Efficacy and safety of non-invasive ventilation in the treatment of acute cardiogenic pulmonary edema: a systematic review and meta-analysis

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CRD summary
The authors concluded that both continuous positive airway pressure ventilation and noninvasive positive pressure ventilation (NPPV) decrease mortality and the need for endotracheal intubation for acute cardiogenic pulmonary oedema; neither increases the risk of acute myocardial infarction. The review was well-conducted and these conclusions appear reliable, except that the evidence that NPPV reduces mortality is not statistically significant.

Authors' objectives
To evaluate the efficacy and safety of continuous positive airway pressure ventilation (CPAP) and noninvasive positive pressure ventilation (NPPV) in the treatment of acute cardiogenic pulmonary oedema (ACPE).

Searching
The following databases were searched to May 2005, without language restrictions: MEDLINE, ACP Journal Club, the Cochrane CENTRAL Register, the Cochrane Database of Systematic Reviews, Digital Academic Repositories and the meta Register of Controlled Trials; the search terms were reported. The reference lists of relevant articles and the abstracts and proceedings of relevant scientific meetings were also searched from 2000 to 2005. Authors and experts in the field were consulted. A study published in Chinese was excluded.

Study selection
Studies eligible for inclusion were parallel-group randomised controlled trials (RCTs) comparing CPAP or NPPV plus standard medical therapy (SMT) with SMT alone or with each other. Studies were excluded if there was probable patient overlap, or if sufficient data on study characteristics could not be obtained. CPAP and NPPV could use any mode of delivery. SMT was defined as oxygen by face mask, nitroglycerine, nitroprusside, frusemide and morphine. There were major differences between the included studies in the delivery modes and technical characteristics of the ventilation devices. The participants in eligible studies were adults presenting to hospital with ACPE, defined as sudden onset dyspnoea, increased respiratory rate, congruent physical signs on examination, bilateral pulmonary infiltrates on chest X-ray and significant hypoxaemia. Studies that included patients with other causes of acute respiratory failure were excluded unless ACPE patients were randomised separately. Most of the studies in the review included the review-defined criteria of ACPE in their definition of ACPE. Study populations varied: some excluded patients with chronic obstructive pulmonary disease or acute myocardial infarction (AMI). Outcomes in eligible studies were the need for endotracheal intubation (ETI) (as determined in the primary study), all-cause mortality and risk of new AMI after the intervention. There was wide variation in the included studies in their definition of the need for ETI, and the duration of follow-up for ETI outcomes varied from 1 to 36 hours. Mortality invariably referred to in-hospital mortality.

Two reviewers independently selected the studies, with any disagreements settled by consensus.

Assessment of study quality
The following methodological criteria were considered when assessing the risk of bias: sample size, allocation concealment, clarity of selection criteria, blinding, standardisation of cointerventions, intention-to-treat analysis, completeness of follow-up details and clarity of outcome definition. Topic-specific quality criteria were also considered; these included the clinical criteria used for patient selection and for initiating endotracheal intubation, and the technical characteristics of the CPAP and NPPV methods used.

Two reviewers independently assessed the validity of the studies, with any disagreements settled by consensus.

Data extraction
Data were extracted as the risk difference (RD) between the two groups in each study, with 95% confidence intervals.
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**Methods of synthesis**
The data were pooled in a meta-analysis to calculate an overall RD and 95% CI. The Mantel-Haenszel fixed-effect model and DerSimonian and Laird random-effects model were used. Heterogeneity was assessed by scanning the forest plots and with the Q statistic (p≤0.1) and the $I^2$ statistic. The random-effects model was preferred and was always used if heterogeneity was present. Subgroup analyses were conducted to test the effect of NPPV in studies using higher levels of pressure support ventilation and to compare the effects of CPAP and NPPV in studies with differing proportions of hypercapnic patients at baseline. Funnel plots and Begg's rank correlation test were used to check for publication bias.

**Results of the review**
Seventeen RCTs were included (n=938).

Twelve studies had adequate allocation concealment, all had clear inclusion criteria, fifteen used strategies to standardise cointerventions and all had complete follow-up details for all participants. However, eleven failed to describe blinding strategies and only one clearly blinded physicians, nurses and patients to the intervention. Four did not report an intention-to-treat analysis and six had inadequate or unclear outcome definitions.

**CPAP versus SMT.**

Mortality (10 RCTs, n=490): there was a statistically significant reduction in risk in the CPAP group (RD -13%, 95% CI: -22, -5, p=0.003).

Need for ETI (10 RCTs, n=490): there was a statistically significant reduction in risk in the CPAP group (RD -22%, 95% CI: -34, -10, p=0.0004). There was statistically significant heterogeneity associated with this finding (p=0.0004; $I^2$=70.1%). However, the direction of effect was consistent for all but one study.

Risk of AMI (3 RCTs, n=112): there was no statistically significant difference between the groups for this outcome.

**NPPV versus SMT.**

Mortality (6 RCTs, n=315): there was no statistically significant difference between the groups for this outcome, though there was a trend for benefit in the NPPV group that was of borderline statistical significance (RD 7%, 95% CI: -14, 0, p=0.06).

Need for ETI (6 RCTs, n=315): there was a statistically significant reduction in risk in the CPAP group (RD -18%, 95% CI: -32, -4, p=0.010). There was statistically significant heterogeneity associated with this finding (p=0.02; $I^2$=62.9%). However, the direction of effect was consistent for all but one study.

Risk of AMI (5 RCTs, n=278): there was no statistically significant difference between the groups for this outcome.

**CPAP versus NPPV.**

There was no statistically significant difference between the groups for the outcomes of mortality (7RCTs, n=299), need for ETI (7 RCTs, n=299) or risk of AMI (6 RCTs, n=263).

Subgroup analyses did not show increased benefit from NPPV compared with CPAP, either when using higher levels of pressure support ventilation, or for hypercapnic patients.

For the comparison of CPAP versus NPPV, the funnel plot suggested a lack of small studies favouring CPAP. There was less indication of publication bias for other comparisons and in all cases Begg's test was non significant.

**Authors' conclusions**
Both CPAP and NPPV decrease mortality and the need for endotracheal intubation in the treatment of ACPE, and
neither increases the risk of AMI compared with SMT.

**CRD commentary**
The study objective and inclusion criteria were clear and the search was thorough, though the exclusion of a study in Chinese might have introduced bias. Suitable steps were taken to limit error and bias in the study selection, validity assessment and data extraction processes. Combining the studies in a meta-analysis appears justified, and heterogeneity was appropriately assessed and explored where it occurred. Potential publication bias was also addressed. The review was well-conducted and the authors' conclusions are likely to be reliable, except that they appear to have overstated their findings by suggesting that NPPV reduces mortality in comparison with SMT, as the effect estimate for this outcome reached only borderline statistical significance.

**Implications of the review for practice and research**

**Practice:** The authors stated that CPAP should be considered the first-line intervention for patients with ACPE, because it is as effective as NPPV but is cheaper and easier to use.

**Research:** The authors stated that it would be unethical to conduct further studies comparing noninvasive ventilation methods with SMT for the treatment of ACPE. Research is needed, however, to define when NPPV is indicated rather than CPAP; to determine optimal pressure levels when using NPPV; and to define the best time to start noninvasive ventilation. Researchers in the field should develop consensus guidelines on methods to define population, interventions and outcome measures.

**Funding**
Not stated.

**Bibliographic details**


**PubMedID**
16646987

**DOI**
10.1186/cc4905

**Original Paper URL**
http://ccforum.com/content/10/2/R69

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Acute Disease; Continuous Positive Airway Pressure /adverse effects; Humans; Pulmonary Edema /mortality /therapy

**AccessionNumber**
12006004155

**Date bibliographic record published**
03/08/2007
Date abstract record published
30/09/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.