Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis

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Summary

Background Non-invasive positive pressure ventilation (NIPPV), using continuous positive airway pressure (CPAP) or bilevel ventilation, has been shown to reduce the need for invasive mechanical ventilation in patients with acute cardiogenic pulmonary oedema. We assessed additional benefits of NIPPV in a meta-analysis.

Methods Meta-analysis comparison in acute cardiogenic pulmonary oedema was undertaken to compare (1) CPAP with standard therapy (oxygen by face-mask, diuretics, nitrates, and other supportive care), (2) bilevel ventilation with standard therapy, and (3) bilevel ventilation with CPAP, incorporating randomised controlled trials identified by electronic and hand search (1966–May, 2005). In 23 trials that fulfilled inclusion criteria, we assessed the effect of NIPPV on hospital mortality and mechanical ventilation, estimated as relative risks.

Findings CPAP was associated with a significantly lower mortality rate than standard therapy (relative risk 0·59, 95% CI 0·38–0·90, p=0·015). A non-significant trend towards reduced mortality was seen in the comparison between bilevel ventilation and standard therapy (0·63, 0·37–1·10, p=0·11). We recorded no substantial difference in mortality risk between bilevel ventilation and CPAP (p=0·38). The need for mechanical ventilation was reduced with CPAP (0·44, 0·29–0·66, p=0·0003) and with bilevel ventilation (0·50, 0·27–0·90, p=0·02), compared with standard therapy; but no significant difference was seen between CPAP and bilevel ventilation (p=0·86). Weak evidence of an increase in the incidence of new myocardial infarction with bilevel ventilation versus CPAP was recorded (1·49, 0·92–2·42, p=0·11). Heterogeneity of treatment effects was not evident for mortality or mechanical ventilation across patients' groups.

Interpretation In patients with acute cardiogenic pulmonary oedema, CPAP and bilevel ventilation reduces the need for subsequent mechanical ventilation. Compared with standard therapy, CPAP reduces mortality; our results also suggest a trend towards reduced mortality after bilevel NIPPV.

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Introduction

In the past two decades, non-invasive respiratory support has received a great deal of interest in the management of patients presenting with acute cardiogenic pulmonary oedema. This non-invasive respiratory support has been provided either by continuous positive airway pressure (CPAP) or by bilevel ventilation (both inspiratory and expiratory support), which are often collectively termed as non-invasive positive pressure ventilation (NIPPV). Although CPAP is not a true ventilatory mode, it is often referred to as NIPPV. The physiological effects of CPAP include augmentation of cardiac output and oxygen delivery,[1] improved functional residual capacity and respiratory mechanics, reduced effort in breathing,[2] and decreased left ventricular afterload.[3,4]

The combination of inspiratory assistance with expiratory positive airway pressure (EPAP) has been argued to reduce the work of breathing and to alleviate respiratory distress more effectively than CPAP alone. Physiological studies in acute cardiogenic pulmonary oedema have shown that bilevel ventilation to be more effective at unloading the respiratory muscles than CPAP.[5] However, enthusiasm for bilevel ventilation in acute cardiogenic pulmonary oedema was reduced after adverse effects were recorded by Mehta and colleagues.[6] These adverse effects included a higher myocardial infarction rate with bilevel ventilation than that with CPAP; this difference occurred despite more rapid reductions in arterial carbon dioxide tension ($PaCO_2$) with bilevel ventilation than with CPAP.

Thus, the best respiratory support for treatment of an episode of acute respiratory failure due to acute cardiogenic pulmonary oedema remains unclear. The British Thoracic Society guidelines[7] recommend the use of CPAP in patients who still have hypoxia despite the best medical treatment, and reserve the use of bilevel ventilation for patients in whom CPAP is unsuccessful. Subsequent to the first meta-analysis on this subject,[8] several published randomised controlled trials have shown the benefits of CPAP and bilevel ventilation in reducing the need for mechanical ventilation in patients with acute cardiogenic pulmonary oedema. This meta-analysis was undertaken to assess and compare the benefits of CPAP and bilevel ventilation beyond a reduction in mechanical ventilation needs to other clinically relevant endpoints in patients with acute cardiogenic pulmonary oedema, such as mortality and length of hospital stay.

Methods

Trial selection

Randomised trials on acute cardiogenic pulmonary oedema in human beings that compared CPAP or bilevel ventilation with standard therapy (oxygen by facemask, diuretics, nitrates, and other supportive care) or CPAP with bilevel ventilation were considered for inclusion. Only trials reporting hospital mortality or the need for invasive mechanical ventilation were included. We excluded studies reporting only physiological endpoints (improvements in gas exchange) and descriptive studies. Our search had no language restrictions. Trials were classified into three groups: CPAP versus standard therapy, bilevel ventilation versus standard therapy, and CPAP versus bilevel ventilation. For the purposes of this study, CPAP was deemed part of NIPPV.

Search strategy and quality assessment

We did an extensive electronic search for publications between 1966, and May, 2005, using Ovid MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Evidence Based Medicine reviews, Cochrane Central Register of Controlled Trials, Cochrane Database of systematic reviews, American College of Physicians (ACP) Journal Club, and Database of Abstracts of Reviews of Effectiveness (DARE). We restricted the search to studies on adult human populations, using the terms: “pulmonary edema”, “heart failure”, “respiratory insufficiency”, “positive pressure respiration”, “continuous positive airway pressure”, “noninvasive ventilation”, “noninvasive positive pressure ventilation”, “nasal ventilation”, and “BIPAP”. Abstracts of trials generated by electronic search were reviewed and trials pertaining to respiratory support in acute cardiogenic pulmonary oedema were retrieved for detailed assessment. Review articles were examined to identify additional articles. Authors were contacted to clarify details of trials if necessary. Additionally, abstracts of scientific forums were searched by hand, which included abstracts published in the *American Journal of Respiratory and Critical Care Medicine*, *American Heart Association*, *Chest*, *Critical Care Medicine*, *European Heart Journal*, *European Respiratory Journal*, *Intensive Care Medicine*, and *Thorax*.

Unmasked quality assessment on the selected published studies (not abstract reports) was done by two investigators (JLM, ADB) on composite aspects of study quality (11 aspects in total, with scores 0 or 1; minimum total score 0, maximum total score 11). This assessment used a quality score[9] modified for patients with acute cardiogenic pulmonary oedema. Differences in opinion were settled by consensus. Data abstraction was done independently by two investigators (JVP, JPH) using standardised data collection forms. Four investigators (JVP, JLM, JPH, ADB) reviewed abstracted data before analysis.

Outcome measures

Primary outcomes assessed were hospital mortality, defined as deceased when discharged from hospital, and the need for mechanical ventilation. Secondary outcomes included failure rates of treatment (standard therapy or NIPPV), length of hospital stay (defined as the time from admission to discharge), duration of NIPPV, and incidence of new myocardial infarction. We had difficulty defining treatment failure; the varying physiological or clinical endpoints at disparate timepoints, as well as the decision by some trial authors to make a distinction between failure rates and intubation rates, presented substantial potential for (mis)classification bias.[10] Thus, we presented and analysed author-defined failure rates and composite failure rates (failure rates and mechanical ventilation rates combined, if a specific failure rate was not provided) separately.

Statistical analysis

The effect of CPAP and bilevel ventilation on mortality, need for invasive mechanical ventilation, incidence of new myocardial infarction, and failure were expressed as relative risks (values <1 indicating benefit) with 95% CIs, and length of hospital stay and duration of NIPPV were expressed as mean weighted differences. For continuous variables (length of hospital stay and duration of NIPPV), pooled estimates were only available if the mean and SD were reported. We analysed data with Stata Release 9 using the METAN program.[11] DerSimonian and Laird (random-effects) estimates were reported. We did separate analyses of CPAP and bilevel ventilation effect on mortality and the need for

	Number
Studies on APO identified by electronic search	43 160
Abstracts screened for inclusion	1354
Retrieved for detailed analysis	110
Excluded studies (n=90)	
Reviews, comments, and letters	41
Observational or non-randomised studies	29
Physiological endpoints	6
Alternate populations	6
Retrospective	3
Alternate protocols	3
Part of larger study	1
Pseudorandomised trial	1*
Included studies (n=20)†	
CPAP *vs* standard care	12
Bilevel ventilation *vs* standard care	7
CPAP *vs* bilevel ventilation	10
Articles (abstracts) identified by hand search	3

APO=acute pulmonary oedema. *Parallel-group sequential trial with mode of randomisation not clearly defined. †Three published articles had three treatment arms.

Table 1: Profile of included and excluded studies

	Year of study completion	Country	Location	Quality score	Mortality*	Invasive mechanical ventilation†
Standard therapy *vs* CPAP						
Rasanen et al[30]	1985‡	Finland	n/a	5	6 (14)/3 (17)	12 (8)/6 (14)
Bersten et al[21]	1990	Australia	ED/ICU	9	4 (16)/2 (17)	7 (13)/0 (19)
Lin et al[27]	1992	Taiwan	ED	5	6 (44)/4 (46)	18 (32)/8 (42)
Takeda et al[31]	1997‡	Japan	ICU	4	3 (12)/1 (14)	6 (9)/1 (14)
Takeda et al[32]	1998‡	Japan	CCU	5	7 (4)/1 (10)	8 (3)/2 (9)
Delclaux et al[23]	1999	France	n/a	7	7 (13)/7 (15)	6 (14)/6 (16)
Park et al[28]	1997	Brazil	n/a	4	0 (10)/1 (8)	4 (6)/3 (6)
Kelly et al[25]	2002‡	UK	ED	7	7 (24)/2 (25)	0 (31)/0 (27)
Hao et al[24]	1995	China	n/a	5	n/a	9 (17)/1 (24)
Crane et al[22]	2001	UK	ED	7	6 (14)/0 (20)	0 (20)/1 (19)
L'Her et al[26]	2001*	France	ED	7	14 (32)/12 (31)	4 (42)/2 (41)
Park et al[29]	2000	Brazil	ED	6	6 (20)/1 (26)	11 (15)/2 (25)
Standard therapy *vs* bilevel ventilation						
Masip et al[35]	1998	Spain	ED/ICU	6	2 (16)/0 (19)	6 (12)/1 (18)
Levitt et al[34]	1997	USA	ED	4	3 (14)/3 (18)	7 (10)/5 (16)
Park et al[28]	1997	Brazil	n/a	4	0 (10)/0 (7)	4 (6)/0 (7)
Nava et al[36]	2003‡	Italy	ED	9	9 (56)/6 (59)	16 (49)/13 (52)
Ferrer et al[33]	2003‡	Spain	ICU	6	2 (13)/1 (14)	2 (13)/1 (14)
Crane et al[22]	2001	UK	ED	7	6 (14)/5 (15)	0 (20)/1 (19)
Park et al[29]	2000	Brazil	ED	6	6 (20)/2 (25)	11 (15)/2 (25)
CPAP *vs* bilevel ventilation						
Mehta et al[6]	1994	Canada	ED	7	2 (11)/1 (13)	1 (12)/1 (13)
Park et al[28]	1997	Brazil	n/a	4	1 (8)/0 (7)	3 (6)/0 (7)
Bollaert et al[39]	2002‡	France	n/a	Not done	4 (15)/4 (13)	4 (15)/5 (12)
Martin-Bermudez et al[42]	2002‡	Spain	n/a	Not done	5 (34)/2 (39)	n/a
Liesching et al[41]	2003‡	Canada	n/a	Not done	n/a	1 (13)/0 (13)
Cross et al[40]	2003‡	Australia	ED	6	5 (31)/3 (32)	4 (32)/1 (34)
Crane et al[22]	2001	UK	ED	7	0 (20)/5 (15)	1 (19)/1 (19)
Bellone et al[38]	2003	Italy	ED	5	2 (20)/0 (24)	1 (21)/2 (22)
Park et al[29]	2000	Brazil	ED	6	1 (26)/2 (25)	2 (25)/2 (25)
Bellone et al[37]	2002	Italy	ED	7	1 (17)/0 (18)	1 (17)/2 (16)

n/a=not available. ED=emergency department. ICU=intensive care unit. CCU=coronary care unit. *Data are number of patients who died (survived). †Data are number of patients receiving ventilation (not receiving ventilation). ‡Year of publication, if year of completion was not available.

Table 2: Study characteristics, quality scores, and primary outcome data

mechanical ventilation using the quality scores as weights (fixed-effects estimator).

Heterogeneity of treatment effects was assessed as the extent, diagnosed by use of the *Q* statistic, and regarded as significant if p≤0·1;[12] and the effect on the variation of pooled treatment effect, calculated by use of the I^2 measure (I^2<30% indicates mild heterogeneity, 30–50% moderate, and <50% severe heterogeneity).[13] Meta-analysis regression[13] was undertaken to (1) assess the (potential) effect of predefined confounders (age, sex, quality score; and $PaCO_2$, pH, and arterial oxygen tension [PaO_2] at admission) on mortality and the need for mechanical ventilation; and (2) investigate predictors of the reported increased incidence of new myocardial infarction with bilevel ventilation,[6] pertaining to the recorded positive end-expiratory pressure (PEEP) values, as suggested by Bersten.[14] We assessed publication bias using the rank correlation test of Begg, the regression-based test of Egger,[15] and the non-parametric trim and fill method of Duval and Tweedie[16] if more than ten studies were included in the meta-analysis.[17] Cumulative meta-analysis was done[18] to study possible time trends in treatment effects.

We used a fully Bayesian meta-analysis regression to determine the effect of underlying population[19] risk (as log [risk] of the standard therapy group) on the treatment effect (as relative risks) of mortality, mechanical ventilation, and treatment failure.[20] Results were reported as the median (regression) slope associated with underlying risk and 95% CIs.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in

the study and had final responsibility for the decision to submit for publication.

Results

Of the 43 160 articles on respiratory failure or insufficiency that were screened, one investigator (JVP) reviewed abstracts of the 1354 articles pertaining to respiratory support in acute cardiogenic pulmonary oedema, and three investigators (JVP, JLM, ADB) reviewed 110 articles for further assessment (table 1). 23 articles fulfilled criteria for inclusion, including three abstracts. 12 studies compared CPAP with standard therapy,[21–32] seven compared bilevel ventilation with standard therapy,[22,28,29,33–36] and ten compared CPAP with bilevel ventilation.[6,22,28,29,37–42] Three of these studies assessed all three treatments: CPAP, bilevel ventilation, and standard therapy.[22,28,29] Table 2 summarises study characteristics, quality scores, and primary outcome data; webtable 1 lists the baseline characteristics of the three comparative groups.

See **Online** for webtables 1 and 2

With respect to mortality, only hospital mortality was considered and analysed; if unavailable from trial reports, we requested data from authors. CPAP was associated with a significant reduction in mortality (table 3) compared with standard therapy (figure 1). Bayesian analysis showed no substantial effect of underlying risk of the standard therapy group on the relative risk of mortality (slope 1·13, 95% CI –5·64 to 6·41). A non-significant trend favouring a reduction in mortality with bilevel ventilation over standard therapy was recorded. By contrast, no significant mortality effect was shown between bilevel ventilation and CPAP (figure 1, table 3). We did not record any heterogeneity of treatment effects (p>0·34, I^2=0–11%). Underlying risk did not substantially affect the relative risk of mortality comparing bilevel ventilation with standard therapy (slope 1·31, 95% CI –6·60 to 9·67).

Both CPAP and bilevel ventilation were associated with significant reductions in the need for invasive mechanical ventilation (figure 2) when compared with standard therapy. No difference in ventilatory requirements was seen between bilevel ventilation and CPAP (table 3). We recorded mild heterogeneity of treatment effects (p>0·27, I^2=0–21%). Underlying risk was not associated with the need for mechanical ventilation in either CPAP (slope 0·19, 95% CI –0·79 to 2·01) or bilevel ventilation (–0·04, –9·14 to 8·61) versus standard therapy.

Author-defined failure rates were reported additionally in a total of ten studies in the three comparison groups (table 3), in which a distinction was made between intubation rates and failure rates (webtable 2). Composite failure rates were significantly reduced with CPAP and bilevel ventilation compared with standard therapy (table 3). We saw little evidence for a favourable trend between bilevel ventilation and CPAP. Underlying risk was not associated with composite failure rates in either CPAP (slope 1·62, 95% CI –1·96 to 8·82) or bilevel ventilation (–0·31, –10·12 to 8·98), compared with standard therapy. For author-defined failure rates

	Number of contributing studies	Total number of patients	Relative risk (95% CI)	p	I^2 (%)	Number needed to treat*	Number of events avoided per 1000 patients treated (95% CI)
Mortality							
CPAP *vs* standard therapy	11	263/269	0·59 (0·38–0·90)	0·015	11	10	101 (24–151)
Bilevel ventilation *vs* standard therapy	7	174/171	0·63 (0·37–1·10)	0·11	0	n/a	n/a
Bilevel ventilation *vs* CPAP	9	203/203	0·75 (0·40–1·43)	0·38	0	n/a	n/a
Need for mechanical ventilation							
CPAP *vs* standard therapy	12	288/295	0·44 (0·29–0·66)	0·0003	12	6	161 (98–204)
Bilevel ventilation *vs* standard therapy	7	174/171	0·50 (0·27–0·90)	0·02	21	7	136 (26–196)
Bilevel ventilation *vs* CPAP	9	175/178	0·94 (0·48–1·86)	0·86	0	n/a	n/a
Composite failure rates							
CPAP *vs* standard therapy	12	288/295	0·42 (0·27–0·65)	0·0005	37	5	220 (131–276)
Bilevel ventilation *vs* standard therapy	7	174/171	0·51 (0·30–0·87)	0·01	12	7	135 (36–193)
Bilevel ventilation *vs* CPAP	9	175/178	0·75 (0·44–1·30)	0·31	74	n/a	n/a
Author-defined failure rates							
CPAP *vs* standard therapy	6	187/179	0·45 (0·25–0·82)	0·009	40	5	198 (65–271)
Bilevel ventilation *vs* standard therapy	1	20/20	1·00 (0·07–14·9)	1·0	n/a	n/a	n/a
Bilevel ventilation *vs* CPAP	3	72/75	0·58 (0·21–1·56)	0·28	47	n/a	n/a
Incidence of new myocardial infarction							
CPAP *vs* standard therapy	3	74/77	0·83 (0·43–1·61)	0·58	0	n/a	n/a
Bilevel ventilation *vs* standard therapy	4	133/128	1·19 (0·68–2·10)	0·50	0	n/a	n/a
Bilevel ventilation *vs* CPAP	8	174/172	1·49 (0·92–2·42)	0·11	0	n/a	n/a

n/a=not calculated for non-significant results. *Number needed to treat for benefit.

Table 3: **Effect of NIPPV on study outcomes**

(table 3), significant benefits were seen only with CPAP versus standard therapy, albeit with moderate heterogeneity ($I^2=40\%$). We recorded no evidence of an effect of underlying risk on author-defined failure rates in the comparison of CPAP with standard therapy (slope 1·39, 95% CI –2·13 to 11·33).

The point estimate and interval for the occurrence of new cases of myocardial infarction tended towards being adverse for bilevel ventilation versus CPAP, but this result was not significant (table 3). Compared with standard therapy, neither CPAP nor bilevel ventilation had any effect on new myocardial infarction rates (table 3). Length of hospital stay was not reduced by either CPAP or bilevel ventilation, compared with standard therapy (p=0·39 and p=0·76, respectively) or between the two assisted ventilatory modes (p=0·44; data not shown). There was no evidence indicating that the duration of non-invasive ventilation differed between bilevel ventilation and CPAP (mean weighted difference –7·5 min, 95% CI –27 to 12, p=0·46, $I^2=41\%$).

The bilevel ventilation versus CPAP group contained three studies reported only in abstract form.[39,41,42] A sensitivity analysis was undertaken, with the defined outcomes with these studies removed; no substantial effect was shown by this removal on mortality (relative risk 0·76, 95% CI 0·32–1·78; p=0·52), need for subsequent mechanical ventilation (0·80, 0·33–1·94, p=0·62), or duration of NIPPV (mean weighted difference 2·9 min, 95% CI –13·7 to 19·6, p=0·73). However, the estimates of new myocardial infarction incidence were increased in the bilevel ventilation versus CPAP group (relative risk 1·99, 95% CI 1·06–3·74; p=0·03), although the analytical weight given to the study by Mehta and colleagues[6] was substantial (51%). We recorded no evidence of publication bias with the Egger's or Begg's tests (p≥0·07), nor with the trim and fill method in the CPAP versus standard therapy group.

Meta-analysis regression showed that for both CPAP and bilevel ventilation, compared with standard therapy, none of the predefined clinical variables (age, sex; and $PaCO_2$, pH, and PaO_2 at admission) predicted either of the primary outcomes (p≥0·08 for mortality; p≥0·2 for mechanical ventilation) on univariate analysis. Missing data precluded multivariable analysis. Unlike non-invasive ventilation in exacerbations of chronic obstructive pulmonary disease,[10] no pH or $PaCO_2$ efficacy thresholds could be identified. The association between ventilatory modes and new cases of myocardial infarction was restricted because of the number of available studies: four for bilevel ventilation versus standard therapy and eight for bilevel ventilation versus CPAP. We recorded no substantive relations between the risk of new myocardial infarction and EPAP, for the bilevel ventilation versus standard therapy group; or the CPAP-EPAP difference, for the CPAP versus bilevel ventilation group.

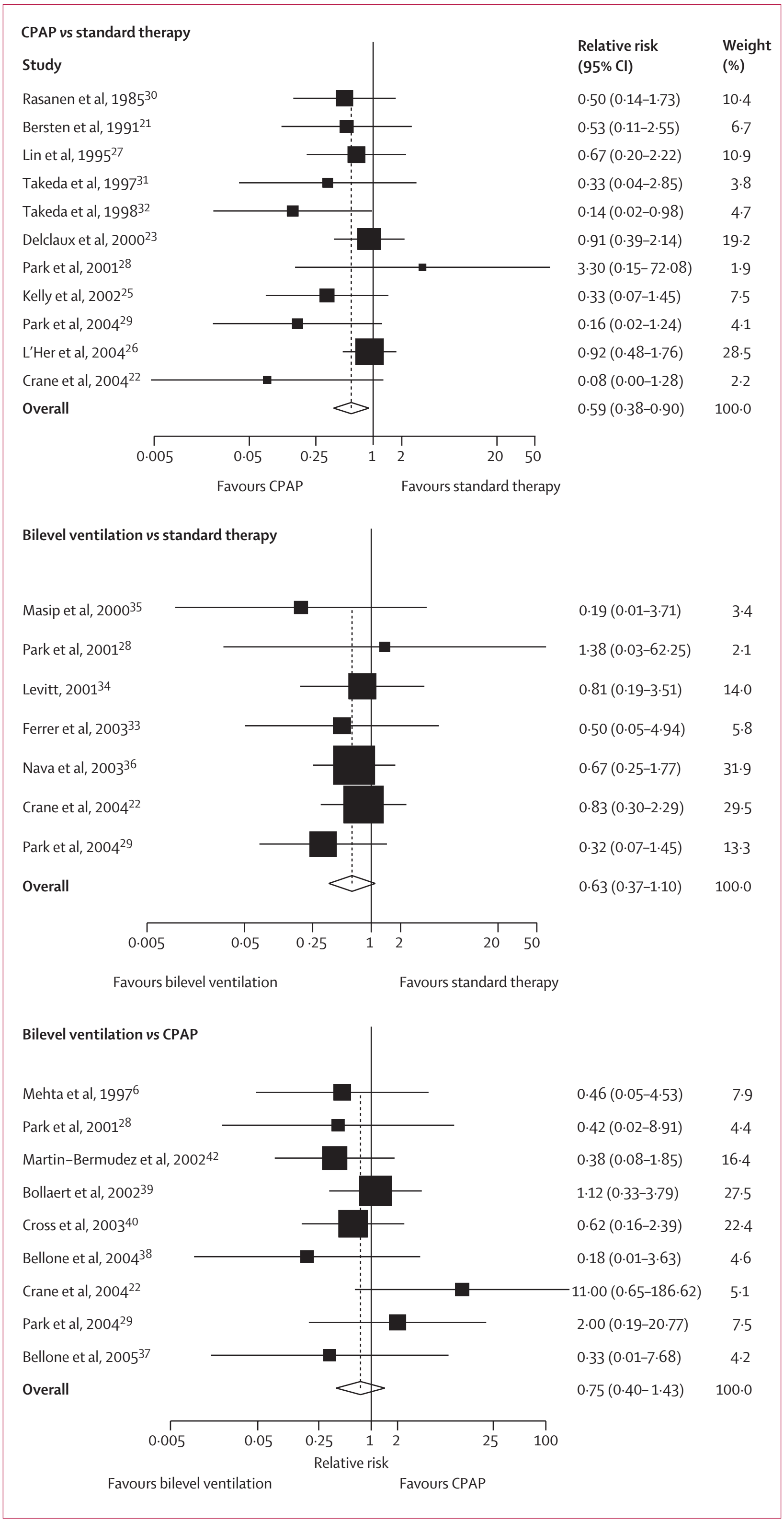

Figure 1: **Effect of NIPPV on mortality**
Vertical solid line=null effect. Vertical dotted line=overall mortality effect of treatment. Boxes and horizontal lines=relative risk (95% CI).

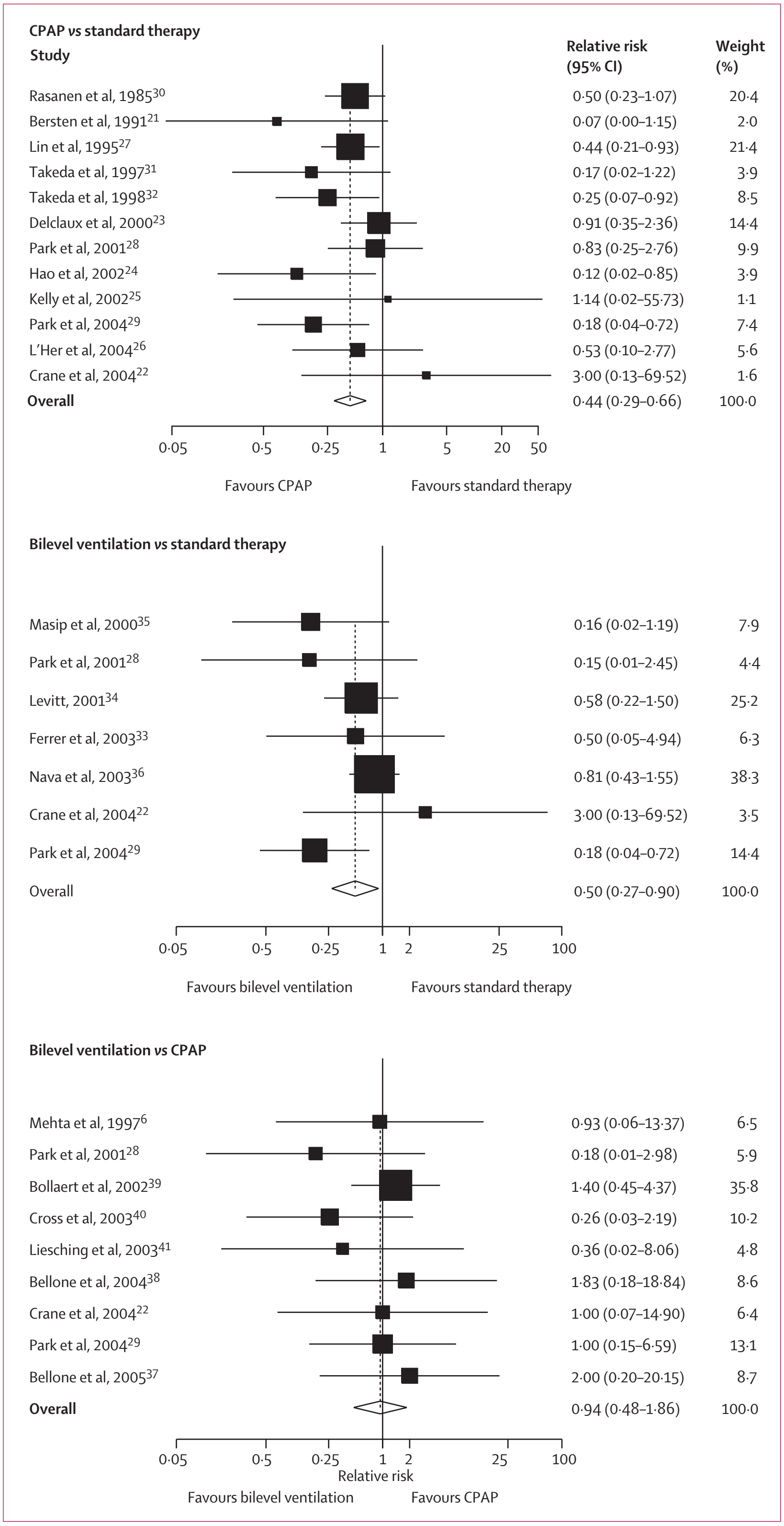

Figure 2: **Effect of NIPPV on the need for invasive mechanical ventilation**
Vertical solid line=null effect. Vertical dotted line=overall mortality effect of treatment. Boxes and horizontal lines=relative risk (95% CI).

The effect of trial quality scores on mortality or mechanical ventilation, assessed as either weights for fixed-effect pooled estimates or as a univariate covariate in metaregression, was very small, since the number of studies was reduced by the exclusion of abstracts; only in the CPAP versus standard therapy group did the mortality estimate show substantial change (relative risk 0·64, 95% CI 0·45–0·94, p=0·02).

Discussion

This systematic review has shown the benefit of NIPPV in the management of patients presenting with acute cardiogenic pulmonary oedema. A significant reduction in the need for invasive mechanical ventilation was seen with both CPAP and bilevel ventilation compared with standard therapy. The mortality benefit of NIPPV reached significance for CPAP (*vs* standard therapy) and tended towards significance for bilevel ventilation versus standard therapy. Mortality did not differ significantly between CPAP and bilevel ventilation.

Many factors could account for the non-significance of mortality recorded with bilevel ventilation (compared with standard therapy), including: a true lack of benefit; the beneficial effect might have been offset by an increase in the incidence of new myocardial infarction; an increased severity of illness in the bilevel ventilation group; or insufficient study power to detect a true reduction in mortality.

The favourable mortality effects of NIPPV should be interpreted in the context of substantial differences in the average standard therapy mortalities between CPAP versus standard therapy (24·5%) and bilevel ventilation versus standard therapy (16·4%) in the current meta-analysis (table 2). Hospital mortality for acute cardiogenic pulmonary oedema has varied over time, from 16–17% in the 1980s[43,44] to 3–4% in the mid-1990s,[45,46] despite acute myocardial infarction rates of 17–27% in these later two trials. With cumulative meta-analysis, both the groups that compared CPAP or bilevel ventilation with standard therapy showed little change of point estimate of treatment effect in relation to the line of null effect (where relative risk is 1; webfigure). Similarly, for both CPAP and bilevel ventilation versus standard therapy, “(calendar) year” as a covariate (similar to the predefined covariates in the meta-regression above) did not predict mortality and there was no change of standard therapy mortality over the timespan of the trials considered (non-parametric trend; p≥0·34 for all estimates). With the heuristic use of conventional power calculations, as suggested by Flather and colleagues,[47] the CPAP versus standard therapy meta-analysis was moderately powered (82%) to detect the differences, whereas the bilevel ventilation versus standard therapy meta-analysis was not (38%). However, the number of outcome events (deaths) in both meta-analyses (100 and 45, respectively) was less than the number of 200 suggested by Flather and colleagues to generate “more reliable and...clinically useful" meta-analyses.[47] For the CPAP versus bilevel ventilation comparison, the low event number (n=38) and power (7·4%) were problematic.

The significant benefit of both CPAP and bilevel ventilation reducing the need of invasive mechanical ventilation in acute cardiogenic pulmonary oedema, as seen in previous controlled trials, was reiterated in this meta-analysis. Although the beneficial effects with respect to numbers needed to treat to avoid invasive mechanical ventilation are impressive (six for CPAP and seven for bilevel ventilation), only a proportion of patients presenting with features of acute cardiogenic pulmonary oedema were actually enrolled in the trials: 20% (36/179) by Mehta and colleagues,[6] 11% (60/524) by Crane and colleagues,[22] and 31% (46/149) by Bellone and colleagues.[37]

The finding that underlying risk of the standard therapy groups had no substantial effect on either mortality or mechanical ventilation is not surprising, in view of the apparent homogeneity recorded between the studies.[48]

With secondary outcomes, no beneficial effects were seen with the length of hospital stay or the duration of NIPPV between ventilatory modes. The lack of benefit in the length of hospital stay despite reduction in mechanical ventilation and mortality with NIPPV might be an indication of early deaths in the control group, although confirmation of this explanation would need access to individual patients' or time-to-event data.

Composite failure rates seemed to be greatly reduced with NIPPV compared with standard therapy. However, interpretation of these failure rates is difficult for several reasons. The criteria for failure were variable in terms of both time to failure, which ranged from just 10 min[30] to more than 12 h, and definition.[26] A head-to-head comparison of bilevel ventilation with CPAP suggested preference for bilevel ventilation, although this finding could be offset by an increased potential for new cases of myocardial infarction. Author-defined failure rates were significant only for CPAP compared with standard therapy.

The reasons for the potential excess of myocardial infarction with bilevel ventilation were not immediately apparent; patients' numbers were small and there were many confounding factors. However, if PEEP is deemed an analogue of diastole, the increased PEEP in CPAP could have been more crucial in acute cardiogenic pulmonary oedema than the ventilation-augmenting benefits of bilevel ventilation.[14] A review of the studies comparing CPAP with bilevel ventilation suggests that the initial PEEP (10 cm H_2O in six of eight studies) used with CPAP was much higher than the EPAP (≤5 cm H_2O in seven of eight studies) used with bilevel devices (webtable 3). Furthermore, bilevel devices usually need a more complex apparatus and might impose a greater effort of breathing than conventional valve ventilators,[49] with well-designed, continuous-gas-flow CPAP devices as the most efficient.[50,51] Any increase in the risk of myocardial infarction with bilevel ventilation could be a function of more rapid correction of $PaCO_2$ values[6] with potential coronary vasoconstriction and asynchrony between patient and bilevel ventilator, which could induce adverse physiological changes.

See **Online** for webfigure and webtable 3

For three studies,[22,28,29] the meta-analyses resulted in pairwise comparisons between the three treatment arms. It might be argued that a correction should be made to the overall significance level and CI to account for these comparisons.[52] Use of a Bonferroni correction would result in widened CIs and a rejection of the null hypothesis at smaller p values. In the present study, which used a nominal 5% level with Bonferroni correction, a test of the relative risk being different from 1 would be regarded as significant only if $p<0·0167$ (ie, 0·05 divided by 3). Based on this method, the CPAP versus standard therapy comparison in mortality would be only marginally significant and no substantial association would exist between quality scores and mortality. The conclusions for all other results would remain the same.

In conclusion, this study has shown benefits of CPAP (compared with standard therapy) on mortality and failure rates, as well as benefits of bilevel ventilation over standard therapy on ventilation needs and composite failure rates, which has not been seen in a previous meta-analysis.[8] The mortality benefit of NIPPV over standard therapy in acute cardiogenic pulmonary oedema was evident for CPAP and only weakly so for bilevel ventilation. We found a substantial reduction in invasive mechanical ventilation for both CPAP and bilevel ventilation. The inclusion of only a proportion of patients presenting with acute cardiogenic pulmonary oedema in these studies restricts the generalisability of these results to all patients with the disorder. The tendency towards an increased risk of new myocardial infarction with bilevel ventilation (compared with CPAP) could offset potential benefits of reduced failure rates. Future studies focusing on the role of PEEP on outcomes and the role of bilevel ventilation in the hypercapnic cohort of patients with acute cardiogenic pulmonary oedema would add insights into the pathophysiology and management of the disorder. Until then, the British Thoracic Society guidelines[7] on the use of CPAP and bilevel ventilation seem apposite.

Contributors

J V Peter, J L Moran and A D Bersten conceived and designed the study. J V Peter, J L Moran, and J Phillips-Hughes did the electronic search, data collection, abstraction, hand-search of journals, and data entry. J L Moran and A D Bersten were responsible for the quality assessment of trials and quality scores. J L Moran and P Graham were statistical advisers. J V Peter, J L Moran, P Graham and A D Bersten were responsible for the overall direction of the text and discussion.

Conflict of interest statement

We declare that we have no conflict of interest.

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