of 193 patients in two French sleep centers. Chest 1995.107:375-381.
140. Hayes MJ, McGregor FB, Roberts DN, Schroter RC, Pride NB. Continuous nasal positive pressure with a mouth leak: effect on nasal mucosal blood flow and nasal geometry. Thorax 1995;50:1179-1182.
141. Strumpf DA, Harrop P, Dobbin J, Millman RP. Massive epistaxis from nasal CPAP therapy. Chest 1989;95: 1141.
142. Stauffer JL, Fayter N. MacLurg BJ. Conjunctivitis from nasal CPAP apparatus. Chest 1984;86:802.
143. Beswick FJ, Branthwaite MA, Chadwick MV. Sepsis in a CPAP system. Anaesthesia 1976; 31:658-661.
144. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP. Echocardiographic evaluation of ventricles during continuous positive airway pressure breathing. J Appl Physiol 1984;56:619-627.
145. Hodges MR, Stanley TH, Johansen RK. Pulmonary shunt and cardiovascular reponses to CPAP during nitroprusside-induced hypotension. Anesthesiology 1977;46:339-341.
146. Meurice JC, Mergy J, Rostykus C, Dore P, Paquereau J, Patte F. Atrial arrthymia as a complication of nasal CPAP. Chest 1992; 102:640-642.
147. Haring HP, Hormann C, Schalow S, Benzer A. Continuous positive airway pressure breathing increases cerebral blood flow velocity in humans. Anesth Analg 1994;79:883-885
148. Hormann C, Mohsenipour I, Gottardis M, Benzer A. Response of cerbrospinal fluid pressure to continuous positive airway pressure in volunteers. Anesth Analg 1994;78:54-57.
149. Alvarez-Sala R, Diaz S, Prados C, Villasante C, Villamor J. Increase of intraocular pressure during nasal CPAP. Chest 1992;101:1477.
150. Alvarez-Sala R, Garcia IT, Garcia F, et al. Nasal CPAP increases intraocular pressure in glaucoma. Monaldi Arch Chest Dis 1994;49:394-395.
151. Alpan G, Goder K, Glick B, Peleg O, Avital A, Eyal F. Pneumopericardium during continous positive airway pressure in respiratory distress syndrome. Crit Care Med 1984;12:1080-1081.
152. Wang W, Tovar JA, Eizaguirre I, Aldazabal P. Continuous positive airway pressure and gastrooesophageal reflux: an experimental study. J Pediatr Surg 1994; 29:730-733.
153. Kerr P, Shoenut JP, Steens RD, Millar T, Micflikier AB, Kryger MH. Nasal continuous positive airway pressure. A new treatment for nocturnal gastroesophageal reflux. J Clin Gastroenterol 1993;17:276-280.