Noninvasive ventilation administered through non-invasive positive pressure ventilation or continuous positive airway pressure reduced mortality and the need of invasive mechanical ventilation in patients with acute cardiogenic pulmonary oedema. Due to potential publication bias and some weak results, the review conclusions may not be sufficiently cautious (particularly the risk of mortality), so they may not be reliable.

Authors' objectives
The evaluate the effectiveness of non-invasive ventilation in patients with acute cardiogenic pulmonary oedema.

Searching
Seven databases (including MEDLINE, EMBASE and DARE) were searched from 1980 up to January 2011 for studies published in any language. Search terms were reported. Reference lists of relevant articles and conference abstracts were also consulted.

Study selection
Randomised controlled trials (RCTs) that compared continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) with either standard therapy or each other in adult patients with acute cardiogenic pulmonary oedema were eligible for inclusion.

The included trials were published from 1985 to 2010. Participant inclusion criteria and definitions of acute cardiogenic pulmonary oedema varied across the trials. Interventions were generally delivered in an emergency room or intensive care unit. The mean age of included patients ranged from 64 to 78 years, 32% to 83% of patients had a history of diabetes, and 18% and 67% of patients had a history of coronary heart disease. Other patient characteristics included partial pressure of oxygen in arterial blood that ranged from 43.1mmHg to 105mmHg, heart rate from 96.9 to 123.9 beats/minute, and respiratory rate from 29 to 42.4 breaths/minute.

Two reviewers independently selected the studies. Discrepancies were resolved by discussion.

Assessment of study quality
Quality assessment was applied using a modified version of the 5-point Jadad scale, which covered randomisation, blind adjudication of endpoints, and withdrawals and drop-outs.

The authors did not state how many reviewers assessed study quality.

Data extraction
In-hospital mortality (primary outcome), need of intubation and mechanical ventilation, myocardial infarction, length of intensive care unit stay, length of hospital stay and several physiologic outcomes (secondary outcomes) were extracted as risk ratios and mean differences, with 95% confidence intervals.

Two reviewers independently extracted study data. Discrepancies were resolved by discussion.

Methods of synthesis
A meta-analysis (random-effects model, DerSimonian and Laird) was used to pool risk ratios and weighted mean differences and 95% confidence intervals to perform direct comparisons between groups. Heterogeneity and inconsistency were assessed using Q test and $I^2$. Adjusted indirect comparisons were also performed. If there were no significant discrepancies between direct and indirect effect size estimates, both estimates were combined using the Mantel-Haenszel method.

Sensitivity analyses were conducted by excluding trials with less than 50 patients and studies where patients with acute
cardiogenic pulmonary oedema were a subset of a population with acute respiratory failure.

Publication bias was explored using Egger's test and funnel plot.

**Results of the review**

Thirty-four trials (3,041 patients, range 22 to 1,069) were included in the review. Quality scores were modest overall (median 2, range 1 to 4).

Compared with standard therapy, continuous positive airway pressure (CPAP) was associated with a lower risk of in-hospital death (RR 0.64, 95% CI 0.44 to 0.93; 13 trials). Non-invasive positive pressure ventilation (NIPPV) was associated with a lower risk of death compared with standard therapy, although the difference was not statistically significant (RR 0.80, 95% CI 0.58 to 1.10; nine trials). There were no significant differences between NIPPV and CPAP for mortality (16 trials). There was no evidence of significant heterogeneity among trials.

There was a significant reduction in the risk of endotracheal intubation with CPAP compared with standard therapy (RR 0.43, 95% CI 0.29 to 0.64; 13 trials). NIPPV was also associated with a significant reduction of intubation risk (RR 0.48, 95% CI 0.25 to 0.92; nine trials). There were no statistically significant differences between these ventilatory modes (17 trials).

There was no statistically significant difference in the risk of myocardial infarction with either CPAP or NIPPV compared with standard therapy or when compared with each other. There were no statistically significant differences in intensive care unit stay between CPAP and standard therapy, or between CPAP and NIPPV. There were no differences between CPAP, NIPPV, and standard therapy in duration of hospital stay.

Results for physiologic outcomes were reported. Results of indirect comparisons were similar to those of the main analyses. Results of sensitivity analyses showed a similar direction to those found in the main analyses on mortality, although the effect was no longer statistically significant in several cases.

Results of Egger's test suggested the presence of publication bias.

**Authors' conclusions**

Non-invasive ventilation administered through non-invasive positive pressure ventilation or continuous positive airway pressure reduced mortality and the need of invasive mechanical ventilation in patients with acute cardiogenic pulmonary oedema.

**CRD commentary**

The review question and eligibility criteria were clear and appeared reproducible. Several bibliographic sources were searched, including conference abstracts. Although study selection and data extraction were conducted in duplicate, it was unclear whether similar attempts to reduce the risk of error and bias were made during quality assessment.

The quality of the included trials appeared modest overall and trials were often small. Methods of analysis appeared broadly appropriate. There was generally no evidence of significant heterogeneity, where reported. The use of sensitivity analyses was appropriate as the main analyses included several small studies and subgroups. Some evidence of publication bias was found, although tests used were subject to multiple limitations. Visual inspection of forest plots suggested that smaller trials tended to have larger effect estimates for the primary outcome, which was confirmed by the sensitivity analyses that excluded smaller trials. Sensitivity analyses affected the significance of some of the pooled estimates for the primary outcome (although not their direction) which limited the strength of the main results.

Due to the limitations discussed, the review conclusions may not be sufficiently cautious, particularly on the risk of mortality, so they may not be reliable.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that therapy and research could and should define some pending uncertainties on its use. Specifically, clinical trials should be designed to answer the most appropriate setting to initiate non-invasive ventilation,
as well as to prospectively determine strategies to avoid delay in the use of these procedures.

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