

Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

Systematic Review and Meta-analysis

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NONINVASIVE VENTILATION (NIV) is a modality of ventilatory support without endotracheal intubation and sedation that has demonstrated to be useful in several forms of respiratory failure. In patients with severe exacerbation of chronic obstructive pulmonary disease, it has been shown to reduce mortality.^{1,2} In the setting of acute pulmonary edema, NIV has been shown to reduce the intubation rate in several randomized trials, either using continuous positive airway pressure (CPAP)³⁻⁸ or bilevel noninvasive pressure support ventilation (NIPSV).^{8,9} The technique of CPAP is simpler and may be performed with an oxygen source connected to a tight-fitting face mask or helmet, with an expiratory valve to maintain constant positive intrathoracic pressure. Conversely, NIPSV is more complex, requires a ventilator to provide 2 levels of pressure: one to assist patients with inspiratory positive airway pressure (IPAP) and the other, like CPAP, to maintain expiratory positive pressure (EPAP).

With widespread adoption of NIV in patients with acute and chronic respiratory failure over the last 2 decades, acute pulmonary edema is currently the second most common indication for NIV in clinical prac-

Context In patients with acute cardiogenic pulmonary edema noninvasive ventilation may reduce intubation rate, but the impact on mortality and the superiority of one technique over another have not been clearly established.

Objective To systematically review and quantitatively synthesize the short-term effect of noninvasive ventilation on major clinical outcomes.

Data Sources MEDLINE and EMBASE (from inception to October 2005) and Cochrane databases (library issue 4, 2005) were searched to identify relevant randomized controlled trials and systematic reviews published from January 1, 1988, to October 31, 2005.

Study Selection and Data Extraction Included trials were all parallel studies comparing noninvasive ventilation to conventional oxygen therapy in patients with acute pulmonary edema. Comparisons of different techniques, either continuous positive airway pressure (CPAP) or bilevel noninvasive pressure support ventilation (NIPSV), were also included.

Data Synthesis Fifteen trials were selected. Overall, noninvasive ventilation significantly reduced the mortality rate by nearly 45% compared with conventional therapy (risk ratio [RR], 0.55; 95% confidence interval [CI], 0.40-0.78; $P=.72$ for heterogeneity). The results were significant for CPAP (RR, 0.53; 95% CI, 0.35-0.81; $P=.44$ for heterogeneity) but not for NIPSV (RR, 0.60; 95% CI, 0.34-1.05; $P=.76$ for heterogeneity), although there were fewer studies in the latter. Both modalities showed a significant decrease in the "need to intubate" rate compared with conventional therapy: CPAP (RR, 0.40; 95% CI, 0.27-0.58; $P=.21$ for heterogeneity), NIPSV (RR, 0.48; 95% CI, 0.30-0.76; $P=.24$ for heterogeneity), and together (RR, 0.43; 95% CI, 0.32-0.57; $P=.20$ for heterogeneity). There were no differences in intubation or mortality rates in the analysis of studies comparing the 2 techniques.

Conclusions Noninvasive ventilation reduces the need for intubation and mortality in patients with acute cardiogenic pulmonary edema. Although the level of evidence is higher for CPAP, there are no significant differences in clinical outcomes when comparing CPAP vs NIPSV.

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tice,^{10,11} but its use is often based more on perceived efficacy than on scientific evidence.¹¹ This may be explained because no single trial has shown an impact in hospital mortal-

ity, and considerable controversy remains over which technique is superior to the other.^{12,13}

We undertook a systematic review to investigate the effect of NIV on the

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main outcomes (intubation and mortality) comparing the 2 techniques to each other and to conventional oxygen therapy.

METHODS

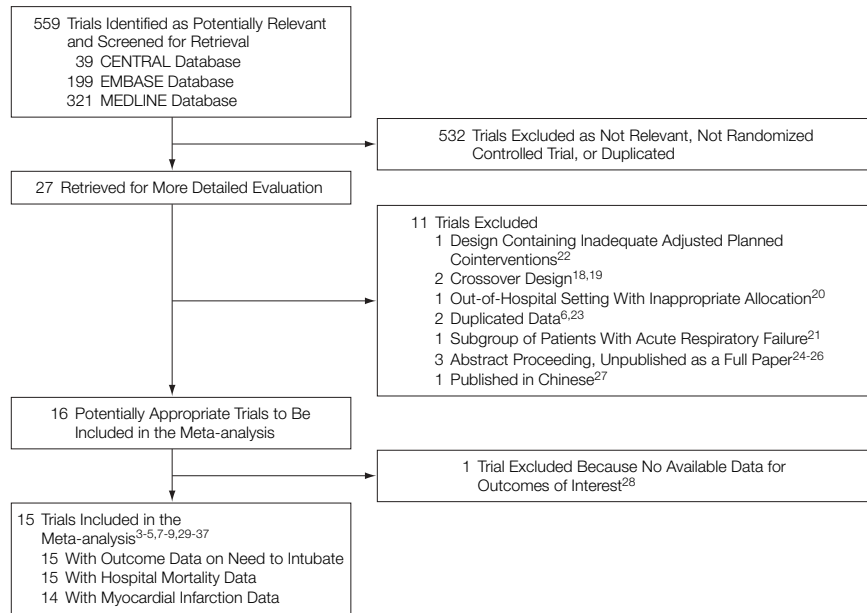
Search Strategy

We aimed to identify all randomized controlled trials assessing the efficacy of NIV in patients with acute pulmonary edema. The electronic search strategy applied standard filters for identification of randomized clinical trials. Databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 4, 2005), MEDLINE (from inception to October 2005), and EMBASE (from inception to October 2005). We did not apply language restrictions. In addition to the electronic search, we checked out cross-references from original articles and reviews and sometimes contacted authors to obtain additional unpublished data. Our search included the following: *continuous positive airway pressure* (Medical Subject Headings [MeSH]); *continuous positive airway**; *biphasic intermittent positive airway*; *bilevel positive airway**; *noninvasive ventilatory-assistance apparatus*; *noninvasive support ventilation*; *noninvasive ventilat**; *non-invasive ventilat**; *CPAP*; *Bipap*; *pulmonary edema* (MeSH); *acute pulmonary edema*; *heart failure, congestive* (MeSH); *edema, cardiac* (MeSH); *acute cardiogenic edema* linked with *randomized controlled trial* OR *controlled clinical trial* OR *randomized controlled trials* OR *random allocation* OR *double-blind method* OR *single-blind method* OR *clinical trial* OR *clinical trials* in various combinations.

Selection of Studies

We restricted the analysis to parallel randomized trials comparing NIV to conventional oxygen therapy or to another NIV modality. Study designs containing inadequately adjusted planned cointerventions and crossover trials were not included. Studies that analyzed the application of NIV in patients with acute pulmonary edema as a part of a group of patients with acute

Figure 1. Flow Diagram of Trial Selection



respiratory failure were excluded, as were studies published only in abstract form and those written in a non-accessible language after failure to obtain more complete data.

Data Collection

The initial selection was performed by distributing references among pairs of independent reviewers. A full-text copy of all studies of possible relevance was obtained and data from each study was extracted independently by paired reviewers, using a prestandardized data abstraction form. Data extracted were checked by a third reviewer (J.M. or M.R.) for accuracy. The reviewers decided which trials fitted the inclusion criteria focusing on study design, patients' characteristics, protocol of the interventions, outcomes measured, and main results. Any disagreement appearing during the process was solved by discussion and team consensus.

Methodological quality of the included trials was assessed collecting data on key domains related to validity^{14,15}: reporting of allocation concealment, description of an adequate randomization method, and specification of loss of subjects.

The primary outcomes for the included trials were treatment failure, endotracheal intubation, myocardial infarction, resolution time, therapeutical success at 2 hours, 48-hour mortality, in-hospital mortality, and specific laboratory or physiological parameters. The primary outcomes for the present study were treatment failure and in-hospital mortality because all the included trials presented data about these items. However, treatment failure was often reported using different definitions. It was endotracheal intubation in some studies, "criteria for intubation" (which was not necessarily performed) in others, and some arbitrary clinical or blood gas criteria at different intervals of time in others. For this item, we finally decided to select the variable "need to intubate," which included those patients who were intubated and those who needed to be intubated but were not, either due to successful rescue NIV, patient's refusal, or a medical decision on account of serious comorbidities.

Myocardial infarction was considered a secondary outcome in the present study. This complication was computed whether it was identified as the cause of acute pulmonary edema or was

diagnosed soon after admission. Previous episodes of myocardial infarction were not counted. Other terms like intensive care unit (ICU) length of stay, hospital length of stay, one-year mortality, physiological measurements at baseline and at 1 hour, and adverse effects were also collected but were not analyzed because there was a lack of this information in many of the studies.

Although there were heterogeneities in the definition of acute pulmonary edema, it was generally described as dyspnea of acute onset, with physical and radiological signs of pulmonary edema. In addition, in almost all the studies hy-

poxemia was required for diagnosis, whether assessed by pulse-oximetry or arterial blood gas samples.

Analysis

We summarized available data for all trials reporting results on need to intubate or mortality, computing pooled risk ratios (RRs) and their respective 95% confidence intervals (CIs) by means of a fixed-effects meta-analysis model. We examined heterogeneity using a χ^2 test. All statistical analyses were performed with Review Manager (Revman version 4.2 for Windows, Oxford, England), the Cochrane Collaboration's software for

preparing and maintaining Cochrane systematic reviews. Although the main analysis was made considering available data as finally published by authors, an intention-to-treat sensitivity analysis was also performed in order to obtain more exact results, assuming that lost or withdrawn patients experienced outcomes (either need to intubate or death). Three-arm trials were analyzed as 2-arm separate trials in each comparison, duplicating the control group data. A sensitivity analysis was performed correcting for this artificial sample size increase, showing no relevant differences with respect to the main analysis.

Table. Randomized Studies Analyzing Noninvasive Ventilation

Source	Location	Sample Size*	Mask	CPAP, cm H ₂ O	IPAP/EPAP, cm H ₂ O	Primary Outcomes	Other Considerations
Continuous Positive Airway Pressure vs Oxygen Therapy							
Räsänen et al, ³ 1985	1 ICU in Finland	40	Full face	10		Clinical outcomes	
Bersten et al, ⁴ 1991	1 ICU in Australia	40 (39)	Full face	10		Intubation	
Lin et al, ⁵ 1995	1 ICU in Taiwan	100	Full face	2.5-12.5		Intubation In-hospital mortality	Swan-Ganz catheterization
Takeda et al, ²⁹ 1997	1 ICU in Japan	30 (29)	Full face or nasal	4-10		Laboratory parameters	Measurement of plasma endothelin 1
Kelly et al, ³¹ 2002	1 ED and ICU in the United Kingdom	58	Full face	7.5		Clinical outcomes Laboratory parameters	Measurement of plasma neurohormonal concentrations
L'Her et al, ⁷ 2004	4 EDs in France	89	Full face	7.5		48-h mortality	Elderly patients (>75 y)
Noninvasive Pressure Support Ventilation vs Conventional Oxygen Therapy							
Masip et al, ⁹ 2000	1 ICU in Spain	40 (37)	Full face		20/5, Mean	Intubation Resolution time	IPAP was adjusted to tidal volume
Levitt, ³³ 2001	1 ED in the United States	38	Full face or nasal		8/3 Initial	Intubation	Prematurely interrupted when the study by Mehta et al ³⁵ was published
Nava et al, ³⁴ 2003	5 EDs in Italy	130	Full face		14.5/6.1, Mean	Intubation	Post hoc analysis in hypercapnic patients
Trials With 3 Study Groups							
Park et al, ³⁰ 2001	1 ED in Brazil	26	Full face and nasal	5-12.5	8/3 Initial	Intubation	Full-face mask for CPAP and nasal for NIPSV
Crane et al, ³² 2004	2 EDs in the United Kingdom	60	Full face	10	15/5 Fixed	Success in ED (2 h) In-hospital mortality	Prehospital nitrates therapy evaluated
Park et al, ⁸ 2004	1 ED in Brazil	83 (80)	Full face	10 Initial up to 16	15/10 Initial	Intubation	
Continuous Positive Airway Pressure vs Noninvasive Pressure Support Ventilation							
Mehta et al, ³⁵ 1997	1 ED in the United States	27	Nasal and full face	10	15/5 Fixed	Intubation Physiological improvement	Prematurely stopped for higher rate of AMI in NIPSV group
Bellone et al, ³⁶ 2004	1 ED in Italy	36	Full face	10	15/5 Initial	AMI	Study restricted to patients with hypercapnia
Bellone et al, ³⁷ 2005	1 ED in Italy	46	Full face	10	15/5 Initial	Resolution time	Primary end point was AMI rate Only nonischemic APE

Abbreviations: AMI, acute myocardial infarction; APE, acute pulmonary edema; CPAP, continuous positive airway pressure; ED, emergency department; EPAP, positive expiratory airway pressure (equivalent to CPAP); ICU, intensive care unit; IPAP, inspiratory positive airway pressure; NIPSV, bilevel noninvasive pressure support ventilation.

*Numbers in parentheses denote the number of patients finally included after withdrawals.

Publication bias was assessed applying the Egger et al¹⁶ and Begg et al¹⁷ statistical tests to the 2 main outcomes of the included trials: intubation and in-hospital mortality. Publication bias was studied separately for trials comparing NIV with control and for trials comparing modalities of NIV.

RESULTS

Study Selection

Our initial electronic search identified 559 studies. Of these, 532 were excluded because they were not randomized trials, did not evaluate NIV in patients with acute pulmonary edema, were duplicated references, or were not relevant. Twenty-seven studies were retrieved for more detailed analysis, 11 of which were excluded. Two were excluded because of crossover design^{18,19}; 1 for out-of-hospital setting with inappropriate allocation²⁰; 1 for recruitment of patients with acute pulmonary edema as a part of a series with acute respiratory failure²¹; 1 for study design containing inadequately adjusted planned cointerventions²²; 2 for duplicated publications, partial⁶ or complete²³; 3 for results reported exclusively in proceedings,²⁴⁻²⁶ and 1 study published in a nonaccessible language.²⁷

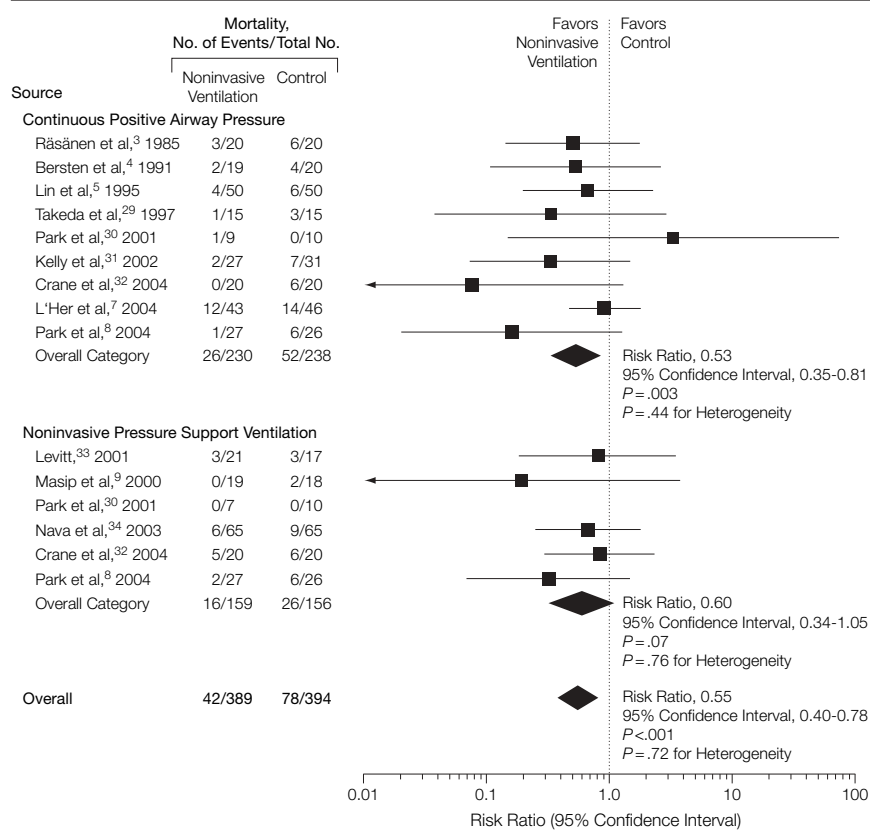
The flow diagram of the trial selection process is shown in FIGURE 1. Sixteen studies were selected, one of which was finally excluded because the reported outcomes did not meet our selection criteria.²⁸ Thus, we included 15 trials in the meta-analysis.^{3-5,7-9,29-37}

Study Description

Trial characteristics are summarized in the TABLE. Although all were published in English, they represent an international experience, including data from 11 countries. Three studies were multiple-center trials, whereas the others were conducted in a single center.

Causes of acute pulmonary edema were reported in 11 of the studies^{3-5,7-9,29,30,34,36,37} and were described as acute coronary syndrome in 203 (31%) of the patients, hypertension in 178 (27%), or worsening heart failure in 92 (14%). Other precipitants like respira-

Figure 2. Effects of Noninvasive Ventilation on Death



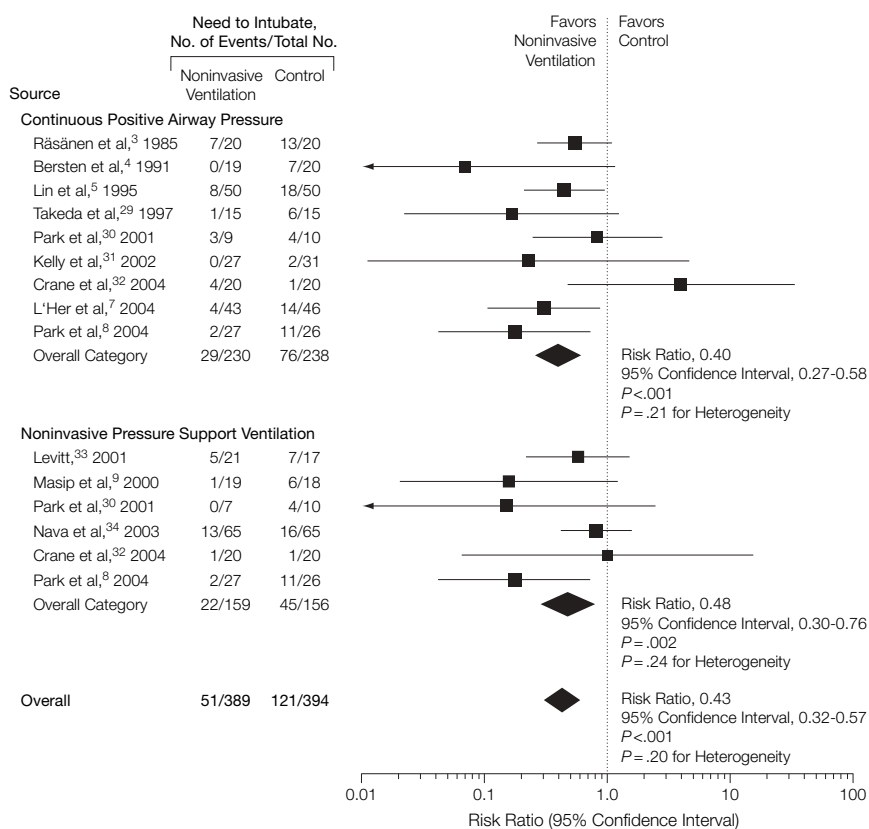
Data markers are proportional to the amount of data contributed by each trial.

tory tract infection, arrhythmia, volume overload, or treatment noncompliance, accounted for 28% of the cases. Causes of death were reported in few studies^{5,8,9,30,35,36} and half of the cases were related to shock.

All trials used full face masks (oro-nasal) but nasal masks were also used in 27% of them. Nine studies compared CPAP with conventional oxygen therapy,^{3-5,7,8,29-32} 3 of them involved in a 3-branch design concomitantly analyzing NIPSV.^{8,30,32} Six studies compared NIPSV with conventional oxygen therapy,^{8,9,30,32-34} 3 being those mentioned with 3 branches. Finally, 6 studies compared CPAP with NIPSV^{8,30,32,35-37} and again, 3 of them also compared conventional therapy. The CPAP level used in these trials ranged from 2.5 to 12.5 cm H₂O although the most frequent pressure was 10 cm H₂O. The level of NIPSV was variable. Aver-

age IPAP ranged from 14.5 to 20 cm H₂O with 15 cm H₂O being the most repeated value. Conversely, EPAP was set at 5 cm H₂O in most trials. Ventilators used for NIPSV differed substantially from one study to another. Intensive care unit ventilators were used in one trial,⁹ whereas specific NIV portable ventilators were used in the others. Early studies used very simple devices.

In general, methodological quality was acceptable. Eleven out of 15 trial reports described the use of appropriate randomization methods, mainly computer-generated randomization lists.^{4,7-9,31-37} Nine of the studies described the use of a concealed allocation method, all but one using sealed envelopes with or without external randomization,^{3,7-9,31,32,34,36,37} and all studies reported the number of patients, if any, lost to follow-up. Nine studies included sample-size calculations.^{4,7-9,33-37}

Figure 3. Effects of Noninvasive Ventilation on Need to Intubate

Nine of the studies found significant improvement in at least 1 of the main outcomes for which the trial was designed, whereas all the studies found significant improvement in secondary outcomes.

The analysis of the publication bias yielded no significant results for either test or comparison group.

Evidence Synthesis

NIV and Conventional Oxygen Therapy. Pooled data included 727 patients. Overall, NIV significantly reduced the risk of mortality compared with conventional oxygen therapy ($P < .001$; FIGURE 2). The results were significant for CPAP, whereas NIPSV tended toward a 40% reduction in the risk of mortality ($P = .07$). However, the number of patients studied with NIPSV was lower than with CPAP and the proportional weight for NIPSV in the pooled data analysis was only 35%.

When the analysis was performed by intention-to-treat, computing withdrawals as events, RRs and 95% CIs from a random-effects model did not differ significantly, showing a global reduction in mortality risk of 43% for NIV (RR, 0.57; 95% CI, 0.41-0.79; $P = .73$ for heterogeneity), which was 46% for CPAP (RR, 0.54; 95% CI, 0.36-0.82; $P = .40$ for heterogeneity) and 37% for NIPSV (RR, 0.63; 95% CI, 0.37-1.06; $P = .87$ for heterogeneity).

Taken together the 2 NIV modalities demonstrated a significant 57% reduction in the need-to-intubate risk ($P < .001$; FIGURE 3). The decrease was statistically significant either for CPAP or NIPSV. Similar results were seen when the analysis was performed by intention to treat: 56% reduction in need-to-intubate risk for pooled data (RR, 0.44; 95% CI, 0.34-0.59; $P = .31$ for heterogeneity), 60% reduction for CPAP (RR, 0.40; 95% CI, 0.28-0.58; $P = .23$ for

heterogeneity), and 49% for NIPSV (RR, 0.51; 95% CI, 0.33-0.78; $P = .42$ for heterogeneity).

The overall myocardial infarction rate for NIV was 78 (22.5%) of 346, which was similar to that observed for conventional therapy, 78 (26.8%) of 292 (RR, 0.89; 95% CI, 0.69-1.17; $P = .99$ for heterogeneity). In about 60% of the cases, myocardial infarction was reported as a cause of acute pulmonary edema. Adverse effects like vomiting, abdominal distention, claustrophobia, or skin reactions were infrequent and were reported only in a few patients.

Comparison Between CPAP and NIPSV. Six studies compared CPAP with NIPSV, and 3 of these also compared the 2 techniques with conventional treatment. Overall, the number of patients included in these studies was 219. No differences were seen in the main outcomes, mortality and need-to-intubate rate, in the studies comparing CPAP to NIPSV (FIGURE 4). Although a slight tendency in favor of NIPSV was observed in relation to the intubation rate, no directional trend in mortality was seen.

COMMENT

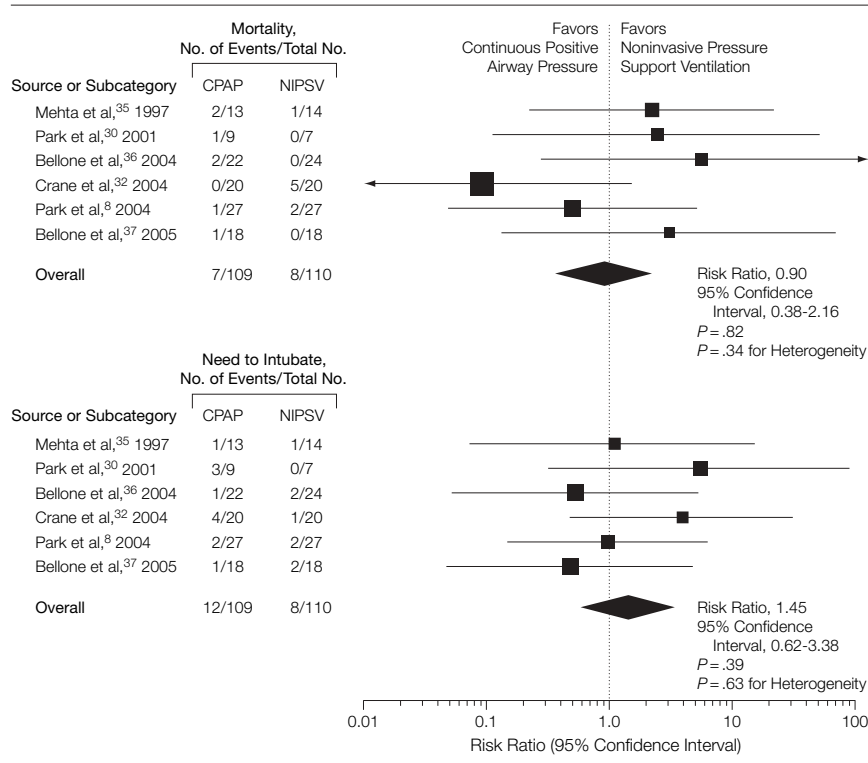
This systematic review and meta-analysis demonstrates the effectiveness of noninvasive ventilation to reduce intubation rate and mortality in patients with acute pulmonary edema. In a previous systematic review published in 1998,³⁸ CPAP was associated with a decrease in need for intubation (risk difference -26%) and a trend to decrease mortality, but there was insufficient evidence on the effectiveness of NIPSV, either compared with standard therapy or CPAP, because there were no randomized trials at that time. Nevertheless, in the last 7 years, many studies have been published evaluating either CPAP or NIPSV in patients with acute pulmonary edema. Probably as a result of increased sample size, our meta-analysis including these trials has clearly reinforced the role of CPAP in comparison with conventional therapy, showing a dramatic reduction in the need for intubation (reduction in risk 60%) and a decrease in mortality (47%), which reached

statistical significance. Parallel to these results, NIPSV demonstrated a similar reduction in the need for intubation (52%) and a trend to decrease mortality in comparison with conventional therapy. As in the previous meta-analysis with CPAP,³⁸ the impact of NIPSV on mortality did not reach statistical significance, possibly because the number of patients included in the model remains underpowered to demonstrate a substantial decrease in mortality. Although additional research would resolve this issue, current evidence on the effectiveness of NIV, especially CPAP, over conventional treatment supports the use of this technique as standard therapy and further comparisons between NIPSV and conventional oxygen therapy would not be considered acceptable.

In the comparison of NIV modalities, NIPSV has the potential advantage over CPAP of assisting the respiratory muscles during inspiration, which would result in faster alleviation of dyspnea and exhaustion.¹² Nevertheless, these physiological benefits did not translate into primary outcomes in our meta-analysis, which did not find differences between CPAP and NIPSV in terms of intubation or mortality. This equivalence remained whether some nonpublished trials^{24,25} not included in the analysis, were incorporated into the model (data available on request). In addition, even in patients with acute pulmonary edema and hypercapnia, a condition usually associated with muscle fatigue, a recent study did not demonstrate differences between these techniques either.³⁷ Hypercapnic patients were expected to be the target population for NIPSV for physiological reasons and especially after the favorable results in the post hoc analyses of some studies using NIPSV.^{34,39}

The incidence of myocardial infarction for the interventional therapies analyzed in the studies was similar. Although a preliminary study³⁵ described a higher rate of acute myocardial infarction with NIPSV, no other trial found this incidence and a recent study, specifically addressing this issue, showed no differences between both techniques.³⁶ Therefore, the question of whether one

Figure 4. Effects of Continuous Positive Airway Pressure vs Noninvasive Pressure Support Ventilation



technique offers advantage over the other and what subset of patients would benefit more with either one of these techniques remains unresolved.¹³

The present meta-analysis has several limitations. First, criteria for diagnosis of acute pulmonary edema are not well established. In the new guidelines on the diagnosis and treatment of acute heart failure proposed by the European Society of Cardiology,⁴⁰ 2 types of acute pulmonary edema are recognized: hypertensive crisis and non-hypertensive pulmonary edema. The prognosis in terms of intubation and mortality differs⁴¹ and the proportion of each type of acute pulmonary edema included in the studies was not well defined. Second, the characteristics of the ventilators (displays, leakage compensation, FiO₂ range, trigger, etc), the level of NIPSV used and the experience of the teams were relatively different in the trials and all of these variables may influence the results of this technique.⁴² This is not the case for CPAP because it

is less dependent on the experience or the device and shows much lower variability in the studies. Third, besides ameliorating fatigue, the main advantage of NIV is to avoid intubation and its associated complications, subsequently reducing the mortality rate. Several studies used rescue NIV, sometimes NIPSV in CPAP groups or either NIPSV or CPAP in conventional groups. This might have introduced some conservative bias in the estimation of the mortality rate. Fourth, although our analysis did not find significant publication bias, this result must be taken with caution due to the low power of tests analyzing this issue when the number of trials is small. Finally, although many trials of this meta-analysis included a small sample size, more than half were powered enough to demonstrate significant differences between interventions in the main outcomes. The limited size of some of these trials, however, reinforces the necessity of our meta-analysis. In addition, it should be men-

tioned that the critical phase of acute pulmonary edema, when patients are eligible, may be extremely short because some patients may require immediate intubation or may rapidly ameliorate after starting medical therapy. This rapid evolution has seriously limited the recruitment capacity of the studies.

Despite these limitations our quantitative systematic review of existing literature demonstrates that NIV reduces intubation rate and mortality in patients with acute pulmonary edema. Noninvasive ventilation has recently been categorized as class IIa, level of evidence A, in the guidelines on the diagnosis and treatment for acute heart failure by the European Society of Cardiology,⁴⁰ based on some of the trials analyzed in the present study.^{3-6,9,22,31,35} Given the results of our review, we think that NIV should be strongly considered as a first-line treatment.

Author Contributions: Dr Masip had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Masip, Roque, Sánchez, Fernández.

Acquisition of data: Masip, Roque, Sánchez, Subirana, Expósito.

Analysis and interpretation of data: Masip, Roque, Sánchez, Subirana, Expósito

Drafting of the manuscript: Masip.

Critical revision of the manuscript for important intellectual content: Masip, Roque, Sánchez, Fernández, Subirana, Expósito.

Statistical analysis: Masip, Roque.

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Administrative, technical, or material support: Roque, Sánchez, Fernández, Subirana, Expósito.

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