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Continuous positive airway pressure vs. proportional assist ventilation for noninvasive ventilation in acute cardiogenic pulmonary edema

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Abstract *Objective:* To compare continuous positive airway pressure (CPAP) and proportional assist ventilation (PAV) as modes of noninvasive ventilatory support in patients with severe cardiogenic pulmonary edema. *Design and setting:* A prospective multicenter randomized study in the medical ICUs of three teaching hospitals. *Patients:* Thirty-six adult patients with cardiogenic pulmonary edema (CPA) with unresolving dyspnea, respiratory rate above 30/min and/or SpO_2 above 90% with O_2 higher than 10 l/min despite conventional therapy with furosemide and nitrates. *Interventions:* Patients were randomized to undergo either CPAP (with PEEP 10 cmH_2O) or PAV (with PEEP 5–6 cmH_2O) noninvasive ventilation through a full face mask and the same ventilator. *Measurements and results:* The main outcome measure was the failure rate as defined by the onset of predefined intubation criteria, severe arrythmias or patient's refusal. On inclusion CPAP ($n = 19$) and PAV ($n = 17$) groups were similar with regard to age, sex ratio, type of heart disease, SAPS II, physiological parameters (mean arterial pressure, heart rate, blood gases), amount of infused nitrates and furosemide. Failure was observed in 7 (37%) CPAP and 7 (41%) PAV patients. Among these, 4 (21%) CPAP and 5 (29%) PAV patients required endotracheal intubation. Changes in physiological parameters were similar in the two groups. Myocardial infarction and ICU mortality rates were strictly similar in the two groups. *Conclusions:* In the present study PAV was not superior to CPAP for noninvasive ventilation in severe cardiogenic pulmonary edema with regard to either efficacy and tolerance.

Keywords Noninvasive ventilation · Acute cardiogenic pulmonary edema · Continuous positive airway pressure · Proportional assist ventilation · Pressure support ventilation

Introduction

Currently the use of noninvasive ventilation (NIV) is widely recommended in acute respiratory failure related to cardiogenic pulmonary edema (CPE) [1, 2]. It has been demonstrated to reduce the need for subsequent endotracheal intubation and mortality [3–5]. NIV can be delivered either by continuous positive airway pressure (CPAP), a method which maintains a permanent positive airway pressure while the patient is breathing sponta-

neously, or bilevel pressure support ventilation (NIPSV), where an assistance by an inspiratory positive airway pressure is added to maintaining an expiratory positive airway pressure. Both CPAP [6–10] and NIPSV [11–13] have proven effective as conventional therapy. However, the best technique of NIV in CPE has not yet been established. Although NIPSV more effectively unloads the respiratory muscles than CPAP [14], comparative randomized controlled trials confirm the clinical relevance of this physiological benefit [15–19]. In addition, one of these studies was prematurely terminated due to an increased incidence of myocardial infarction in the NIPSV group [15]. For these reasons CPAP, a method widely available, relatively inexpensive, and easy to use, remains a first-intention technique [1, 2, 20].

Proportional assist ventilation (PAV) is a ventilatory mode which is designed to generate an inspiratory positive airway pressure in proportion to the patient's instantaneous inspiratory effort [21]. Several studies that have compared PAV with pressure support ventilation (PSV) have been published [22–26]. Two of these compared patients in acute respiratory insufficiency [22, 23]. They enrolled relatively heterogeneous patients with regard to the cause of respiratory failure, including a few patients with CPE. PAV was associated with more rapid improvement in some physiological variables, more comfort and better tolerance than with NIPSV. Therefore we hypothesized that PAV as a more "physiological" method of noninvasive respiratory support would be better than CPAP for CPE with regard to physiological effects and clinical benefit.

Patients and methods

Patients

The study was conducted in three French medical ICUs. The study design was approved by the "Comité Consultatif des personnes se prêtant à une recherche biomédicale" according to French laws. Written consent was obtained from the patients or their relatives. Inclusion criteria were as follows: (a) an acute clinical condition consistent with acute CPE including acute dyspnea, widespread crackles or wheezing, and absence of an alternative diagnosis, (b) typical findings of congestion on chest radiography, (c) prior adequate, standardized treatment in the prehospital setting or in the emergency ward (1 mg/kg furosemide and 0.4–3 mg/h nitrates as continuous infusion), (d) at least two of the following: respiratory rate (RR) higher than 30/min, unresolving dyspnea with the use of the accessory respiratory muscles or paradoxical abdominal motion, SpO_2 less than 90% with O_2 greater than 10 l/min or FIO_2 more than 0.5 (Venturi mask) for at least 15 min. Exclusion criteria were: (a) requirement of immediate endotracheal intubation, which was considered mandatory in cases of cardiogenic shock (systolic arterial pressure < 90 mmHg), severe ventricular arrhythmia, bradycardia at less than 45/min, ventilatory or cardiac arrest or clinical judgment from the attending physician, (b) second- or third-degree atrioventricular block; (c) Glasgow Coma Score (GCS) less than 12, (d) acute myocardial infarction [AMI; on clinical and electrocardiographic (ECG) evidence], (e) chronic obstructive pulmonary disease with chronic respiratory failure as defined by at least one of the following: previous acute exacerbation, chronic resting dyspnea, current therapy with bronchodilators or steroids, home oxygen therapy, (f) age under 18 years; (g) pregnancy, (h) contraindications to full face mask (facial wounds or dermal abrasions), (i) severe chronic renal failure (requiring hemodialysis), and (j) terminal chronic underlying illness.

Between January 1999 and January 2001 the study enrolled 36 patients. Randomization to receive either PAV ($n = 17$) or CPAP ($n = 19$) used a computer-generated random number sequence with stratification by center; assignments were placed in sealed envelopes available in each center. On inclusion the groups were similar regarding age, gender, overall severity, presumed cause of acute CPE and the amount of drugs administered for the acute event prior to inclusion (Table 1). Median time from the onset of medical treatment and randomization was 60 min (range 15–150 min) in the CPAP group and 90 min (range 30–190 min) in the PAV group ($p = 0.27$). Baseline physiological parameters did not differ between groups. Time from randomization to beginning of NIV was less than 5 min for all patients.

Study design

Patients transported to the ICU by ambulance or through the emergency room were treated with nasal O_2 or Venturi mask and conventional medical treatment. All patients were ventilated using a flow-triggering ventilator (Vision, Respironics, Murrysville, PA, USA) through

Table 1 Patients' baseline characteristics (*PAV*, proportional assist ventilation; *CPAP*, continuous positive airway pressure; *SAPS II*, Simplified Acute Physiology Score version II)

	PAV ($n = 17$)	CPAP ($n = 19$)	p
Age (years)	72 ± 15	77 ± 9	0.26
Sex: M/F	9/8	9/11	0.65
SAPS II	39 ± 17	38 ± 9	0.81
History			
Ischemic heart disease	10 (59%)	13 (68%)	0.73
Hypertension	8 (47%)	8 (42%)	0.99
Idiopathic myocardiopathy	2 (12%)	1 (5%)	0.59
Valvular disease	4 (24%)	3 (16%)	0.68
Drugs before inclusion			
Furosemide (mg)	85 ± 43	103 ± 66	0.33
Nitrates (mg)	4.9 ± 5.3	3.3 ± 3.3	0.32

a commercially available full face mask (Respironics). In the CPAP group positive end-expiratory pressure (PEEP) was set at 10 cmH_2O and reevaluated if needed according to patient tolerance. In the PAV group patients were ventilated in PAV mode with the following initial standard settings: volume assist (VA) 5 cmH_2O/ml, flow assist (FA) 2 $cmH_2O\ ml^{-1}\ s^{-1}$, proportional assist 100%, and PEEP 4 cmH_2O. VA and then FA were increased in increments of 2 cmH_2O until the "runaway" [21, 27, 28], and then reduced by 2 cmH_2O. The runaway was defined by sudden uncomfortable ventilation, the use of abdominal muscles at the end of inspiratory time, a prolonged inspiratory time and end-inspiratory "spikes" on flow and pressure curves for VA, and by uncomfortable ventilation and sudden inspiratory increase for FA. In both groups FIO_2 was 100% initially and then reduced every 10 min by 20% decrements to maintain SpO_2 above 90%.

Medical treatment during ventilation was standardized as follows: continuous infusion of nitroglycerin or isosorbide dinitrate from 1 to 4 mg/h to maintain a systolic arterial pressure between 120 and 150 mmHg. A single additional bolus of furosemide (1 mg/kg) or bumetanide (0.05 mg/kg) could be administered if diuresis after 1 h was below 100 ml/h. The minimal ventilation duration was 1 h. Weaning was attempted only in patients with a RR less than 25/min and SpO_2 more than 90% with FIO_2 of 50% or less. After weaning, ventilation was resumed if RR was greater than 30/min or SpO_2 was lower than 90% with FIO_2 above 50%.

Physiological measurements

Baseline assessment of patients included RR, SpO_2, heart rate, mean arterial pressure, GCS, chest radiography, ECG, arterial blood gases, creatine kinase, troponine I, Simplified Acute Physiology Score (SAPS) II. Clinical parameters were monitored regularly as long as necessary. Arterial blood gases were measured 30 min after starting ventilation and then 2 h after weaning or in the case of treatment failure. Creatine kinase, troponine I measurements and ECG were performed 6 h after starting ventilation. The following side effects were recorded: mask intolerance, severe arrythmia, cardiac arrest, severe arterial hypotension, complications of endotracheal intubation, AMI. The final diagnosis of AMI was established by an external cardiologist unaware of patient assignation group on the following: typical chest pain or evocative ECG findings and increase in CPK and/or troponine I.

Outcome measures

The primary outcome measure was the failure rate as defined by at least one of the following: (a) fulfillment of endotracheal intubation criteria defined after 30 min of NIV by at least one of the following: PaO_2 lower than 60 mmHg or SpO_2 greater than 90% with FIO_2 of 1, worsening of the dyspnea and either decrease less than 20% of RR or decrease in $PaCO_2$ less than 10% compared with baseline, stabilization of dyspnea but decrease below 20% of RR and decrease below 10% of $PaCO_2$ compared with baseline; (b) GCS less than 10; (d) respiratory rate lower than 8/min; (d) ventricular tachycardia; (e) circulatory arrest; and (f) patient's refusal. Improvement in physiological variables, duration of ventilatory support, myocardial infarction rate, and ICU mortality were defined as secondary outcome measures.

Table 2 Physiological mevasurements on inclusion. (*PAV*, proportional assist ventilation; *CPAP*, continuous positive airway pressure)

	PAV ($n=17$)	CPAP ($n=19$)	p
Respiratory rate (breaths/min)	39 ± 6	36 ± 4	0.07
Heart rate (beats/min)	111 ± 20	106 ± 25	0.59
Arterial pressure (mmHg)			
Systolic	137 ± 26	148 ± 38	0.32
Diastolic	69 ± 17	75 ± 25	0.48
Arterial pH	7.27 ± 0.10	7.21 ± 0.12	0.08
PaO_2 (mmHg)	66 ± 18	77 ± 31	0.22
$PaCO_2$ (mmHg)	51 ± 25	52 ± 20	0.83
Lactate (mmol/l)	4.6 ± 3.8	4.9 ± 3.6	0.82

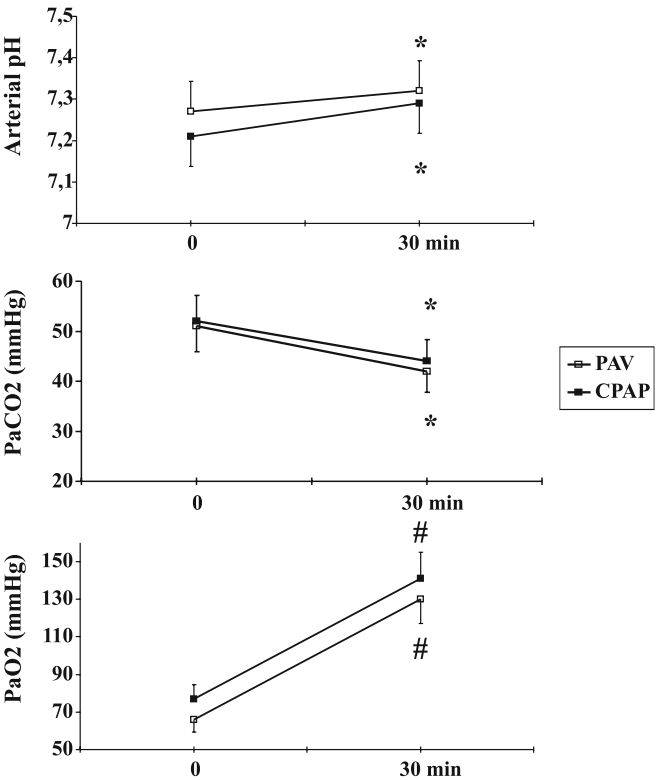

Fig. 1 Arterial pH, PaO_2, and $PaCO_2$ values just before (0) and 30 min after the onset of noninvasive ventilation. *PAV*, proportional assist ventilation; *CPAP*, continuous positive airway pressure. Values are means; *error bars* SEM. $^{*}p<0.05$, $^{\#}p<0.005$ vs. baseline

Statistical analysis

Based on our primary endpoint we hypothesized a 40% failure rate in the CPAP group and a 10% failure rate in the PAV group. The expected failure rate chosen for CPAP was deliberately higher than the average of 20% observed in previously published studies [6–8] since the failure criteria used in the present study were broader than in these studies where the failure rate was only related to endotracheal intubation. The 10% failure rate in the PAV group was determined arbitrarily since no data were available at the time of the study. With a β error of 20% and an α error of 5% we expected 25 patients per group under a unilateral hypothesis. We compared baseline categorical variables using Pearson's χ^2 or Fisher's exact test and quantitative variables using unpaired *t* test or Mann–Whitney test when appropriate. Within group comparisons across time were performed using analysis of variance for repeated measurements and paired *t* test when appropriate. Quantitative values are reported as mean ± standard deviation unless otherwise indicated. Difference with a *p* value less than 0.05 were considered statistically significant.

Results

Average PEEP was $9.3 \pm 2.0\,cmH_2O$ in the CPAP group and $4.2 \pm 0.6\,cm$ in the PAV group (Table 2). Peak inspiratory pressure was $14 \pm 5\,cmH_2O$ in the PAV group. After 30 min of ventilation the improvement in PaO_2 ($p < 0.005$), $PaCO_2$ ($p < 0.05$), and arterial pH ($p < 0.05$) were significant in both groups compared with baseline but did not differ with respect to the assignment group (Fig. 1). As presented in Fig. 2, time-related changes in

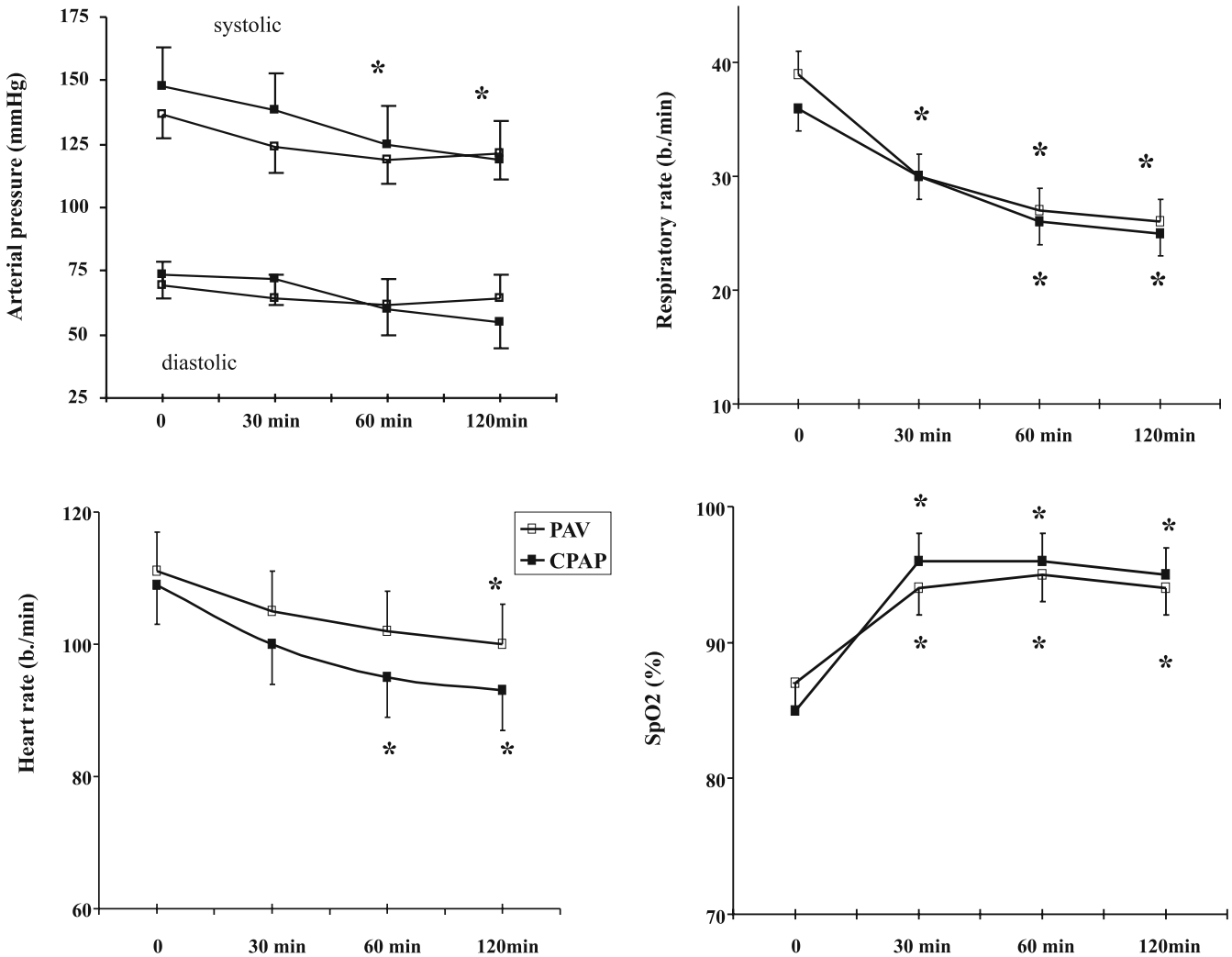

Fig. 2 Changes in physiological parameters for the first 120 min after inclusion. *PAV*, proportional assist ventilation; *CPAP*, continuous positive airway pressure. Values are means; *error bars* SEM. * $p < 0.05$ vs. baseline

Table 3 Patients outcomes according to study endpoints. (*PAV*, proportional assist ventilation; *CPAP*, continuous positive airway pressure)

	PAV ($n = 17$)	CPAP ($n = 19$)	p
Failures	7 (41%)	6 (31%)	0.99
Intubation criteria	5 (29%)	5 (26%)	
Patient refusal	2 (12%)	0	
Circulatory arrest	0	1 (5%)	
Endotracheal intubation	5 (29%)	4 (21%)	0.71
Time on NIV for failure, median (min; range)	105 (30–420)	52 (30–165)	0.82
Time on NIV for success, median (min; range)	127 (60–240)	145 (60–690)	0.85
Myocardial infarction	6 (35%)	7 (37%)	0.99
On admission[a]	3 (18%)	3 (16%)	
Within the first 6 h[b]	3 (18%)	4 (21%)	
ICU mortality	4 (23%)	4 (21%)	0.99
Length of ICU stay, median (days; range)	1 (0–39)	1 (0–33)	0.78

[a] Confirmed by significant enzymatic changes on sample drawn on admission
[b] Confirmed only by significant enzymatic changes on sample drawn 6 h after admission (normal enzymes on admission)

arterial pressure, heart rate, respiratory rate, and SpO_2 were statistically significant ($p < 0.01$), but there were no significant group-related differences.

According to our predefined criteria, there were 7 failures (41%) in the PAV group and 6 (31%) in the CPAP group ($p = 0.99$; Table 3). Of these, intubation criteria were fulfilled in five patients in each group. In the PAV group all patients who displayed intubation criteria were intubated, while the two patients who refused PAV were subsequently placed on other NIV modes (one with CPAP and one with NIPSV). In the CPAP group only three of the five patients with intubation criteria underwent intubation; the other two were kept on CPAP and recovered uneventfully. Finally, one additional patient was intubated in the CPAP group for sudden circulatory arrest. Median time on noninvasive ventilation until success was similar for each group (Table 3). Myocardial infarction and ICU mortality rates were similar in the two groups (Table 3).

Discussion

To summarize the present study, PAV was not associated with a better outcome with regard to failure rate, intubation rate, or ventilation time in acute, unresolving CPE. To our knowledge, this is the first randomized study to compare PAV and CPAP in CPE. Previously Patrick and colleagues [29] reported the use of PAV with a nasal or face mask in patients with acute respiratory failure. Five of these had acute CPE, and PAV was successful in four of these. Two studies [22, 23] comparing PAV and NIPSV, with 12% and 20% of patients having CPE, respectively, and most of the others having chronic obstructive pulmonary disease. The method used was very similar to ours. There were no differences between NIPSV and PAV in failure and mortality rates, but fewer complications and more comfort and tolerance with PAV.

Some limitations should be acknowledged. First, the number of patients screened and not included was not recorded; although there were no exclusions for consent refusal and no withdrawal in the included patients, we cannot speculate more about the reference population, which limits the impact of our conclusions. Second, the number of patients included was lower than planned since the progressive implementation of NIV both in the prehospital emergency medical units and in emergency departments during the course of our study considerably reduced the number of patients with severe CPE referred to our ICUs that constrained us to prematurely stop the study.

The failure rate in our study was rather high, in the upper range of those of previously published reports whether regarding our predefined failure rate, completion of endotracheal intubation, or ICU death. In a recent meta-analysis [3] gathering 389 patients with CPE, ventilated with either CPAP or NIPSV, 13% of them (range 0–35%) required endotracheal intubation and 11% died (range 0–28%). It is not easy to assess with precision whether the overall severity in the patients included in the present study could account for these failure rates. Although mean SAPS II was far higher in our study than in the large multicenter study by Nava et al. [12], the intubation rates were similar in the two studies. A recent prospective survey of 70 French ICU [30] observed NIV failure in 38 of 225 patients (17%) with CPE or acute on chronic respiratory failure, with a median SAPS II of 38, a severity close to that of our population. Lactate levels on inclusion, which might be interpreted as an additional severity index, were higher than in similar studies in which intubation rates were 5% [11] and 20% [12], respectively. Their significance in cardiac failure is probably more related on respiratory muscle production than global tissue hypoxia [31]. However, specific prognosis variables for immediate success of noninvasive ventilation have

not yet been determined. For instance, CPE related to hypertensive crisis may have different prognosis than non-hypertensive CPE [32]. Finally, the patients we included still presented hypoxemia, despite medical treatment considered satisfactory for many patients in clinical practice. Therefore NIV may be considered as a kind of rescue therapy, thus selecting a more severe population than in some other studies.

We found no differences in the rates of myocardial infarction between the two groups. To further evaluate the potential role of NIV we differentiated between the rates of AMI present on inclusion from AMI occurring within 6 h. All patients with AMI displayed no evocative clinical symptoms, and this diagnosis was therefore made only on the basis of enzymatic elevation and consistent ECG changes. This explains why three patients in each group were included despite having AMI, the diagnosis of which being confirmed only after the results of the enzymes sampled on admission became available. These findings are consistent with a trial specifically designed to address the potential role of NIV on myocardial infarction which found no difference in the AMI rates between CPAP and NIPSV [17]. In addition, a recent meta-analysis [5] suggested that either CPAP or NIPSV in patients with CPE does not increase the risk of AMI.

PAV, as with PSV, may unload respiratory muscles during an increase in the patient's inspiratory effort [33]. The potential value of PAV to improve patient-ventilator synchrony, breathing comfort, and physiological variables in comparison to PSV has been confirmed by several randomized studies [22, 23, 26]. These findings are not confirmed in the present study where the reference group received CPAP. Several hypotheses may be raised to explain these data. First, the number of patients was relatively low, thus reducing the power of this trial to detect relatively small differences between PAV and CPAP. However, we observed no trend to a smaller failure rate with PAV, either with regard to intubation rate or patient's refusal of the technique that discourages one to plan a large scale study. Second, it is possible that VA and FA settings in PAV were suboptimal, at least in some patients. In NIV it is not possible to know the patient's respiratory elastance and resistance to set proportionality between inspiratory pressure generated by ventilator and patient's instantaneous inspiratory effort, justifying the runaway method to adjust VA and FA. Was this method inappropriate? Although the answer remains uncertain, the fact that two patients refused the technique after a few minutes of application would be consistent with this hypothesis.

Third, did we compare comparable methods? As in several previous studies [15, 17–19], PEEP was set at a higher level in CPAP (about 10 cmH_2O) than in PAV (about 5 cmH_2O), probably resulting in close mean intrathoracic pressures in each group. In CPE cases CPAP has been demonstrated to improve oxygenation and lung mechanics and to decrease work of breathing [14, 33]. These effects were more marked for a CPAP level at 10 cmH_2O than 5 cmH_2O in one study [34], but not in the other [14]. A superimposed inspiratory positive airway pressure increased tidal volume and further decreased work of breathing by inspiratory unloading [14]. However, this potential benefit was not found to be clinically relevant in a study which displayed neither benefit nor harm by using a bilevel positive airway pressure (expiratory 10 cmH_2O, inspiratory 15 cmH_2O) compared with a 10 cmH_2O CPAP [16]. Although 80 patients were included in this study, only 20% had hypercapnia ($PaCO_2 > 45$ mmHg) which keeps open the possibility of positive effects of bilevel positive airway pressure in a more severe sample population. Taken together the data from available literature and the present findings suggest that applying an expiratory pressure in these patients is probably more relevant than relief of inspiratory workload by inspiratory pressure support.

In conclusion, our study found no differences between PAV and CPAP in patients with acute respiratory failure subsequent to CPE. There was no evidence of increased risk for myocardial infarction in patients with PAV. Since the implementation of NIV in the prehospital setting and emergency departments is now widely developed, CPAP, an easy to use, relatively cheap method of NIV, remains the gold standard in these patients.

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