The Effect of Positive Pressure Airway Support on Mortality and the Need for Intubation in Cardiogenic Pulmonary Edema*

A Systematic Review

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Objective: To critically appraise and summarize the trials examining the addition of continuous positive airway pressure (CPAP) or noninvasive positive pressure ventilation (NPPV) to standard therapy on hospital mortality, need for endotracheal intubation, and predischARGE left ventricular function in patients admitted to the hospital with cardiogenic pulmonary edema with gas exchange abnormalities.

Data sources: We searched MEDLINE (1983 to June 1997) and bibliographies of all selected articles and review articles. We also reviewed the abstracts from the proceedings of relevant meetings from 1985 to 1997.

Study selection: (1) Population: patients presenting to hospital with cardiogenic pulmonary edema; (2) intervention: one of the following three: (a) the use of CPAP and standard medical therapy vs standard medical therapy alone; (b) the use of NPPV and standard medical therapy vs standard medical therapy alone; and (c) the use of NPPV and standard therapy vs CPAP and standard therapy; (3) outcome: hospital survival, need for endotracheal intubation, or predischARGE left ventricular dysfunction; and (4) study design: randomized controlled trial (RCT); if there were fewer than two RCTs, other study designs were included.

Data extraction: Two authors independently extracted data and evaluated the methodologic quality of the studies.

Data synthesis: CPAP was associated with a decrease in need for intubation (risk difference, −26%, 95% confidence intervals, −13 to −38%) and a trend to a decrease in hospital mortality (risk difference, −6.6%; +3 to −16%) compared with standard therapy alone. There was insufficient evidence to comment on the effectiveness of NPPV either compared with standard therapy or CPAP and standard therapy. Evidence was also lacking on the potential for either intervention to cause harm.

Conclusions: A modest amount of favorable experimental evidence exists to support the use of CPAP in patients with cardiogenic pulmonary edema. CPAP appears to decrease intubation rates and data suggest a trend toward a decrease in mortality, although the potential for harm has not been excluded. The role of NPPV in this setting requires further study before it can be widely recommended.

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Key words: BIPAP; continuous positive airway pressure; critical appraisal; critical care; evidence-based medicine; heart failure; intensive care; noninvasive positive pressure ventilation; pulmonary edema

Abbreviations: CPAP = continuous positive airway pressure; NPPV = noninvasive positive pressure ventilation; CI = confidence interval
Cardiogenic pulmonary edema is a common reason for admission to acute care hospital beds. While the majority of patients with pulmonary edema respond to conventional therapy, including the use of supplemental oxygen, diuretics, opiates, and nitrates, some patients require ventilatory support.\textsuperscript{1-3} Traditionally, this has been provided via endotracheal intubation and mechanical ventilation. Positive pressure ventilation has been demonstrated to decrease cardiac afterload, decrease respiratory muscle work, and recruit atelectatic lung, thereby decreasing shunt and improving hing compliance.\textsuperscript{4-7} However, complications in the form of both traumatic injury to the upper airway and an increased risk of ventilator-associated pneumonia are associated with conventional mechanical ventilation.\textsuperscript{8-10} Noninvasive approaches to applying positive airway pressure to patients with cardiogenic pulmonary edema came into favor in the early 1980s to avoid the need for endotracheal intubation.\textsuperscript{6} Continuous positive airway pressure (CPAP) applied by face mask was found to decrease the need for endotracheal intubation; however, no survival benefit was demonstrated by the individual trials.\textsuperscript{1-3} In the 1990s, noninvasive positive pressure ventilation (NPPV) has been used as an alternative to conventional ventilation in acute respiratory failure arising secondary to multiple etiologies.\textsuperscript{11-20} A systematic review of randomized trials of NPPV in acute respiratory failure demonstrated a decrease in hospital mortality in COPD exacerbations (odds ratio, 0.22; 95\% confidence intervals, 0.09 to 0.54) but insufficient evidence to suggest benefit elsewhere.\textsuperscript{21} A recent consensus conference stated that it is recognized that NPPV is used in other acute circumstances but available evidence is less solid in establishing efficacy in these settings.\textsuperscript{22}

Despite trials suggesting that CPAP may be beneficial when used in patients with acute pulmonary edema, the utilization of this technology is variable. Potential explanations for this are as follows: (1) a perceived problem with the original studies; (2) concern about unreported adverse effects; (3) a problem in research transfer (the process of delivering the results of research to clinicians); and (4) lack of experience with and availability of this technology.

The primary objective of this systemic review was to determine the effect of two modes of noninvasive positive pressure airway support (CPAP and NPPV) in patients with cardiogenic pulmonary edema on hospital mortality. Secondary objectives were to determine the effect of these therapies on the need for endotracheal intubation and predischarge left ventricular function. We assessed three different interventions: (1) CPAP and standard medical therapy vs standard medical therapy alone; (2) NPPV and standard medical therapy vs standard medical therapy alone; and (3) NPPV and standard therapy vs CPAP and standard therapy.

**Materials and Methods**

**Search Strategy**

We used a number of search strategies to identify the relevant literature, including computerized literature searches of the National Library of Medicine’s MEDLINE from 1983 to June 1997, using the key words pulmonary edema (therapy) and respiratory insufficiency (therapy) separately, with and without positive pressure respiration. These searches were limited to studies on humans and those published in English. Bibliographies of all selected articles and review articles were reviewed for other relevant articles. Finally, the supplements of the following journals were hand searched from 1985 to June 1997, to identify relevant abstracts that had not been published as peer-reviewed articles: CHEST, American Journal of Cardiology, Circulation, Thorax, American Journal of Respiratory and Critical Care Medicine, Intensive Care Medicine, Critical Care Medicine, and the European Respiratory Journal.

**Study Selection**

Articles were included after examining their title and abstract if they fulfilled the following criteria: (1) population: patients presenting to hospital with acute pulmonary edema; (2) interventions: one of the following three: (a) CPAP and standard medical therapy vs standard medical therapy alone; (b) NPPV and standard medical therapy vs standard medical therapy alone; and (c) NPPV and standard therapy vs CPAP and standard therapy; (3) outcomes: hospital survival, need for endotracheal intubation, or predischarge left ventricular dysfunction; and (4) study design: randomized, controlled trial; if there were fewer than two randomized controlled trials, other study designs were included.

**Assessment of Validity**

The selected studies were independently reviewed by two of us (D.P. and S.P.K.) for the following features of study validity: randomization concealment—measures taken to conceal allocation using either a central randomization center or appropriate local measures (yes, no, not available); objective criteria for study population (yes, no, not available); objective criteria for need for endotracheal intubation (yes, no, not available); description of potential confounders (yes, no, partial); complete follow-up (yes, no); mention of cointervention standardization (yes, no); and intention-to-treat analysis (yes, no).

**Analysis**

For each of the three different management strategies, the following approach was taken. If two or more randomized controlled trials were available, the trials were first assessed for clinical heterogeneity by the authors abstracting data, and tested for statistical heterogeneity of study results using the Breslow-Day test. If the trials were found to be homogeneous, hospital mortality results for the individual studies were pooled using the DerSimonian and Laird random effects model, to obtain an overall risk reduction (the risk of hospital mortality in the control group, risk of mortality in the
treatment group) and 95% confidence intervals (CIs). As long as the 95% CIs did not cross zero, the number needed to treat was calculated with its respective CIs. Similarly, data on the need for endotracheal intubation and predischarge left ventricular function were pooled when available.

For the outcomes of hospital mortality and need for endotracheal intubation, a strong trend was defined as a pooled risk reduction of 10% with 95% CI including zero. A trend was defined as a pooled risk reduction of 5 to 10% with 95% CI including zero. If fewer than two randomized, controlled studies were available for analysis, study results were qualitatively summarized.

**RESULTS**

**Search and Study Selection**

A total of 497 potentially relevant articles were identified using the search strategy described. Of these, only three randomly assigned trials fulfilled all four selection criteria for studies comparing CPAP with standard therapy1-3 (Table 1). Reasons for exclusion of others were: nonrandomized clinical trials (n = 466), alternative study population (patients other than those with cardiogenic pulmonary edema) (n = 436), crossover trial (n = 1), and one study in which the patients may have been included in another trial (n = 1).

No randomized, controlled trials were identified that compared the use of NPPV with standard medical treatment alone in cardiogenic pulmonary edema. The best evidence available consisted of seven case series reports and these were included in this review. Reasons for exclusion were alternative study population or intervention (n = 481).

One randomized, controlled trial, was identified that compared the use of CPAP to NPPV in cardiogenic pulmonary edema.23

**Validity Assessment of Randomized Controlled Trials**

The three trials comparing CPAP with standard therapy alone fulfilled the validity criteria well with the exception of reporting concealed randomization, which was mentioned in one trial (Table 2). The two reviewers agreed on each item evaluating methodologic quality.

The single trial comparing CPAP with NPPV fulfilled all validity criteria with the exception of a potentially important difference between the two groups at baseline, which could affect outcomes. The NPPV group had a higher rate of chest pain on presentation (10/14, 71%) compared with the CPAP group (4/13, 31%, p = 0.06). In addition, the NPPV group had a lower mean pH (7.25 vs 7.32, no statistical test reported).

**CPAP vs Standard Medical Therapy Alone**

In the three randomized trials, the populations appeared similar (Table 1) and included cardiogenic pulmonary edema (bilateral pulmonary infiltrates, bilateral crackles on auscultation, a cardiac gallop, elevated jugular venous pressure) with either respiratory distress, evidenced by increased respiratory rate and accessary muscle use, or a rising PaCO2.1-3 The baseline pH was lowest in the

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**Table 1—Randomized Trials of CPAP vs Standard Therapy in Patients With Cardiogenic Pulmonary Edema**

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Sample Size</th>
<th>Country</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasasen et al.1 1985</td>
<td>40</td>
<td>Finland</td>
<td>Cardiogenic pulmonary edema&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Unresponsive to speech</td>
<td>CPAP 10 cm H2O face mask</td>
<td>Need for intubation Hospital mortality</td>
</tr>
<tr>
<td>Bersten et al.2 1991</td>
<td>40</td>
<td>Australia</td>
<td>Cardiogenic pulmonary edema&lt;sup&gt;†&lt;/sup&gt;</td>
<td>MI with shock, SBP &lt; 90 mm Hg severe stenotic valvular heart disease, COPD with CO2 retention</td>
<td>CPAP 10 cm H2O by face mask</td>
<td>Need for intubation Hospital mortality</td>
</tr>
<tr>
<td>Lin et al.3 1995</td>
<td>100</td>
<td>Taiwan</td>
<td>Cardiogenic pulmonary edema&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Unresponsive to speech, unable to maintain own airway, cardiogenic shock, ventricular septal rupture, severe outflow tract obstruction, COPD with CO2 retention</td>
<td>CPAP titrated up to 2.5, 5.0, 7.5, 10, and 12.5 cm H2O by face mask</td>
<td>Need for intubation Left ventricular function Hospital mortality</td>
</tr>
</tbody>
</table>

<sup>*</sup>RRA = respiratory rate; FIO2 = fraction of inspired oxygen; MI = myocardial infarction; SBP = systolic BP.

<sup>†</sup>Cardiogenic pulmonary edema was diagnosed clinically when bilateral pulmonary infiltrates were found on chest radiograph and the patient had a compatible clinical examination (bilateral crackles on auscultation, elevated jugular venous pressure, a cardiac gallop).
Table 2—Validity Criteria for Trials of CPAP vs Standard Therapy

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Randomization concealed</th>
<th>Objective Criteria for Study Population</th>
<th>Objective Criteria for Intubation</th>
<th>Potential Confounders</th>
<th>Standardization of Cointerventions</th>
<th>Complete Follow-up</th>
<th>Intention-to-Treat Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasen et al.1 1985</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bersten et al.2 1991</td>
<td>Not available</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lin et al.3 1995</td>
<td>Not available</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

study by Bersten and colleagues2 (7.15 ± 0.11 for control and 7.18 ± 0.08 for treatment groups), intermediate for Rasen and coworkers1 (7.36 ± 0.10 for control and 7.33 ± 0.10 for treatment groups), and most normal for Lin and associates5 (pH not reported at baseline for either group, but within the control arm, pH was 7.40 ± 0.08 for the 32 patients not requiring intubation and was 7.36 ± 0.09 for the 18 who were intubated). These differences suggest a spectrum of illness severity across the three studies. CPAP was administered as either 10 cm H2O immediately or titrated to achieve a PaO2 of >80 mm Hg. All studies assessed hospital mortality and need for endotracheal intubation, but only one assessed left ventricular dysfunction.3

While the point estimates of all three trials suggested a survival benefit from the addition of CPAP to standard therapy, each 95% CI included zero (Table 3 and Fig 1). Pooling the results of these three trials yielded a risk difference of 6.6%, suggesting a trend toward decreased mortality in the CPAP group (Fig 1). However, the 95% CIs reflect a potential decrease in risk of 16% to a potential increase in risk of mortality of 3%. The Breslow test of homogeneity was not significant (p = 0.996).

All three studies found a reduction in the need for intubation, the pooled results estimating a risk difference of 26% (95% CI, of 14 to 38%). This suggests that four patients with acute pulmonary edema eligible for CPAP would need to be treated with CPAP to prevent one endotracheal intubation (number needed to treat = 4, 95% CI, 3 to 8) (Table 3 and Fig 2). The Breslow-day test of homogeneity was not significant (p = 0.583).

One of these three studies assessed left ventricular function.3 Lin and colleagues3 found no difference in baseline left ventricular ejection fraction (33.5 ± 5.4% [n = 47] vs 33.6 ± 5.3% [n = 46], for CPAP and control groups, respectively) or ejection fraction at 1 year (35.4 ± 4.8% [n = 38] vs 35.3 ± 5.0% [n = 36], respectively).

NPPV vs Standard Medical Therapy Alone

We found no randomized controlled trials exclusively in patients with pulmonary edema that compared NPPV with standard therapy. Two trials have been conducted that included pulmonary edema patients,11,12 but the presentation of results preclude interpretation of the effect of NPPV on this subgroup alone. Several case reports and case series have described the use of NPPV in patients with pulmonary edema.13-20 Overall, intubation rates

Table 3—Effectiveness of CPAP on Hospital Mortality in Patients With Cardiogenic Pulmonary Edema

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>CPAP Group</th>
<th>Control Group</th>
<th>Risk Reduction for Mortality (95% CI)</th>
<th>Risk Reduction for Intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasen et al.1 1985</td>
<td>Died</td>
<td>Intubated</td>
<td>Total</td>
<td>Died</td>
</tr>
<tr>
<td>Bersten et al.2 1991</td>
<td>2</td>
<td>0</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Lin et al.3 1995</td>
<td>4</td>
<td>8</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Pooled results</td>
<td>9</td>
<td>14</td>
<td>89</td>
<td>16</td>
</tr>
</tbody>
</table>

*Breslow-Day test of homogeneity: p = 0.996 for mortality, p = 0.583 for intubation.
ranged from 0 to 44%, mortality rates from 0 to 22% (Table 4). Left ventricular function was not reported in these studies.

**CPAP vs NPPV**

One randomized trial directly compared the use of CPAP with NPPV in patients with cardiogenic pulmonary edema. This study had (1) objective criteria for study population and need for intubation, (2) listed potential confounders and co-interventions, (3) had complete follow-up of patients in hospital, and (4) used an intention-to-treat analysis. No mention was made regarding concealment of allocation. No difference was found between groups for hospital mortality (one in the NPPV group and two in the CPAP group) or rate of reintubation (one in each group), and data for predischarge left ventricular function were not collected. However, there appeared to be a strong trend toward a greater improvement in both PaCO₂ (p = 0.057) and pH (statistical test result not reported) in the NPPV group than the CPAP group.

An increase in the rate of myocardial infarction was found in the NPPV group (10/14 patients, 71%) compared with the CPAP group (4/13 patients, 31%, p = 0.06), which prompted early discontinuation of the study. Examination of baseline differences showed that there was a trend toward more patients with chest pain in the NPPV group, 10 of 14 (71%), vs the CPAP group, 4 of 13 (31%) in the CPAP group. This raises the possibility that the trend of...
increased myocardial infarction in the NPPV group may have been due to differences in baseline characteristics rather than the treatment received.

**DISCUSSION**

From our systematic review of the literature, we conclude that the use of CPAP by face mask in patients with cardiogenic pulmonary edema and respiratory distress may decrease the need for endotracheal intubation. The three randomized controlled trials suggest a trend toward a decrease in hospital mortality in patients treated with CPAP; however, the 95% CI does not allow the exclusion of harm.1-3 The only study examining the impact of CPAP on left ventricular function found no difference between treatment groups.3 Currently, the literature describing the use of NPPV in cardiogenic pulmonary edema consists of case series and case reports. While these suggest a benefit from NPPV, to our knowledge, there are no control groups to compare outcomes. This level of evidence and the total number of patients studied are insufficient to allow conclusions regarding benefit or harm to be drawn. Finally, the only study examining the use of CPAP vs NPPV in patients with cardiogenic pulmonary edema was stopped early because of a higher rate of myocardial infarction in the NPPV group.23

In this systematic review, we minimized bias by using an extensive search strategy, including computerized literature searches, review of bibliographies and personal files, and hand searching of abstracts. Our objective was to identify the best clinical evidence available to examine each of the three strategies, and therefore we included only randomized controlled trials unless fewer than two randomized controlled trials were available. Two independent reviewers assessed the validity of the randomized controlled trials using well-established criteria. Finally, the study results were summarized quantitatively or qualitatively as appropriate.

Although the statistical test of homogeneity did not identify a clear difference in CPAP study results, this test has low power and, on inspection, some degree of clinical heterogeneity in patient population appeared to be present. As noted in the “Results” section, baseline pH values for the three trials differed and seemed to be inversely related to the risk difference in intubation rates: Lin et al2 reported a risk difference of 20%, pH in control arm 7.40 for those not intubated and 7.36 for those intubated, mean of 7.39 (data not available for CPAP arm); Rasanen et al1 found a risk difference of 30%, pH 7.36 for control, 7.33 for CPAP; and Bersten et al3 noted a risk difference of 35%, pH 7.15 for control and 7.18 for CPAP. In addition, the trial by Lin and colleagues5 also had the lowest risk difference for hospital mortality of 4%. If CPAP has a role for patients with pulmonary edema, it may be most likely to benefit patients with a greater degree of ventilatory failure.

Although CPAP may decrease the need for endotracheal intubation, the potential for harm may still exist if CPAP leads to greater myocardial demand in the setting of an acute myocardial infarction. An increase in myocardial demand could occur if the work of breathing is greater in patients treated with CPAP than those intubated and sedated. This increase in demand could cause more severe and extensive ischemia resulting in malignant dysrhythmias, cardiac arrest, and/or death. In survivors, more extensive myocardial damage may result in worse left ventricular function and long-term disability. Only one of the three trials reviewed addressed the potential for harm.3 Lin and coworkers3 found no difference in left ventricular function between groups either at baseline or 1 year later. While there is currently no evidence that CPAP causes harm in patients with cardiogenic pulmonary edema, the evidence available is insufficient to exclude this concern.

At present, there is no strong evidence to support
the use of NPPV in patients presenting with respiratory distress due to cardiogenic pulmonary edema. Two randomized controlled trials have included a heterogeneous group of patients, some of whom had pulmonary edema. In one study, only 2 of 31 patients had pulmonary edema, the majority being patients with acute exacerbations of COPD. The other study found no benefit in a heterogeneous group of patients with acute respiratory failure. While the latter study included 14 of 41 patients with pulmonary edema, we were unable to obtain data on the pulmonary edema patients alone. Although case series and case reports suggest that NPPV may be of potential benefit, randomized trials in patients with pulmonary edema are required to confirm or refute the promising observational studies of NPPV for pulmonary edema.

The only study directly comparing the use of CPAP and NPPV in cardiogenic pulmonary edema enrolled 27 patients and was too small to draw any conclusions about impact on mortality or intubation. This trial did raise concern about the potential for harm through increased risk of myocardial infarction, although differences in baseline characteristics of the two groups may have been a stronger contributing factor than the experimental treatment. As both forms of positive airway support continue to be used, further work is required to clarify the risks and benefits of CPAP and NPPV in patients with pulmonary edema.

This systematic review suggests that there is a modest amount of favorable evidence to support the use of CPAP in patients with cardiogenic pulmonary edema due to its association with a decrease in the need for intubation and a trend toward a decrease in mortality. However, between-study differences suggest that the greatest benefit may be obtained in those patients with severe ventilatory failure. The decision to use CPAP for a specific patient is dependent on patient, provider, and institutional factors in addition to the reported findings of clinical trials. The potential for harm needs to be minimized by paying close attention to each patient’s response to CPAP. Patients should become more comfortable as evidenced by a drop in heart rate, respiratory rate, and improvement in gas exchange. This does not occur early, consideration should be given to intubation and mechanical ventilation. Case series evidence supports the use of NPPV in cardiogenic pulmonary edema, although randomized controlled trials are needed. Currently, there is insufficient evidence to suggest that NPPV confers additional benefit to CPAP alone in this patient population. As clinical experience with positive pressure airway support grows for patients with cardiogenic pulmonary edema, further data on the benefits and safety of this approach will help us to understand its role in practice.

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