Noninvasive Ventilation in Patients With Acute Cardiogenic Pulmonary Edema

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Acute cardiogenic pulmonary edema (ACPE) is a common cause of respiratory failure that necessitates endotracheal intubation. In some patients intubation and its attendant complications can be avoided with noninvasive ventilation (NIV). Both continuous positive airway pressure (CPAP) and NIV have been evaluated in patients with ACPE. Compared to conventional treatment, both CPAP and NIV improve vital signs and physiologic variables, and reduce intubation rate, in patients with ACPE. Both CPAP and NIV appear to be well tolerated and are not associated with any serious adverse events. Initial concern that NIV may be associated with a greater risk of myocardial infarction than CPAP was laid to rest by later studies. Despite a physiologic rationale that NIV should offer greater benefit than CPAP, NIV has not been found to offer any advantages regarding intubation rate or mortality compared with CPAP. We review the randomized controlled trials and summarize the evidence on NIV and CPAP in patients with ACPE. *Key words: acute cardiogenic pulmonary edema, congestive heart failure, noninvasive ventilation, mechanical ventilation, continuous positive airway pressure, CPAP, bi-level positive airway pressure, BiPAP respiratory failure*. [Respir Care 2009;54(2):186–195.

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Introduction

Acute cardiogenic pulmonary edema (ACPE) is a common cause of acute respiratory failure and often necessitates ventilatory support. The use of noninvasive ventilation (NIV) in the acute care setting in general has been fueled by the desire to avoid the complications associated with intubation and invasive ventilation,[1-3] including trauma to the larynx, pharynx, and trachea; arrhythmia; hypotension; aspiration of gastric contents; sinusitis; pneumonia; and loss of the ability to eat and communicate verbally. By avoiding those complications NIV may, in some patient groups, reduce hospital morbidity, facilitate ventilator weaning, shorten hospital stay, lower costs, and improve patient comfort.[1-3] This paper reviews the potential benefit from continuous positive airway pressure (CPAP) and NIV in patients with acute respiratory failure caused by ACPE.

We searched PubMed with the terms "noninvasive ventilation," "non-invasive ventilation," "noninvasive positive pressure ventilation," "non-invasive positive pressure ventilation," "nasal ventilation," "bipap" (bi-level positive airway pressure), "continuous positive airway pressure," and terms that describe pulmonary edema and heart failure. We also scanned the citation lists of selected papers and reviewed our personal files. Two of us regularly conduct literature searches on NIV in MEDLINE, EMBASE, and the Cochrane databases. Though there were some interesting cohort studies published that initially described the use of NIV and CPAP in cardiogenic pulmonary edema,[4-9] in this review we will restrict ourselves primarily to randomized controlled trials; we use studies of other designs for background only. We did not include trials that have been published only in abstract form. We do include information from recent systematic reviews of NIV for ACPE.

To expect benefit from any therapy in a specific patient population there should be a supportive physiologic rationale for its effectiveness. Although not a form of mechanical ventilatory assistance per se, CPAP is commonly used to treat ACPE. Possible benefits of CPAP on ACPE include increased functional residual capacity, reduced atelectasis, reduced right-to-left intrapulmonary shunt, decreased work of breathing from improved pulmonary compliance (Table 1), and increased cardiac output from decreased left-ventricular preload and after-load. Presumably as a result of these physiologic factors, CPAP reduces mitral regurgitation in selected patients.[10] NIV may provide all these benefits plus inspiratory assistance to unload the respiratory muscles[11] and alleviate respiratory distress more quickly and effectively than CPAP alone.

Table 1. Potential Mechanisms of Action of CPAP and NIV in Patients With Acute Cardiogenic Pulmonary Edema

CPAP
Increased functional residual capacity
Reduced atelectasis
Reduced right-to-left intrapulmonary shunt
Reduced work of breathing from improved pulmonary compliance
Increased cardiac output from reduced pre-load and after-load
Reduced mitral regurgitation
NIV
Same benefits as CPAP
Unloads the respiratory muscles

CPAP = continuous positive airway pressure
NIV = noninvasive ventilation

Summary of the Randomized Controlled Trials

In this section we will describe the trials that have compared CPAP to standard therapy, NIV to standard therapy, and CPAP to NIV. The trials included 2 or 3 arms (the latter included CPAP, NIV, and standard therapy). We will also briefly discuss the systematic reviews of NIV and CPAP for ACPE.

Continuous Positive Airway Pressure Compared to Conventional Treatment in Patients With Acute Cardiogenic Pulmonary Edema

We included 10 randomized controlled trials[12-21] that compared CPAP to conventional treatment in patients with ACPE (Table 2 and 4). The inclusion criteria were similar in most trials, and included respiratory distress, rales, and typical chest radiographic findings. The usual exclusion criteria were coma, inability to protect the airway, hemodynamic instability, or need for immediate intubation. Later trials of both CPAP and NIV generally also excluded patients with acute myocardial infarction that required revascularization with thrombolytics or invasive procedures. All of the trials were conducted in only one center. A minority of trials reported whether consecutive patients were enrolled and whether randomization was concealed. All of the trials were unblinded because of the inherent difficulty of blinding the treating physician to the NIV mode. Most trials had either medication protocols for treatment of ACPE or similar administered medication doses in both patient groups.

CPAP was delivered via face mask, for durations ranging from 3 hours[12] to 9.3 hours.[13] Most trials found significant improvements in vital signs and gas exchange in the CPAP groups. Six of the trials showed lower intubation and failure rates with CPAP (at 10–12.5 cm H_2O).[12-15,20]

Two of the trials merit extra discussion.[16,17] These trials applied CPAP at 7.5 cm H_2O via face mask to elderly patients (> 75 y old) with ACPE. The CPAP-treated patients in the trial by Kelly et al[16] had more significant symptom and physiologic improvement in the first hour, but no difference in intubation rate, compared to the control group.[16] However, there were no treatment failures in the CPAP group, and only 2 treatment failures in the control group, one of whom was successfully treated with

Table 2. Randomized Controlled Trials That Compared CPAP to Standard Therapy in Patients With Acute Cardiogenic Pulmonary Edema

Study Year	CPAP Pressure (cm H_2O)	Patients		Intubation/Failure Rate		*P* (CPAP vs control intubation/ failure rate)	Other Outcomes
		CPAP (*n*)	Control (*n*)	CPAP (%)	Control (%)		
Räsänen[12] 1985	10	20	20	35	65	.07	CPAP group: respiratory rate, heart rate, blood pressure, P_{aCO_2}, and P_{aO_2} improved within 10 min.
Bersten[13] 1991	10	19	20	0	35	.005	At 30 min the CPAP group had lower respiratory rate, heart rate, and P_{aCO_2}; higher pH and P_{aO_2}. CPAP group had shorter ICU stay.
Lin[14] 1995	12.5	50	50	16	36	.01	Over the 6 h of the study the CPAP group had lower respiratory rate and heart rate, and higher P_{aO_2}. All the patients had pulmonary artery catheter.
Takeda[15] 1997	4–10	15	15	7	40	.05	Over the 12 h of the study the CPAP group had lower respiratory rate and higher P_{aO_2}/F_{IO_2}. All the patients had pulmonary artery catheter.
Kelly[16] 2002	7.5	27	31	0	7	NS	At 1 h the CPAP group had lower respiratory rate, heart rate, acidosis, and dyspnea. Two patients who failed the control therapy were successfully treated with CPAP.
L'Her[17] 2004	7.5	43	46	9	30	.01	Patients > 75 y old. The CPAP group had lower respiratory rate and heart rate; higher P_{aO_2}/F_{IO_2}; and lower 48-h mortality (7% vs 24%, $P = .002$). The control group had more serious complications.

CPAP = continuous positive airway pressure
ICU = intensive care unit
F_{IO_2} = fraction of inspired oxygen
NS = nonsignificant

CPAP, which raises the possibility that the patients were not that ill. Kelly et al also measured plasma epinephrine, norepinephrine, and brain natriuretic peptide, and found no differences in neurohormone levels in the CPAP-treated patients versus the controls.

The trial by L'Her and colleagues[17] was suspended after the first interim analysis because of a higher 48-h mortality in the control group (7% vs 24%, $P = .002$), but there was no difference in hospital mortality. However, 4 of the patients in the control group who died had treatment withdrawn after study enrollment, which raised the mortality in the control group. There were more "serious complications" in the control group (17 vs 4, $P = .002$), but that was based on a composite outcome of coma, cardiac arrest, and worsening hypoxemia, and only the difference in coma was statistically significant between the groups. Failure of therapy (defined as the need for CPAP, noninvasive pressure-support ventilation [PSV], or intubation) occurred more commonly in the control group (9% vs 30%, $P = .01$). Surprisingly, the most common precipitant of ACPE was respiratory-tract infection, which occurred more frequently in the control group, which raised the concern that patients failed to improve because they did not have ACPE.

In the trial by Lin and colleagues, all the patients had a pulmonary artery catheter inserted for the study.[14] Though patients treated with CPAP had lower intrapulmonary shunt than the control group, there were no differences in cardiac output or pulmonary artery occlusion pressures.

One small study, not included in the tables, found CPAP safe and effective in patients with acute myocardial infarction.[22] Twenty-two patients with severe pulmonary edema associated with acute myocardial infarction were random-

ized to either CPAP or oxygen therapy. Two patients (18%) in the CPAP group and 8 patients (73%) in the oxygen group required intubation ($P = .03$), and hospital mortality was lower in the CPAP group than in the oxygen group (9% vs 64%, $P = .02$).

The trials by Kelly and colleagues[16] and L'Her and colleagues[17] both found early clinical and physiologic benefits from CPAP within the first hour, which suggests that CPAP should be commenced as soon as possible after admission. No serious complications related to mask ventilation were reported in any of these studies. Notably, none of the trials found improvement in other outcome variables, such as intensive-care-unit complications, intensive-care-unit or hospital stay, or mortality.

Several recent systematic studies explored the effectiveness of CPAP and NIV, compared to each other and to standard treatment, in patients with ACPE.[23-27] Pooling the trials included in those reviews, which differ among themselves and from the current review, suggested that CPAP may be associated with lower hospital mortality (Fig. 1). Compared to standard care, CPAP improved clinical and physiologic variables, reduced intubation rate, and may have significantly lowered hospital mortality.[23-27]

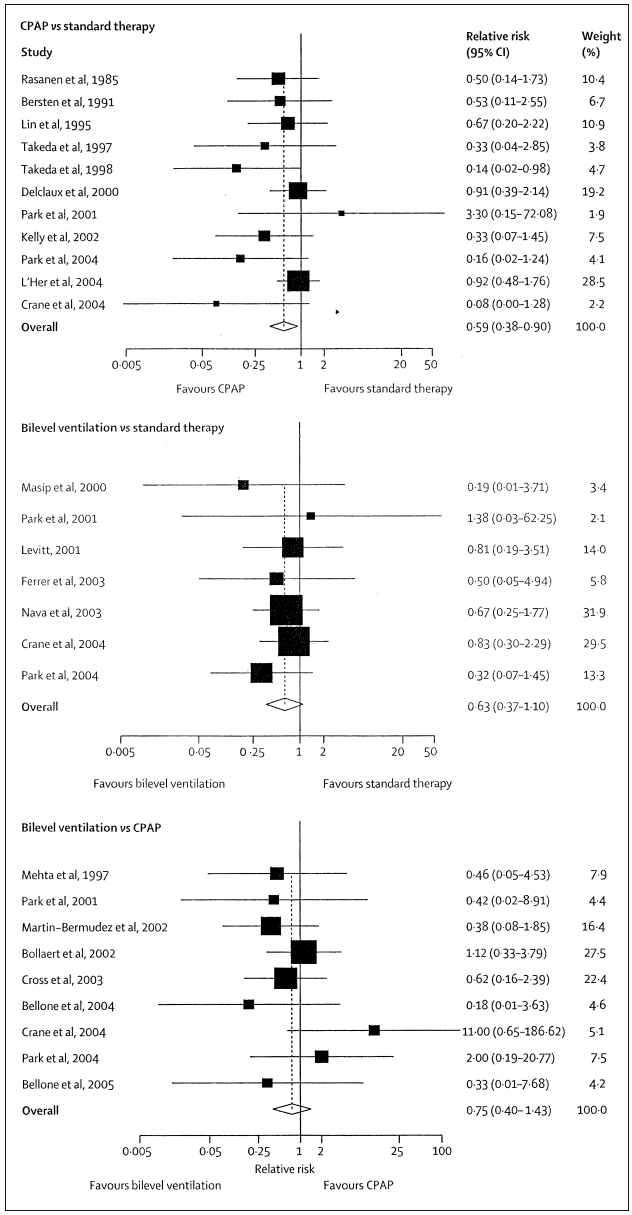

Fig. 1. Meta-analysis of effect of noninvasive ventilation on mortality. The vertical dotted line indicates the overall mortality effect of the treatment. The boxes indicate the relative risk. The horizontal lines indicate the 95% confidence intervals. CPAP = continuous positive airway pressure. (From Reference 24, with permission.)

Noninvasive Ventilation Compared to Conventional Treatment in Patients with Acute Cardiogenic Pulmonary Edema

In the 8 trials[18-21,28-31] that compared NIV (noninvasive PSV or BiPAP) to conventional oxygen therapy in patients with ACPE (Table 3 and 4), the inclusion and exclusion criteria were similar to those in the trials that compared CPAP to conventional therapy. The trial by Ferrer and co-workers enrolled a heterogeneous group of patients with hypoxemic respiratory failure, and provided some information on the subgroup with ACPE.[31] Other than the trial by Ferrer and colleagues,[31] all the trials enrolled patients in the emergency department. Though most studies delivered NIV predominantly via face mask, Levitt and colleagues[29] also permitted nasal mask. The NIV duration ranged from 2 h to 11.4 ± 3.6 h.[29,30]

In contrast to the trials that compared CPAP to standard therapy, the results of the NIV trials are less consistent. In 5 of the trials NIV improved physiologic variables and gas exchange,[18,20,21,28,30] and in 3 trials[18,20,28] NIV significantly reduced the intubation rate. Compared to standard therapy, NIV was not associated with greater risk of adverse events; specifically, there was no greater risk of myocardial infarction. The individual studies did not suggest a difference in mortality or stay. The differences in the results of these trials probably relate to patient factors (eg, group nonhomogeneity such as inclusion of non-ACPE patients, and different severity of illness between studies) and differences in study design (eg, the individual center's experience with NIV, type of ventilator, pressures applied, delay in initiating NIV, differences in adjunctive treatments, and prospective definitions of NIV failure and intubation criteria).

Masip and colleagues randomized 40 patients to noninvasive PSV or oxygen.[28] The noninvasive PSV group had more rapid improvement in clinical variables (eg, respiratory rate and oxygen saturation) and a lower intubation

Table 3. Randomized Controlled Trials That Compared NIV to Standard Therapy in Patients With Acute Cardiogenic Pulmonary Edema

Study Year	Type of Ventilation	Inspiratory and Expiratory Pressure (cm H_2O)	Patients		Intubation Rate		*P* (NIV vs control intubation rate)	Other Outcomes
			NIV (*n*)	Control (*n*)	NIV (%)	Control (%)		
Masip[28] 2000	PSV	15/5	19	18	5	33	.04	Respiratory rate decreased. Pulse-oximetry readings increased within first 15 min of NIV. P_{aO_2}/F_{IO_2} was higher in PSV group for first 2 h. MI in 33% of control group and 26% of NIV group (NS).
Levitt[29] 2001	BiPAP	8/3 initially	21	17	24	41	NS	No difference in vital signs or gas exchange. MI in 29% of control group and 19% of BiPAP group (NS).
Nava[30] 2003	PSV	14/6	65	65	20	25	.53	PSV group had decreased dyspnea, respiratory rate, and P_{aCO_2}, and increased P_{aO_2}. Less endotracheal intubation in the hypercapnic subgroup. MI in 16% of the control group and 16% of the NIV group.
Ferrer[31] 2003	BiPAP	16/7	15	15 (subgroup)	26	73	ND	Outcomes not reported for subgroup with ACPE. The BiPAP group had decreased respiratory rate and increased P_{aO_2}/F_{IO_2} for entire study population.

NIV = noninvasive ventilation
PSV = pressure-support ventilation
F_{IO_2} = fraction of inspired oxygen
BiPAP = bi-level positive airway pressure
NS = difference not significant
MI = myocardial infarction
ND = no data provided
ACPE = acute cardiogenic pulmonary edema

rate (5% vs 33%, $P = .04$). However, the control group may have had a greater severity of illness at baseline. In patients with hypercapnia, noninvasive PSV was associated with more rapid reduction in P_{aCO_2} than was the control therapy.

In the emergency department, Levitt and colleagues randomized 38 patients with ACPE to either BiPAP or oxygen therapy.[29] Nonconsecutive subjects were enrolled only when one of the study personnel was present. BiPAP was initiated at low pressures (8/3 cm H_2O) and titrated, but the final pressures were not given. BiPAP was administered for a minimum of 120 min. There were no differences in vital signs, gas exchange, or intubation rate between the BiPAP and oxygen groups. Four patients did not tolerate BiPAP and were crossed over to the control arm; those patients' outcome is unclear. Possible explanations for the lack of benefit from BiPAP include the low pressures applied and baseline differences between the groups. No severity-of-illness data were provided. Other limitations of the trial included nonstandardized pharmacologic treatment for ACPE, and a lack of prospectively defined criteria for intubation.

In a rigorously conducted study with 130 patients in 5 emergency departments in Italy, Nava et al defined the intubation/NIV-failure criteria, and used intention-to-treat analysis.[30] Dyspnea, respiratory rate, and gas exchange improved in the patients who received noninvasive PSV. Surprisingly, there was no difference in the intubation rate, except in the a-priori-defined subgroup of patients with hypercapnia, even though the inspiratory and expiratory pressures were similar to that in the study by Masip and colleagues.[28] Nava et al proposed that the limited NIV experience of most emergency departments might explain the failure of NIV to reduce the intubation rate.[30]

Compared to standard care, NIV improved clinical and physiologic variables and reduced the intubation rate. None of the 3 trials found NIV to reduce mortality or stay. However, the systematic reviews[23-25,27] concluded that NIV

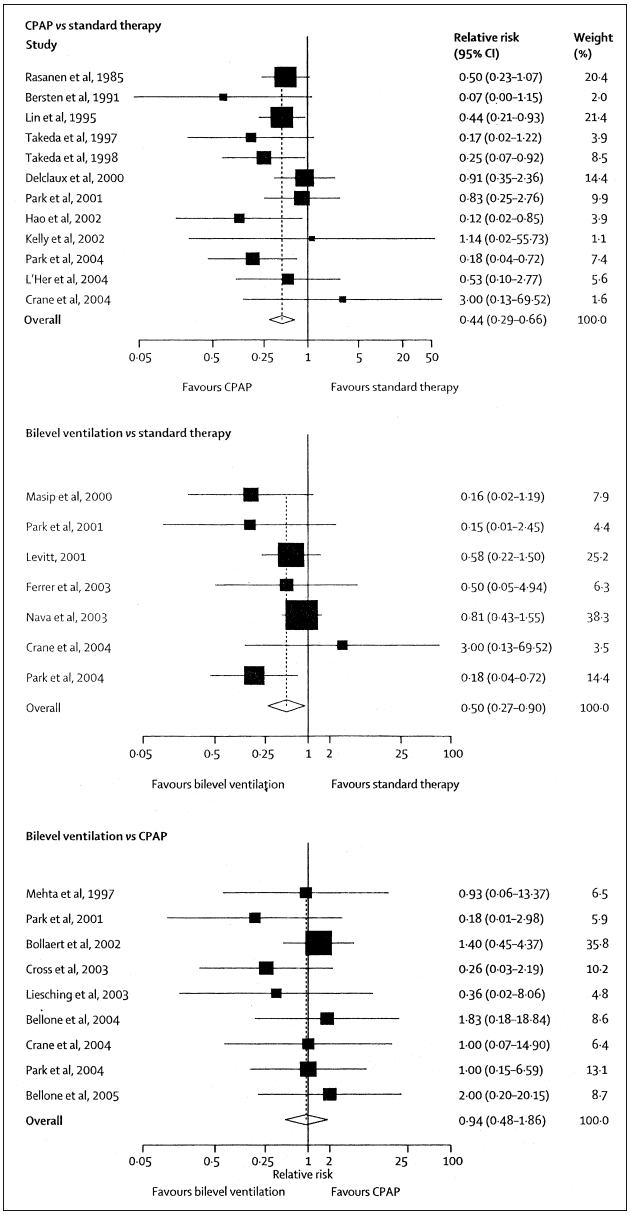

Fig. 2. Meta-analysis of effect of noninvasive ventilation on intubation rate. The vertical dotted line indicates the overall mortality effect of the treatment. The boxes indicate the relative risk. The horizontal lines indicate the 95% confidence intervals. CPAP = continuous positive airway pressure. (From Reference 24, with permission.)

significantly reduced intubation and nonsignificantly reduced mortality (Figs. 1 and 2). However, those authors cautioned that there was substantial trial heterogeneity, particularly in the pooled analysis of need for intubation. In their meta-analysis, Winck and colleagues postulated that (in contrast to CPAP) NIV failed to reduce mortality because of the low study power caused by the small number of patients in the trials.[25]

Continuous Positive Airway Pressure Compared to Noninvasive Ventilation in Patients With Acute Cardiogenic Pulmonary Edema

We included 11 randomized controlled trials that compared CPAP to NIV in patients with ACPE (Table 4).[18-21,32-38] The trial by Ferrari and colleagues[36] was conducted in a high-dependence unit, but all the other trials were conducted in emergency departments. Nine trials delivered CPAP and NIV via face mask, one trial did not specify how CPAP and NIV were delivered,[33] and Mehta and colleagues used nasal mask.[32] Most of the trials applied concealed randomization and included a suggested medication protocol or reported similar medication doses. Mean CPAP pressure ranged from 7.5 cm H_2O to 11 cm H_2O. Mean NIV pressures ranged from 12/4 cm H_2O to 25/5 cm H_2O.[18,33] Moritz and colleagues[37] differed from the other studies in that they used the Boussignac CPAP device, which is a disposable mask that generates 5–10 cm H_2O of CPAP with 15–25 L/min oxygen flow, without a ventilator. The duration of CPAP or NIV ranged from 102 min[18] to 8 hours.[36]

In the first published trial, Mehta and colleagues[32] found that patients treated with NIV had more rapid P_{aCO_2} reduction than the CPAP group, but the myocardial infarction rate was higher (71% in the NIV group vs 31% in the CPAP group, $P = .05$). The intubation rates were similar (7% in the NIV group, 8% in the CPAP group), and were lower than the 33% intubation rate in a historical control group. Morbidity and mortality were similar between the 2 groups. More NIV patients than CPAP patients had chest pain on study entry (10 vs 4, $P = .06$), which suggests inequalities between the groups, despite concealed randomization. Mehta et al concluded that most patients can be managed successfully with CPAP alone.

Ten subsequent randomized trials compared NIV to CPAP. Overall, there does not appear to be any important advantage to NIV over CPAP; both modes similarly improve vital signs and gas exchange, and there is no significant difference in intubation rate or hospital mortality. Two trials[20,32] found more rapid P_{aCO_2} improvement with NIV than with CPAP, but that finding was not confirmed in other trials.

Four of the trials had 3 treatment arms.[18-21] In their first study, Park and colleagues found that CPAP-treated patients had a similar intubation rate to the control group, and none of the BiPAP-treated patients required intubation.[18] These surprising findings were explained by the small numbers of patients in the trial and the relatively low CPAP pressure (7.5 cm H_2O). In a subsequent larger trial, Park and colleagues found that CPAP and NIV were equally effective in reducing the intubation rate, compared to standard care.[20] In addition, 15-day mortality was significantly lower in both NIV groups, compared to standard care, but

Table 4. Randomized Controlled Trials That Compared NIV to CPAP in Patients With Acute Cardiogenic Pulmonary Edema

Study Year	Techniques Compared	Pressure		Patients		Intubation Rate		*P* (CPAP vs NIV intubation rate)	Other Outcomes
		CPAP (cm H_2O)	NIV (cm H_2O)	CPAP (*n*)	NIV (*n*)	CPAP (%)	NIV (%)		
Mehta[32] 1997	CPAP vs BiPAP	10	15/5	13	14	8	7	ND	BiPAP improved P_{aCO_2}, vital signs, and dyspnea faster than did CPAP. MI in 71% of NIV group vs 31% of CPAP group.
Park[18] 2001	CPAP vs BiPAP vs O_2	7.5	12/4	9 10 patients in O_2 arm	7	33 40% of patients in O_2 arm were intubated	0	.05	At 10 min the BiPAP group had lower respiratory rate and higher P_{aO_2}. No difference between the 3 groups at 60 min.
Cross[33] 2003	CPAP vs BiPAP	5–20	10–25/5	36	35	11	3	.5	No differences in any measured variable.
Crane[19] 2004	CPAP vs BiPAP vs O_2	10	15/5	20 20 patients in O_2 arm	20	5 No patients in O_2 arm were intubated	5	NS	No difference in vital signs, gas exchange, or MI rate between 3 the groups. Hospital survival 100% in CPAP, 75% in BiPAP group, and 70% O_2-therapy group ($P = .03$), but there was no difference in 7-d survival.
Bellone[34] 2004	CPAP vs noninvasive PSV	10	15/5	22	24	4.5	8.3	ND	Both groups had similar improvement in vital signs and gas exchange. No difference in MI or mortality rate.
Park[20] 2004	CPAP vs BiPAP vs O_2	11	17/11	27 26 patients in O_2 arm	27	7 42% of patients in O_2 arm were intubated	7	.001	CPAP and BiPAP groups had similar improvement in vital signs and gas exchange (both better than O_2 group). MI in 12% of control group and 4% in BiPAP and CPAP groups.
Bellone[35] 2005	CPAP vs noninvasive PSV	10	15/5	18	18	5.5	11.1	ND	Enrolled only hypercapnic patients. Both groups had similar improvement in respiratory rate, pH, and CO_2, at 1 h.
Ferrari[36] 2007	CPAP vs noninvasive PSV	8.8	15/7	27	25	0	4	ND	The groups had similar vital signs, gas exchange, stay, troponin I, MI rate, and mortality.
Moritz[37] 2007	CPAP vs BiPAP	7.7	12/4.9	59	50	2	4	ND	Both groups had similar vital signs, gas exchange, MI rate, and mortality. Hypercapnic patients had more complications than nonhypercapnic patients.
Rusterholtz[38] 2008	CPAP vs PAV	9.3	14/4.2	19	17	29	31	ND	The groups had similar vital signs, gas exchange, MI rate, and mortality.
Gray[21] 2008	CPAP vs noninvasive PSV vs O_2	10	14/7	346 367 patients in O_2 arm	356	2.4 2.8% of patients in O_2 arm were intubated	3.5	NS	CPAP and noninvasive PSV groups had similar improvements in vital signs, gas exchange (both better than O_2 group). No differences in MI rate, stay, or mortality between the 3 groups.

NIV = noninvasive ventilation
CPAP = continuous positive airway pressure
BiPAP = bi-level positive airway pressure
ND = no data available
MI = myocardial infarction
NS = difference not significant
PSV = pressure-support ventilation

hospital mortality did not differ.[20] In contrast, Crane and colleagues found no difference in intubation rate with CPAP or NIV, compared to standard care, but the intubation rates were extremely low (5% in the CPAP and NIV groups, and zero in the control group).[19] Given that nonconsecutive patients were enrolled, it is possible that the sickest patients were intubated without being considered for study enrollment. Surprisingly, the CPAP patients were more likely to survive to hospital discharge (100%) than were those treated with NIV (75%) or oxygen therapy (70%, $P = .03$). However, it is difficult to ascribe the lower hospital mortality rate in the CPAP group to the ventilation mode, given that the intubation rates were similar, and the 7-day survival did not differ between the groups.

The largest and most recently published trial was powered to detect a difference in 7-day mortality.[21] Gray et al randomized 1,069 patients in 26 Scottish emergency departments to CPAP, noninvasive PSV, or oxygen therapy. Patients > 16 years old with a chest radiograph consistent with ACPE, respiratory frequency > 20 breaths/min, and pH < 7.35 were included. Though medication administration was not standardized, the administered doses were similar in the 3 groups. Compared to standard therapy, both CPAP and noninvasive PSV were associated with similar improvements in dyspnea, heart rate, pH, and P_{aCO_2} within one hour. In contrast to many other trials and to systematic reviews, there was no difference in intubation rate or mortality with either CPAP or NIV, compared to standard therapy; however, the intubation rates were very low (range 2.4–3.5% in the 3 groups).

There are several potential explanations for these surprising results. First, several factors, such as the relatively mild respiratory rate and pH inclusion criteria, the low intubation rates, the short durations (approximately 2 h) of NIV application, and the lower-than-anticipated mortality (9.8% in the control group, compared to a 15% anticipated rate), suggest that the patients were not that ill and did not require any ventilatory intervention. Second, crossovers were permitted, and 19% of the patients in the oxygen arm failed therapy and were treated with CPAP or noninvasive PSV. Had those control patients all been intubated, the intubation rate in the control group might have been significantly higher than both the CPAP and noninvasive PSV groups.

A recently published randomized trial compared proportional-assist ventilation to face-mask CPAP in 36 patients with ACPE.[38] It is not clear whether selected patients were enrolled, because no data regarding patient screening and enrollment were provided. Medical treatment was standardized, and there were objective intubation criteria. The groups had similar improvements in clinical and physiologic variables, including P_{aCO_2}, and there was no difference in intubation rate or mortality. Though they did not evaluate the work load associated with initiation and titration of CPAP and proportional-assist ventilation, the latter appears to require greater expertise. The study did not find any advantages from proportional-assist ventilation over CPAP for patients with ACPE.

Bellone and colleagues[35] randomized 36 patients with ACPE and hypercapnia to NIV (15/5 cm H_2O) or CPAP (10 cm H_2O). The average P_{aCO_2} in the CPAP and BiPAP groups was 60.5 mm Hg and 65.7 mm Hg, respectively. The study was powered to detect a 10-min difference in clinical "resolution" of ACPE. Both modes rapidly improved the major physiologic variables and resolved ACPE, and the intubation and mortality rates did not differ between the modes. Bellone et al concluded that NIV is not superior to CPAP when signs of respiratory pump failure are present. Subgroup analysis of hypercapnic patients enrolled in 2 other trials[36,37] found similar P_{aCO_2}, regardless of assigned noninvasive strategy. However, Moritz and colleagues observed that hypercapnic patients were more likely to develop the combined outcome of intubation, death, or acute myocardial infarction, as well as cardiogenic shock, gastric acid aspiration, or require a switch of the ventilation mode, during the first 24 hours.[37]

Though an early trial suggested greater risk of myocardial infarction with NIV than with CPAP,[32] none of the subsequent trials that reported that outcome confirmed that finding. Two studies that specifically examined myocardial infarction rate found no difference in the risk of myocardial infarction or cardiac enzyme level between the NIV and CPAP patients.[34,36] Other reported complications in the studies that compared CPAP to NIV were minor and infrequent: facial erythema in 5%, vomiting in 5%,[19] and gastric distention in 18% of CPAP patients and 30% of NIV patients.[20] Intolerance of CPAP and NIV was observed in 15% and 10% of patients, respectively.[19]

A study by Sharon and colleagues raised concerns about the safety of BiPAP in the treatment of patients with severe pulmonary edema.[39] Forty consecutive patients were randomized to receive high-dose isosorbide dinitrate, or BiPAP (initially at 8/3 cm H_2O) and standard-dose isosorbide dinitrate. The patients treated with BiPAP had slower resolution of clinical variables, and a higher rate of intubation (80% vs 20%, $P < .001$), myocardial infarction (55% vs 10%, $P = .006$), and death (10% vs 0%, $P > .05$). The study was terminated early because of these findings, and the investigators concluded that "BiPAP…is detrimental to patients with severe pulmonary edema." However, several serious concerns about the study limit the ability to draw that conclusion. Randomization was not concealed, the treatment was delivered pre-hospital by mobile intensive care units, and the intubation criteria were vague. Most importantly, very low inspiratory and expiratory pressures were applied (mean 9/4 cm H_2O), which suggests that the ventilatory assistance may have

been insufficient. Finally, the enrolled patients were quite ill, and may not have been appropriate for NIV, as evidenced by the very high intubation rate (80%) in the BiPAP group.

Compared to CPAP, NIV has been variably found to more rapidly improve clinical and physiologic variables, but NIV does not reduce intubation rate or mortality. Systematic reviews have not found NIV superior to CPAP in avoiding intubation or lowering mortality (see Figs. 1 and 2) or myocardial infarction rate.[24-26]

Summary

In patients with ACPE, numerous randomized trials have compared CPAP to conventional therapy, NIV to conventional therapy, and CPAP to NIV. There were important methodological limitations in many of the trials, such as lack of blinding and inclusion of only a proportion of patients who presented with ACPE, which restricts the generalizability of these results to all patients with ACPE. Nevertheless, based on these trials, noninvasive PSV and CPAP equally and safely improve vital signs and gas exchange, and the systematic reviews found that noninvasive PSV and CPAP reduce the intubation rate in patients with ACPE, compared to conventional therapy. To date, no trial has been sufficiently powered to confirm a mortality benefit from either technique. The suggestion, in the systematic reviews, of a mortality benefit from CPAP but not NIV must be considered cautiously, as those analyses are based on small trials with few events (deaths), and the trials were conducted over almost 2 decades, during which treatment for ACPE has evolved. It remains to be determined in the current era of ACPE therapy whether CPAP or NIV confer a mortality benefit. At this time we cannot conclude that NIV offers any advantages over CPAP.

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Discussion

Pierson: Has anyone looked at patient preferences for NIV versus CPAP?

Mehta: I haven't seen any trials on that.

Gay: The studies you've described span a couple of decades. How much do you think the findings might be confounded by the fact that—and I'm not as cynical as this may sound—we haven't gotten *that* much better at using NIV but the cardiologists have gotten a lot better at treating ACPE?

Benditt: MI [myocardial infarction], you mean?

Gay: Well, the reduction in mortality when they aggressively treat ACPE now, I think, is just as impressive as when they attack acute ischemia.

Mehta: So, you're asking whether medical management has changed in the last 30 years?

Gay: Hasn't better ACPE therapy more likely influenced the outcome than intervention with NIV?

Mehta: I can't tell you whether that's the case. I assume so, but it is difficult to compare doses or medications between trials, and some acute interventions, such as angioplasty, have become more common recently. I think most of the cardiologists I work with tend to intubate people very quickly, and they don't use or are very reluctant to use NIV, and they're uncomfortable with it. NIV doesn't seem to be highlighted at the cardiology conferences the way it is at the pulmonary and critical care conferences.

Hill: Or in the emergency department.

Mehta: Right.

Hill: It's the emergency doctors who are on the front lines for this. You're right about the cardiologists; they seem to be more at ease with the EMT [emergency medical technician] crew than with a CPAP mask.

Benditt: Maybe this is just at my institution, but our cardiologists use a lot of CPAP. The other day there were 4 people in the ward on CPAP. I am a firm believer that CPAP is the better choice, because physiologically it makes a lot more sense to me. On CPAP, as our mentor John Butler

taught us, the endothoracic pressure is higher, and the pre-load and after-load are reduced quite effectively with CPAP, so it makes great physiologic sense to me, and I think the data show that.

Mehta: But BiPAP offers all of these benefits as soon as you have a high enough PEEP [positive end-expiratory pressure].

Benditt: But I'm not sure how the cardiac cycle is interacting with the respiratory cycle; it may change; I don't know. With CPAP you know the pressure you're at, and that's what you're going to get.

Mehta: I agree. In patients with ACPE there are many reasons to use CPAP: it's a lot easier to use, there's no titration involved, anyone can apply it, and it's easier to understand. However, even though I've tried to convince people at my institution to use CPAP, they hardly even seem to know what CPAP is any more. Any time I go down to the emergency department or the critical care unit or step-down unit they're using BiPAP regardless of the etiology of the respiratory failure.

Benditt: And that's the problem, I think.

Hill: When I give NIV talks, I often informally survey the audience about their choice of BiPAP versus CPAP for ACPE. Usually they are overwhelmingly in favor of BiPAP. I'm not disturbed by this though, because, as you said, Geeta, it really doesn't make any difference. You increase intrathoracic pressure either way. As best we can tell, the studies show that they have essentially the same outcomes in the end. I think there are some early physiologic benefits of BiPAP over CPAP, as suggested by our study,[1] especially for patients who are initially hypercapnic or very dyspneic, in which case BiPAP can reduce work of breathing and P_{aCO_2} a little more quickly. Crane et al[2] also saw some of these earlier physiologic benefits. The reason I'm not disturbed, though, is that the BiPAP equipment is there in the emergency department anyway, so there's no cost advantage to CPAP. Furthermore, it's not that hard to titrate BiPAP, and people are usually comfortable with it.

1. Mehta S, Jay GD, Woolard RH, Hipona RA, Connolly EM, Cimini DM, et al. Randomized, prospective trial of bi-level versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med 1997;25(4):620-628.
2. Crane SD, Elliott MW, Gilligan P, Richards K, Gray AJ. Randomised controlled comparison of continuous positive airways pressure, bi-level noninvasive ventilation, and standard treatment in emergency department patients with acute cardiogenic pulmonary oedema. Emerg Med J 2004; 21(2):155-161.

Kacmarek: Stefano, in your subgroup analysis, did you find a benefit from NIV? Although I would agree that it probably doesn't make a difference in the vast majority of patients, it seems reasonable to start out with CPAP, unless the patient is hypercarbic. You can use the same ventilator to do either CPAP or NIV. This could be more of an academic argument than a real discussion on managing patients, unless there is substantial hypercarbia, in which case my bias is to provide ventilation, as opposed to simple CPAP.

Nava: Bellone et al[1] excluded patients with preexisting chronic respiratory disorders, and they found no difference between CPAP and NIV. In our study[2] the large majority of patients with hypercapnia also had a chronic respiratory disorder. So probably what Bob said is very true only when the main cause of hypercapnia may be muscle distress or something. Maybe hypercapnia in ACPE has different meanings.

I think the helmet is one of the biggest advances for ACPE, because it allows treating the patient inside a protected environment. For example, if ACPE occurs in the dialysis unit, you go there with the helmet, you connect the device into the centralized oxygen flow, and you can easily treat ACPE in patients on dialysis. The same applies in an ambulance. Even the cardiologists have changed their mind; they seem to like the helmet a lot.

1. Bellone A, Vettorello M, Monari A, Cortellaro F, Coen D. Noninvasive pressure support ventilation vs continuous positive airway pressure in acute hypercapnic pulmonary edema. Intensive Care Med 2005; 31(6):807-811.
2. Nava S, Carbone G, DiBattista N, Bellone A, Baiardi P, Cosentini R, et al. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomized trial. Am J Respir Crit Care Med 2003;168(12): 1432-1437.

Epstein: In scoring the trials, you gave a check when intubation criteria were specified. How often do the investigators go back to see whether the intubation criteria were accurately applied? In my experience it's still a judgment call. We tend to rate those trials higher, but is that really the right thing to do?

Mehta: I agree. Obviously we have to look for objective intubation criteria when we evaluate trial quality, but I'm not sure how much it actually means to have objective intubation criteria. For example, one of the studies had "deterioration in gas exchange or clinical status" as the intubation criteria. So even if intubation criteria are defined, the intubation decision is generally based on the clinical evaluation.

Hess: Regarding CPAP versus NIV for hypercapnic ACPE, a 1991 randomized controlled trial by Bersten et al[1] found a significant reduction in P_{aCO_2} with CPAP.

1. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure deliv-

ered by face mask. N Engl J Med 1991; 325(26):1825-1830.

Keenan: In your literature summary you said the systematic reviews identified a mortality benefit from CPAP, but not for NIV. That finding is dependent on the trials available. I think we can all accept the strong rationale that NIV or CPAP should prevent intubation in patients with ACPE. I am less certain that NIV or CPAP will have as direct an impact on mortality as we might expect in patients with COPD.

The reason for better survival in patients with COPD is that NIV obviates intubation. Intubated patients with COPD usually require longer duration ventilation than do those with ACPE. The latter generally either require brief ventilation or do very poorly because of their underlying cardiac disease. An intubated patient who is on the ventilator longer is at higher risk of pneumonia and its associated mortality.

Several studies on CPAP were conducted before the NIV studies, and the CPAP studies are driving the apparent mortality benefit. I believe that mortality in these patients is presently linked to their underlying cardiac disease, and treatment for the same. Other than patients with comorbid COPD, I am uncertain whether the apparent mortality benefit of CPAP versus NIV reported in the systematic reviews is relevant today.

Hill: One of the limitations in some of the more recent trials that looked at noninvasive positive pressure on the MI rate was the exclusion of patients with acute coronary syndromes. One cannot determine whether NIV has adverse effects on that population if they're excluded from the studies. Did you take that into consideration? Has somebody looked at NIV in patients with infarcts?

Nava: Takeda et al,[1] in Japan, did one study. A Russian group was scheduled to present another study at the European Respiratory Society meeting 2 years ago, but they didn't show up.

1. Takeda S, Nejima J, Takano T, Nakanishi K, Takayama M, Sakamoto A, Ogawa R. Effect of nasal continuous positive pressure on pulmonary edema complicating acute myocardial infarction. Jpn Circ J 1998;62(8):553-5558.

Mehta: Takeda et al randomized a small number of patients who presented with ACPE due to acute MI to either CPAP or standard therapy. The CPAP group had a lower intubation rate and hospital mortality than the standard-therapy group.

Hill: Is that a concern in exonerating the modes contributing to infarction if you exclude the people at risk? Don't you consider that a problem?

Mehta: Of course, yes.

Doyle:* Is the current standard of care for ACPE endotracheal intubation, CPAP, or standard O_2 therapy?

Mehta: I don't think that's clear. It disturbs me that trials are still being done that include an oxygen arm as standard therapy. Oxygen alone should not be considered standard therapy for patients with ACPE. I'm sure all of you here agree that CPAP or NIV should be the standard therapy, but I don't think any recent surveys have looked at what the first-line ACPE therapy tends to be.

Nava: Park et al[1] found several important things. In their patient population only 30% of those with hypercapnic ACPE fit their criteria, which means that 7 out of 10 patients who were only in the hospital for ACPE did not need any mechanical ventilation.

1. Park M, Sangean MC, Volpe MS, Feltrim MI, Nozawa E, Leite PF, et al. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bi-level positive airway pressure by face mask in ACPE. Crit Care Med 2004;32(12):2407-2415.

Mehta: Yes, many of the trials are plagued with the problem of "cherry-picking" and non-consecutive patient enrollment.

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