Non-invasive ventilation in acute cardiogenic pulmonary oedema

R Agarwal, A N Aggarwal, D Gupta, S K Jindal

Non-invasive ventilation (NIV) is the delivery of assisted mechanical ventilation to the lungs, without the use of an invasive endotracheal airway. NIV has revolutionised the management of patients with various forms of respiratory failure. It has decreased the need for invasive mechanical ventilation and its attendant complications. Cardiogenic pulmonary oedema (CPO) is a common medical emergency, and NIV has been shown to improve both physiological and clinical outcomes. From the data presented herein, it is clear that there is sufficiently high level evidence to favour the use of continuous positive airway pressure (CPAP), and that the use of CPAP in patients with CPO decreases intubation rate and improves survival (number needed to treat seven and eight respectively). However, there is insufficient evidence to recommend the use of bilevel positive airway pressure (BiPAP), probably the exception being patients with hypercapnic CPO. More trials are required to conclusively define the role of BiPAP in CPO.

Non-invasive ventilation (NIV) is the provision of ventilatory support to the lungs without the use of an endotracheal airway. It has emerged as an important tool in the treatment of diverse forms of acute respiratory failure. It not only reduces the need for invasive mechanical ventilation and its associated complications, but also reduces the complications associated with stay in the intensive care unit, length of hospital stay, and mortality in selected patients. Cardiogenic pulmonary oedema (CPO) is a common medical emergency and NIV in addition to conventional medical treatment is beneficial for patients with CPO as it augments cardiac output, results in rapid improvement in gas exchange, decreases the need for endotracheal intubation, and there is a trend towards decreased in-hospital mortality.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF CPO

CPO is defined as an episode of acute heart failure accompanied by severe respiratory distress and oxygen saturation <90% on room air before all treatment. The pathogenesis of CPO is related to a critical interaction between progressive decrease in left ventricular systolic function and acute increase in systemic vascular resistance with resultant exudation of fluid from the intravascular compartment into the lung interstitium and alveoli. This leads to a vicious cycle amplified by three important processes. Firstly, as pulmonary congestion increases, oxygen saturation decreases, resulting in decreased myocardial oxygen supply. This leads to ischaemia in regions with already borderline blood supply, further impairing cardiac performance. Secondly, hypoxemia and increased fluid content in the lungs induces pulmonary vasoconstriction increasing the right ventricular pressure. This compromises left ventricular function through the ventricular interdependence mechanism.

Finally, profound circulatory insufficiency results in metabolic acidosis, which further jeopardises cardiac performance.

CPO is characterised by an increase in extravascular lung water, which causes a decrease in respiratory system compliance, increased airway resistance, air trapping, arterial hypoxaemia, and decreased diffusing capacity.

See end of article for authors' affiliations

Correspondence to:
Dr R Agarwal, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh-160012, India; drntesh1@rediffmail.com

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How does continuous positive airway pressure (CPAP) work?

The immediate goals in the treatment of acute CPO are to improve systemic oxygen saturation by giving oxygen with a high flow facemask, reduction of preload and afterload of both the ventricles by a combination of morphine, diuretics, and nitrates. As early as 1936, CPAP had

Abbreviations:
CPO, cardiogenic pulmonary oedema; NIV, non-invasive ventilation; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure
been shown to be an effective therapy for CPO unresponsive to medical treatment.

CPAP therapy in patients with CPO is associated with immediate and pronounced improvements in respiratory
dysfunction and haemodynamic variables. CPAP augments the inspiratory and expiratory flow and pressure thereby increasing the tidal volume and unloading the inspiratory muscles. It decreases dead space ventilation and improves alveolar theoretic tone in response to CPAP induced lung inflation. CPAP increases pericardial pressure, reduces transmural pressure, and thus decreases afterload. Although CPAP can decrease cardiac index in normal people, it increases cardiac index in patients with CPO. CPAP also causes a significant decrease in the heart rate, resulting from increased parasympathetic tone in response to CPAP induced lung inflation.

However, treatment with NIV in CPO is beneficial only in patients who have systolic dysfunction. In patients with diastolic dysfunction who require a comparatively high filling pressure, the effects of positive pressure therapy compromises venous return, resulting in deterioration of haemodynamics.

### Table 1

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (random)</th>
<th>Weight</th>
<th>OR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Rasanen 1985</td>
<td>6/20</td>
<td>12/20</td>
<td></td>
<td>14.96</td>
<td>0.29</td>
</tr>
<tr>
<td>Lin 1991</td>
<td>7/25</td>
<td>17/30</td>
<td></td>
<td>17.94</td>
<td>0.30</td>
</tr>
<tr>
<td>Bersten 1991</td>
<td>0/19</td>
<td>7/20</td>
<td></td>
<td>4.06</td>
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<tr>
<td>Lin 1995</td>
<td>4/50</td>
<td>3/50</td>
<td></td>
<td>11.81</td>
<td>0.36</td>
</tr>
<tr>
<td>Takeda 1998</td>
<td>2/11</td>
<td>8/11</td>
<td></td>
<td>7.77</td>
<td>0.08</td>
</tr>
<tr>
<td>Park 2001</td>
<td>3/9</td>
<td>4/10</td>
<td></td>
<td>8.81</td>
<td>0.75</td>
</tr>
<tr>
<td>Kelly 2002</td>
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<td></td>
<td>10.56</td>
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</tr>
<tr>
<td>Crane 2004</td>
<td>1/20</td>
<td>0/20</td>
<td></td>
<td>3.37</td>
<td>0.12</td>
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<tr>
<td>L’Her 2004</td>
<td>2/43</td>
<td>4/46</td>
<td></td>
<td>9.83</td>
<td>0.51</td>
</tr>
<tr>
<td>Park 2004</td>
<td>2/21</td>
<td>11/26</td>
<td></td>
<td>10.90</td>
<td>0.11</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>260</td>
<td></td>
<td>100.00</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Figure 1**

Intubation rates: CPAP compared with standard medical therapy (odds ratio with 95% confidence intervals, random effects model).
mechanics to change before any benefits of respiratory muscle unloading are seen.\footnote{Reference}

**CLINICAL EVIDENCE FOR THE ROLE OF NIV**

For the evidence, all the authors independently searched the National Library of Medicine’s Medline database for relevant studies published from 1966 to September 2004 using the keywords: noninvasive ventilation OR continuous positive airway pressure OR bilevel positive airway pressure AND pulmonary edema AND randomized controlled trials (publication type) or controlled clinical trials or clinical trials, randomized. Bibliographies of all selected articles and review articles that included information on NIV in CPO were reviewed for other relevant articles. In addition, we reviewed our personal files. Our search produced 16 citations (table 1), which were randomised controlled trials (blinded or unblinded). We discuss the clinical evidence under the following headings—CPAP compared with conventional medical therapy, BiPAP compared with conventional medical therapy, and CPAP compared with BiPAP. Apart from the potential weaknesses of all meta-analysis like publication bias (negative studies less likely to be submitted or accepted for publication) and heterogeneity (different interventions, different clinical circumstances), the main limitation of this meta-analysis is that the studies have not been adequately blinded and the individual studies have included small number of patients. Thus the results of this analysis need to be confirmed by a larger randomised controlled trial.

**CPAP COMPARED WITH CONVENTIONAL MEDICAL THERAPY**

Almost six decades ago, Poulton and Oxon\cite{Reference} described the use of CPAP delivered by the “pulmonary plus pressure machine” through a facemask to patients with “cardiac asthma.” Several studies have shown that CPAP is effective in patients with CPO as it rapidly improves gas exchange and cardiac haemodynamics, and can decrease intubation rates and inhospital mortality.\cite{Reference1, Reference2, Reference3} However, most studies on CPO have not been adequately powered to detect these differences.

Rasanen et al\cite{Reference4} randomised 40 patients with CPO to either facemask CPAP (10 cm H2O) or standard medical therapy, and showed improvement in gas exchange, decrease in respiratory work, and reduced need for intubation. Lin et al\cite{Reference5} randomised 35 patients to CPAP or high flow oxygen therapy, and showed significant decrease in the intubation rates in the CPAP group compared with controls (28% vs 60% respectively). Bersten et al\cite{Reference6} compared the efficacy of CPAP (10 cm H2O) with that of conventional treatment in 39 patients with CPO and found a significant and rapid improvement in arterial oxygen tension and a significant decrease in arterial carbon dioxide tension in patients treated with CPAP.
BiPAP Compared with Conventional Medical Therapy

Fewer controlled trials have been performed to see if BiPAP is an effective therapy for patients with CPO. Physiological studies have shown that BiPAP is more effective at unloading the respiratory muscles than CPAP alone in patients with COPD and in patients with acute CPO. Several open clinical studies have reported rapid improvements in gas exchange in patients with CPO treated with BiPAP. Rusterholtz et al. applied BiPAP (IPAP 20.5 (4.7) cm H2O, EPAP 3.5 (2.3) cm H2O) in 26 patients with CPO and found improvement in gas exchange in only five patients requiring endotracheal intubation. In a randomised, prospective, trial of 40 patients, Masip et al. found a significantly lower rate of intubation in patients treated with BiPAP (IPAP 15.2 (2.4) cm H2O, EPAP 5 cm H2O) compared with oxygen treated control subjects (5% vs 33% respectively; p < 0.037). Although resolution time (oxygen saturation > 96% and respiratory rate ≤ 30 breaths/min) was significantly shorter in the BiPAP group (p < 0.002), hospital lengths of stay and death rates were similar in the two groups. Importantly, four of the six patients (66%) requiring intubation in the conventional therapy group were hypercapnic, whereas no hypercapnic patients in the BiPAP group required intubation. The small sample size however did not permit a subgroup analysis of the impact of hypercapnia on the outcome.

Other randomised trials have also described improvement in physiological parameters but no decrease in intubation rates or mortality. Masip et al. in another study randomised 100 patients with CPO, and showed favourable effects of incremental CPAP (2.5–12.5 cm H2O) on oxygenation, respiratory rates, and the need for intubation. Although statistically not significant, the study showed trend towards improved hospital survival. Takeda et al. showed beneficial results of CPAP in CPO in the setting of acute myocardial infarction. Recently L’Her et al. randomised 89 elderly patients with CPO to standard medical therapy or CPAP (7.5 cm H2O) plus standard medical therapy, and showed that CPAP decreased intubation rates, and promoted early clinical improvement in patients attending emergency departments for severe pulmonary oedema. However, only the early 48 hour mortality was reduced and no sustained benefits were seen during the overall hospital stay.

Figures 1 and 2 shows the combined data of all randomised trials of CPAP compared with standard medical therapy in CPO, and pooled data (515 patients) suggest that CPAP significantly decreases intubation rates (odds ratio (OR) 0.32; 95% confidence intervals (CI) 0.17 to 0.59) and hospital mortality (OR 0.33; 95% CI 0.18 to 0.59). Also seven patients with CPO need to be treated with CPAP to prevent one intubation whereas the number needed to treat (NNT) to prevent one death is eight.

Table 1

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>BiPAP n/N</th>
<th>Standard therapy n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharon 2000</td>
<td>2/20</td>
<td>0/20</td>
<td>4.67</td>
<td>5.54</td>
<td>0.25, 123.08</td>
</tr>
<tr>
<td>Masip 2000</td>
<td>0/19</td>
<td>2/18</td>
<td>4.65</td>
<td>0.17</td>
<td>0.01, 3.78</td>
</tr>
<tr>
<td>Park 2001</td>
<td>0/7</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levitt 2001</td>
<td>3/21</td>
<td>3/17</td>
<td>14.72</td>
<td>0.78</td>
<td>0.14, 4.46</td>
</tr>
<tr>
<td>Nava 2003</td>
<td>6/65</td>
<td>9/65</td>
<td>37.38</td>
<td>0.63</td>
<td>0.21, 1.89</td>
</tr>
<tr>
<td>Crane 2004</td>
<td>5/20</td>
<td>6/20</td>
<td>23.15</td>
<td>0.78</td>
<td>0.19, 3.13</td>
</tr>
<tr>
<td>Park 2004</td>
<td>2/27</td>
<td>6/26</td>
<td>15.44</td>
<td>0.27</td>
<td>0.05, 1.47</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>179</td>
<td>176</td>
<td>100.00</td>
<td>0.62</td>
<td>0.32, 1.22</td>
</tr>
</tbody>
</table>

Total events: 18 (BiPAP), 26 (Standard therapy)
Test for heterogeneity: Chi² = 3.70, df = 5 (p = 0.59), I² = 0%
Test for overall effect: Z = 1.38 (p = 0.17)

Figure 4 Death rates: BiPAP compared with standard medical therapy (odds ratio with 95% confidence intervals, random effects model).
CPO, and pooled data (355 patients) suggest that BiPAP shows a trend towards decreased intubation rates (OR 0.61; 95% CI 0.16 to 2.33) and hospital mortality (OR 0.62; 95% CI 0.32 to 1.22). However, this is not statistically significant, and more studies are required to settle this issue.

**CPAP COMPARED WITH BiPAP**

The superiority of BiPAP over standard therapy for acute CPO is not surprising, but the question of interest is whether BiPAP is superior to CPAP alone. There have been four randomised trials that have attempted to answer this question. Mehta et al randomised patients to receive either nasal CPAP (10 cm H₂O) or BiPAP (IPAP 15 cm H₂O/EPAP 5 cm H₂O). Although the BiPAP group had greater reductions in PaCO₂, systolic blood pressure, mean arterial pressure, and hypercapnia than did the CPAP group, myocardial infarction rates were higher in the BiPAP group (71%) than in the CPAP group (31%) and the study was stopped prematurely after the enrolment of 27 patients. While this difference could have been attributable to unequal randomisation as more patients in the BiPAP group presented with chest pain, the results none the less raised concerns about the safety of the ventilatory techniques used to treat CPO. On the other hand, Park et al and Bellone et al showed that BiPAP was as effective as CPAP in the treatment of CPO and both methods improved ventilation and vital signs in patients with acute CPO. No significant differences were found in hospital mortality and acute myocardial infarction rates in patients with acute CPO in comparison with CPAP alone. Recently, Crane et al randomised 60 patients presenting with acute CPO to receive conventional oxygen therapy, CPAP (10 cm H₂O), or bilevel ventilation (IPAP 15 cm H₂O, EPAP 5 cm H₂O). Although treatment success (respiratory rate <23 bpm, oxygen saturation >90%, pH >7.35 occurred in three patients in the control group, seven in the CPAP group, and nine in the BiPAP group (p = 0.116), 14 of the control group patients survived to hospital discharge, compared with 20 in the CPAP group and 15 in the bilevel group (p = 0.029).

Figures 5 and 6 show the combined data of all randomised trials of CPAP compared with BiPAP in CPO, and pooled data (183 patients) suggest that BiPAP increases intubation rates (OR 1.17; 95% CI 0.37 to 3.7) and probably hospital mortality (OR 0.99; 95% CI 0.22 to 4.48). However, again like BiPAP compared with standard medical therapy group, this is not statistically significant, and more studies are required to settle this issue.

**PRACTICAL ASPECTS OF NIV IN CPO**

Where are these patients best treated?

While most patients with CPO present to the emergency department, practical issues, including hospital setup and staff determine where NIV is actually performed. It is important to realise that the workload in the first six to eight hours may be greater than that required for a conventionally managed patient. Consequently, patients with severe CPO requiring NIV need to be triaged to an environment with round the clock medical care, adequate nurse-patient ratio, and continuous electrocardiographic and pulse oximetry monitoring facilities. We like many other investigators manage such patients in intensive care units. Many patients with CPO would be as a consequence of myocardial infarction and unlike many investigators who have excluded such patients; many centres (including our centre) concurrently provide support with NIV while proceeding to thrombolysis or percutaneous revascularisation.

Do all patients with CPO require NIV?

Not all patients with CPO require NIV. In fact, a large number of patients rapidly respond to medical treatment and do not need additional intervention. NIV is likely to be beneficial in patients with more severe forms of CPO, especially those who present with a pH <7.25 or systolic blood pressure <180 mm Hg. A potential use for NIV is to support patients who are not candidates for intubation, either because of a previous directive or as a result of poor prognosis related to an underlying disease. Another approach is to give a trial of NIV in all patients with CPO who do not respond to initial medical therapy. However, patients should be carefully monitored and failure to improve after 30 minutes on NIV should be an indication for its withdrawal, with facilities for immediate endotracheal intubation and mechanical ventilation being readily available.

How should NIV be applied initially?

The application of NIV is an art of medicine. All physicians using NIV should personally apply NIV to actually understand what the patient is experiencing. You should not order a specific pressure level for a given patient without first applying NIV and assessing the patient’s tolerance to the device. Initial application of NIV requires careful instruction of the patient, with a goal to gain the patient’s confidence and acceptance of NIV. You must start with low pressures and the mask should be held and not strapped to the patient’s face. As the patient accepts the NIV, pressures are increased to reach the gas exchange goal, but generally should not exceed 20–25 cm H₂O to minimise gastric distension and the risk of vomiting. Although time consuming, the cost savings are large compared with the alternative—that is, invasive ventilation.

What should be the interface?

The masks most commonly used for short term applications of NIV include nasal or oronasal (also called full face) masks.

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**Figure 5** Intubation rates: CPAP compared with BiPAP (odds ratio with 95% confidence intervals, random effects model).
Although nasal mask is theoretically more comfortable for the patient as it is less claustrophobic, has lower dead space volume, permits speech and eating, and better mobilisation of secretions; oronasal masks achieve better control of mouth leak in mouth breathers (common feature during acute respiratory failure) and result in better quality of ventilation, in terms of improved minute ventilation and blood gas pressure.\(^5\) In a study of 70 patients with acute respiratory failure randomised to receive a nasal or oronasal mask, both the masks performed similarly with regard to improvements in gas exchange and avoidance of intubation; however, the nasal mask was less well tolerated because of excessive mouth leaks:\(^6\) probably because mouth leaks with nasal CPAP lead to high unidirectional nasal airflow and increased nasal resistance.\(^7\) In another study, however, no significant differences were noted irrespective of the type of mask used.\(^8\) From the available evidence it cannot be said that any interface is clearly superior to another in terms of important outcomes such as intubation rate or mortality. An oronasal interface may be more effective and better tolerated than the nasal interface for patients with acute respiratory failure. Thus, a sensible approach would be to start with an oronasal mask for most patients with acute respiratory failure, and switch to a nasal mask if prolonged use is necessary.\(^9\)

**CONCLUSIONS**

There is a strong evidence for the use of CPAP by facemask in patients with CPO, and CPAP decreases the need for endotracheal intubation and improves survival. However, there is insufficient evidence to recommend the use of BiPAP, probably the exception being patients with hypercapnic CPO.\(^10\) Although evidence suggests that patients presenting with CPO are more likely to survive to hospital discharge if treated with CPAP, rather than with BiPAP, and probably there is no relation between early physiological changes and hospital survival, the evidence is not strong so as to completely exclude BiPAP, and more studies are required to elucidate the role of BiPAP in CPO.\(^11\)

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**Authors’ affiliations**

R Agarwal, A N Aggarwal, D Gupta, S K Jindal, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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Conflicts of interest: none.

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**REFERENCES**

10. Park M, Lorenzo-Filho G, Faltrim MI, et al. Oxygen therapy, continuous positive airway pressure, or noninvasive bilevel positive pressure ventilation in the non-invasive mode, they are more leak tolerant and use only the alarms essential for the operation of NIV. On the other hand, newer portable devices with graphic monitors, oxygen blenders, and sophisticated alarms have also become available for use in the acute setting.
Non-invasive ventilation in cardiogenic pulmonary oedema


