Intensive Care Med (2011) 37:249–256
DOI 10.1007/s00134-010-2082-3

ORIGINAL

Semir Nouira
Riadh Boukef
Wahid Bouida
Wieme Kerkeni
Kaouther Beltaief
Hamdi Boubaker
Latifa Boudhib
Mohamed Habib Grissa
Mohamed Naceur Trimech
Hamadi Boussarsar
Mehdi Methamem
Soudani Marghli
Mondher Ltaief

Non-invasive pressure support ventilation and CPAP in cardiogenic pulmonary edema: a multicenter randomized study in the emergency department

Received: 18 September 2009
Accepted: 6 July 2010
Published online: 7 December 2010

This article is discussed in the editorial available at:
doi:10.1007/s00134-010-2084-1.

S. Nouira (✉) · R. Boukef · W. Bouida · W. Kerkeni · K. Beltaief · H. Boubaker · L. Boudhib · M. H. Grissa · M. N. Trimech
Emergency Department and Research Unit UR06SP21, Fattouma Bourguiba University Hospital, 5000 Monastir, Tunisia
e-mail: semir.nouira@rns.tn
Tel.: +216-73-532014
Fax: +216-73-460678

S. Marghli
Emergency Department,
Tahar Sfar University Hospital,
5100 Mahdia, Tunisia

M. Methamem
Emergency Department, Sahloul University Hospital, 4000 Sousse, Tunisia

H. Boussarsar
Medical Intensive Care Unit and Emergency Department, Farhat Hached University Hospital, 4000 Sousse, Tunisia

M. Ltaief
Department of Preventive Epidemiology, Fattouma Bourguiba University Hospital, 5000 Monastir, Tunisia

Abstract *Introduction:* Noninvasive pressure support ventilation (NIPSV) and continuous positive airway pressure (CPAP) are both advocated in the treatment of cardiogenic pulmonary edema (CPE); however, the superiority of one technique over the other has not been clearly demonstrated. With regard to its physiological effects, we hypothesized that NIPSV would be better than CPAP in terms of clinical benefit. *Methods:* In a prospective, randomized, controlled study performed in four emergency departments, 200 patients were assigned to CPAP ($n = 101$) or NIPSV ($n = 99$). Primary outcome was combined events of hospital death and tracheal intubation. Secondary outcomes included resolution time, myocardial infarction rate, and length of hospital stay. Separate analysis was performed in patients with hypercapnia and those with high B-type natriuretic peptide (>500 pg/ml). *Results:* Hospital death occurred in 5 (5.0%) patients receiving NIPSV and 3 (2.9%) patients receiving CPAP ($p = 0.56$). The need for intubation was observed in 6 (6%) patients in the NIPSV group and 4 (3.9%) patients in the CPAP group ($p = 0.46$). Combined events were similar in both groups. NIPSV was associated to a shorter resolution time compared to CPAP (159 ± 54 vs. 210 ± 73 min; $p < 0.01$), whereas the incidence of new myocardial infarction was not different between both groups. Similar results were found in hypercapnic patients and those with high B-type natriuretic peptide. *Conclusions:* During CPE, NIPSV accelerates the improvement of respiratory failure compared to CPAP but does not affect primary clinical outcome either in overall population or in subgroups of patients with hypercapnia or those with high B-type natriuretic peptide.

Keywords Cardiogenic pulmonary edema · Continuous positive airway pressure · Non-invasive ventilation

Introduction

Although the majority of patients with cardiogenic pulmonary edema (CPE) respond to conventional medical therapy, some patients require at least temporarily ventilatory support. This has been traditionally accomplished via endotracheal intubation and mechanical ventilation, which is associated with significant complication rates. In the past 2 decades, noninvasive positive pressure ventilation has emerged as an important tool in

the treatment of acute respiratory failure, with strong evidence supporting the use of this technique to treat CPE [1–3]. Essentially, there are two modalities, continuous positive airway pressure (CPAP) and non-invasive pressure support ventilation (NIPSV). Both modalities have shown their superiority over conventional oxygen therapy with respect to gas exchange and physiological parameters [4, 5]. Despite a physiological rationale that NIPSV could provide more benefit than CPAP [6, 7], NIPSV has not been found to offer any advantage in terms of intubation or death rates compared with CPAP [8–15]. In contrast to many other trials and to systematic reviews, the largest and most recently published trial [16] (3CPO) showed that there was no difference in intubation rate or mortality with either CPAP or NIPSV compared to standard therapy; however, the intubation rates were very low. In addition, a high proportion of crossovers were permitted, which led to a considerable cross-contamination among the treatment groups. Consequently, definitive conclusions regarding the effects of NIPSV on clinical outcome cannot be made.

In the present study we assessed the potential beneficial and adverse effects of NIPSV and CPAP in patients admitted to the emergency department (ED) with clinical signs of CPE. Our hypothesis is that NIPSV would be better than CPAP in terms of clinical benefit. We also compared both ventilator support in the subgroup of patients with significant hypercapnia and the subgroup of patients with severe congestive heart failure defined by serum BNP concentrations >500 pg/ml.

Materials and methods

This is a randomized controlled study comparing the effects of CPAP to NIPSV in acute CPE patients. The study design was approved by our institutional ethics committee, and all patients or their next of kin gave written informed consent. Written consent was obtained from the patient's relatives at the start of the protocol. Four tertiary care centers were involved in this prospective study conducted in the Emergency Department from January 2005 to June 2008. Inclusion criteria were the presence of an acute clinical condition consistent with acute CPE including dyspnea, bilateral rales on auscultation, and typical findings of congestion on chest radiography without a history suggesting pulmonary aspiration or evidence of pneumonia. In addition, two of the following criteria had to be present: respiratory rate higher than 30 min^{-1}, use of accessory respiratory muscles or paradoxical abdominal motion, and SpO_2 <90% with oxygen supplementation >5 l/min through a bag reservoir mask. Exclusion criteria were: requirement of immediate endotracheal intubation, systolic arterial pressure <90 mmHg, severe arrhythmia, bradycardia <50 min^{-1}, Glasgow coma score <14, evidence of ongoing acute myocardial infarction, severe chronic renal failure (serum creatinine concentration >250 μmol/l), known chronic lung disease, and serum BNP level <100 pg/ml. Patients were also excluded if they were not able to cooperate, if they had any condition that precluded the application of a face mask, or were pregnant.

Protocol design and measurements

After enrollment, all patients were placed in a semi-recumbent position and received the following standard medical treatment: oxygen therapy to obtain an SpO_2 >90% via a reservoir mask, intravenous boluses of isosorbide dinitrate 5 mg every 3 min, and continued if systolic arterial pressure did not decrease to less than 110 mmHg, and intravenous furosemide 40 mg. Patients with fast atrial fibrillation received digoxin. Monitoring by pulse oximetry and electrocardiography was started, and urinary output was monitored through a Foley catheter. Patients were assigned to CPAP or NIPSV according to a random-numbers table and opaque, sealed, numbered envelopes. Randomization was performed with variable block sizes and was stratified according to the study center. Masking of treatment allocation was not possible. CPAP was performed with the Boussignac CPAP device [17] (Vygon, 95440 ECOUEN, France), which is a small, light weight plastic cylinder that is directly connected to a face mask. The jet flow of the air-oxygen mixed gas was adjusted to apply an end-expiratory pressure level of 10 cmH_2O. The air-oxygen ratio was adjusted to keep SpO_2 above 90%. NIPSV was delivered with a mechanical ventilator (Raphael Silver, Hamilton Medical AG, Switzerland); the fraction of inspired oxygen (FiO_2) was adjusted to achieve the desired SpO_2, and end-expiratory pressure (PEEP) of 5 cmH_2O was administered to all patients. The degree of pressure support was adjusted to obtain an expiratory tidal volume between 6 and 8 ml/kg. Heart rate, breathing frequency, and SpO_2 were monitored continuously. Arterial blood pressure was non-invasively measured every 5 min during the first 2 h, and arterial blood gases were recorded at the time of the study entry and every hour for 3 h then at 6 h. Chest radiograph and routine blood chemistry were obtained at the time of study entry. Severity of acute illness was assessed by the APACHE II (acute physiology and chronic health evaluation II) score determined at admission. Blood samples were performed to measure BNP (Biosite Incorporated, San Diego, CA) at admission and troponin I (third generation) at admission and 6 h later. According to the protocol, the duration of CPAP or NIPSV was 6 h, but if the patient responded rapidly (respiratory rate <30 min^{-1} and SpO_2 >96% under O_2 supplementation <3 l/min in the CPAP group or under FiO_2 <35% in the NIPSV group), protocol treatments could be stopped earlier

[4, 14]. The time interval between protocol start and early respiratory improvement defined the resolution time. At the end of the 6 h study period in the ED, patients were transferred to the medical ward or admitted to the ICU if they required intubation or did not improve (i.e., still fulfilled the inclusion criteria). They were followed up until hospital discharge or death.

Outcome measures

The primary outcomes were combined events including hospital death and tracheal intubation rates. Endotracheal intubation was decided when, despite optimal respiratory assistance, at least two of the following conditions were present: SpO_2 lower than 90%, worsening of the dyspnea with an increase of the respiratory rate more than 20% above its initial value, an increase in $PaCO_2$ more than 10% compared with baseline, Glasgow coma score <13, and respiratory rate lower than 8 breaths/min. Secondary outcomes included resolution time, acute myocardial infarction rate, and length of hospital stay. The diagnosis of acute myocardial infarction was based on ECG findings and cardiac biomarker changes with a senior cardiologist approval.

Statistical analysis

Based on previous studies we hypothesized a 30% rate of combined primary outcomes (mortality, endotracheal intubation) in the CPAP group. We estimate that a sample size of 200 patients would allow detecting a 15% absolute difference in the rate of combined events between the two groups with a study power of 80% at 5% two-sided level of significance. Data are presented as mean ± SD unless otherwise specified. The effects of the two ventilation modes on the primary and secondary outcomes were assessed and compared on an intention-to-treat basis. We compared baseline categorical variables with a chi^2 test. The McNemar test was used for pairwise comparisons. Quantitative variables were compared using unpaired *t* test or Mann-Whitney test when appropriate. Changes in PaO_2 for the NIPSV and CPAP groups were evaluated using repeated measures analysis of variance (ANOVA). Kaplan-Meier analysis was used to estimate respiratory improvement probability over time. A post-hoc analysis was carried out separately among patients with hypercapnia ($PaCO_2$ more than 45 mmHg) and patients with a BNP level >500 pg/ml, a cutoff value that has been shown to be a powerful predictive marker of a low left ventricular ejection fraction [18]. All hypothesis tests were two-sided, and difference with a p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (Version 13.0, Chicago, IL).

Results

Of 245 potentially eligible patients, 200 were screened and underwent randomization; 101 patients were assigned to CPAP therapy and 99 to NIPSV. Twenty-nine patients were excluded from the study because diagnosis of CPE was not confirmed (in all these patients the BNP concentration was <100 pg/ml). In the remaining patients ($n = 16$), no informed consent was obtained ($n = 11$), and immediate intubation was need ($n = 5$). After randomization, eight patients did not receive the allocated intervention (6 in the CPAP group and 2 in the NIPSV group). Thus, 95 patients in the CPAP group and 97 in the NIPSV group (Fig. 1) received the allocated intervention. There were no significant differences in baseline characteristics among the two groups. Hypercapnic patients and those with BNP concentration >500 pg/ml were equally distributed between the two treatment groups (Table 1). After the initial adjustments, the ventilator settings were set at 13.5 ± 3.6 cmH_2O for the inspiratory support and at 5.1 ± 1.2 for PEEP in the NIPSV group. In the CPAP group, the mean applied expiratory pressure was 8.9 ± 2.5 cmH_2O.

Primary outcomes

Table 2 shows that there were no significant differences between the two treatment groups in hospital mortality or the need for endotracheal intubation. The cause of death was related to severe heart failure in all but three patients. The rate of combined events including death and endotracheal intubation was not significantly different between the NIPSV group and CPAP group (11.1 vs. 6.9%, respectively; absolute difference 4.2%; 95% CI −3.7 to 12.1; $p = 0.64$). Combined death and intubation rates occurred significantly more often in patients with hypercapnia than in the overall population (23.2 vs. 9%; $p = 0.009$); however, the difference was not statistically significant between patients with high BNP and overall population (15.5 vs. 9%; $p = 0.178$). There was no statistically significant difference regarding primary outcomes between NIPSV and CPAP in these selected groups (Table 3).

Secondary outcomes

Mean PaO_2 increased, whereas blood pressure, respiratory rate, and heart rate decreased similarly in both groups as shown in Fig. 2. Resolution time was significantly shorter in the NIPSV group compared to the CPAP group (159 ± 54 vs. 210 ± 73 min; $p < 0.01$). The resolution time course of each group is shown in Kaplan-Meier curves (Fig. 3). Four patients in the NIPSV group and two patients in the CPAP group developed an acute myocardial

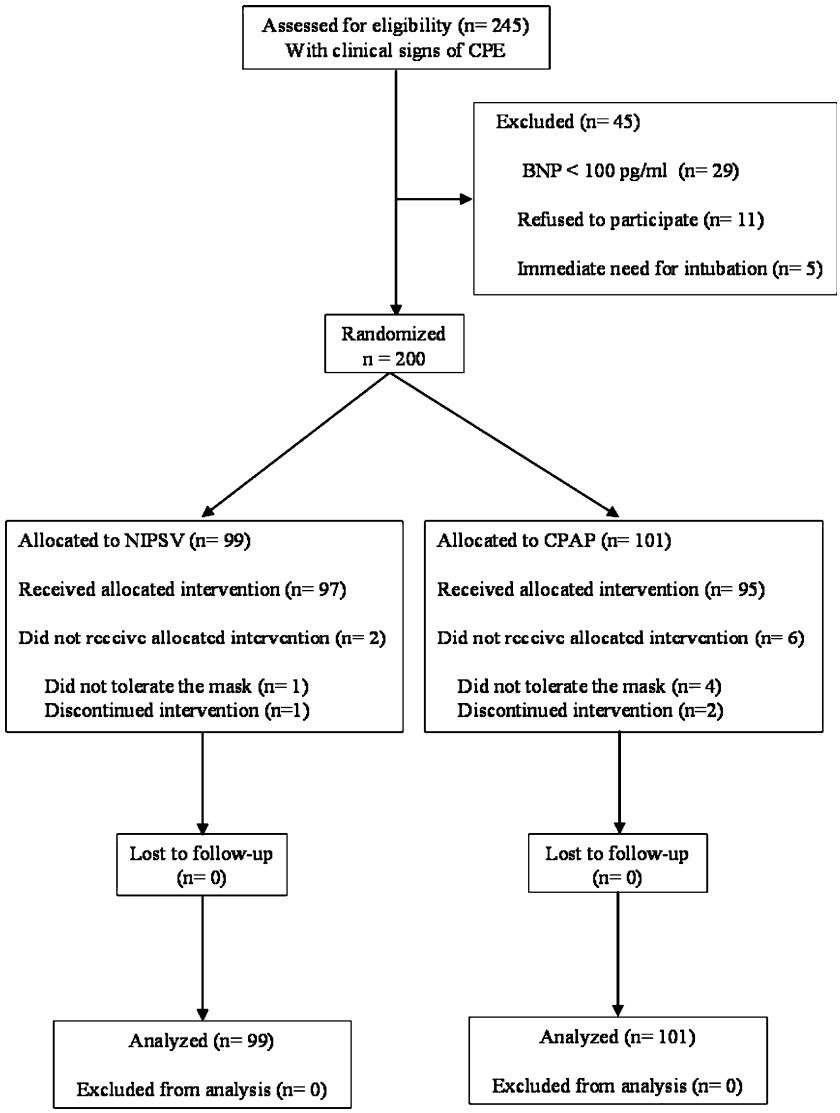

Fig. 1 Trial profile

infarction during their hospital stay (difference not significant). The proportion of patients who increased their troponin level from baseline was similar in both groups (6 ± 4 vs. $4 \pm 3\%$ in NIPSV and CPAP group, respectively), as mean length of hospital stay (9 ± 3 vs. 11 ± 4 days in NIPSV and CPAP group, respectively).

Discussion

The primary finding of this study conducted in patients with CPE is that NIPSV was associated with similar outcome in comparison to CPAP therapy as assessed by combined events of death and intubation rates. In the subgroups of patients with hypercapnia and those with BNP >500 pg/ml, the same results were observed. NIPSV was associated with a significantly shorter resolution time compared to the CPAP group; however, neither the rate of acute myocardial infarction nor the proportion of patients who increased their serum troponin level from baseline was significantly different between the two groups.

Previous studies have suggested that positive pressure ventilation improves hemodynamics in heart failure patients by increasing intrathoracic pressure [19–21]. Positive pressure ventilation reduces cardiac preload by impeding cardiac filling and reduces cardiac afterload by reducing left ventricular trans-mural pressure. These effects could be obtained either by CPAP or pressure support ventilation where an inspiratory positive airway pressure is added. Our study failed to demonstrate a difference in efficacy between both techniques, which is in accordance with previous randomized clinical trials [5, 13, 14, 22] and subsequent meta-analyses [8–12]. Similar efficacy of both CPAP and NIPSV in terms of needs for endotracheal intubation and death was also demonstrated in a recent study conducted in

Table 1 Baseline characteristics

	NIPSV ($n = 99$)	CPAP ($n = 101$)	Difference (95% CI)
Age, years (SD)	69 ± 11	69 ± 9	0 (−2.8 to 2.8)
Male, sex (%)	46	41	5% (−9 to 19)
Cause of heart failure, *n* (%)			
Ischemic heart disease	28 (28)	27 (27)	1% (−11 to 13)
Congestive heart failure	30 (30)	33 (33)	−3% (−16 to 10)
Hypertension	73 (74)	69 (68)	6% (−6 to 18)
Diabetes mellitus, *n* (%)	54 (55)	53 (52)	3% (−11 to 17)
APACHE II	16 ± 5	16 ± 5	0 (−1 to 1)
NYHA class III and IV, *n* (%)	69 (70)	68 (67)	3% (−9.8 to 15.8)
PaO_2, mean (mmHg)	59 ± 16	56 ± 21	3 (−11 to 15)
$PaCO_2$			
Mean (mmHg)	40 ± 13	41 ± 11	−0.8 (−3.7 to 2.2)
≥45 mmHg, *n* (%)	29 (29)	27 (27)	2% (−10 to 10)
Serum BNP[a]			
Median (pg/ml)	407	399	ns
>500, *n* (%)	38 (38)	37 (37)	1% (−12 to 14)
Serum troponin[b], median (pg/ml) (IQR)	0.03 (0.01–0.12)	0.02 (0.01–0.08)	ns

Data are given as mean ± SD or number of patients and percentage of each group as appropriate

CPAP continuous positive airway pressure, *NIPSV* noninvasive pressure support ventilation, *APACHE* acute physiology and chronic health evaluation, *NYHA* New York heart association, PaO_2 partial pressure of arterial oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, *BNP* brain natriuretic peptide, *ns* not significant, *IQR* interquartile range

[a] Normal values <100 pg/ml

[b] <0.1 pg/ml

Table 2 Primary outcomes

	NIPSV ($n = 99$)	CPAP ($n = 101$)	Difference (95% CI)	*p*
Death, *n* (%)	5 (5.0)	3 (2.9)	2.1% (−3.4 to 7.5)	0.563
Intubation, *n* (%)	10 (10.1)	7 (6.9)	3.2% (−4.9 to 11.5)	0.457
Combined events[a], *n* (%)	11 (11.1)	7 (6.9)	4.2% (−3.7 to 12.1)	0.485

CPAP continuous positive airway pressure, *NIPSV* noninvasive pressure support ventilation, *BNP* brain natriuretic peptide

[a] When both events (death and intubation) occurred in the same patient, only the worst one (death) was considered

Table 3 Outcomes in hypercapnic patients and in patients with high BNP (>500 pg/ml) in NIPSV and CPAP groups

	NIPSV	CPAP	Difference (95% CI)	*p*
Death, *n*/total (%)				
Hypercapnia	3/29 (10.3)	2/27 (7.4)	2.9% (−14.4 to 19.9)	0.997
High BNP	1/37 (2.7)	2/34 (5.9)	3.2% (−8.7 to 16.6)	0.603
Intubation *n*/total (%)				
Hypercapnia	7/29 (24.1)	4/27 (14.8)	9.3% (−11.9 to 29.4)	0.588
High BNP	7/37 (18.9)	4/34 (11.7)	2.2% (−10.4 to 24.0)	0.614
Combined events[a], *n*/total (%)				
Hypercapnia	8/29 (27.6)	5/27 (18.5)	9.1% (−12.7 to 30.9)	0.645
High BNP	7/37 (18.9)	4/34 (11.8)	7.1% (−9.5 to 23.7)	0.692

CPAP continuous positive airway pressure, *NIPSV* noninvasive pressure support ventilation, *BNP* brain natriuretic peptide

[a] When both events (death and intubation) occurred in the same patient, only the worst one (death) was considered

26 Scottish emergency departments. Most of these studies were published after we designed our trial, which raised the question whether their results could dissolve the rationale of the present study. We believe that to date, we cannot conclude definitively that there is no difference between CPAP and NIPSV in terms of death and intubation rates. In the most recent meta-analysis by Potts, which included the 3CPO trial, it was shown that non-invasive ventilation was superior to conventional treatment, but no comparison was done between NIPSV and CPAP [23]. Important methodological limitations characterize many of the studies conducted in this issue, including small sample size, patient selection, and few observed events which restrict the generalizability of the results to all patients with CPE. Although

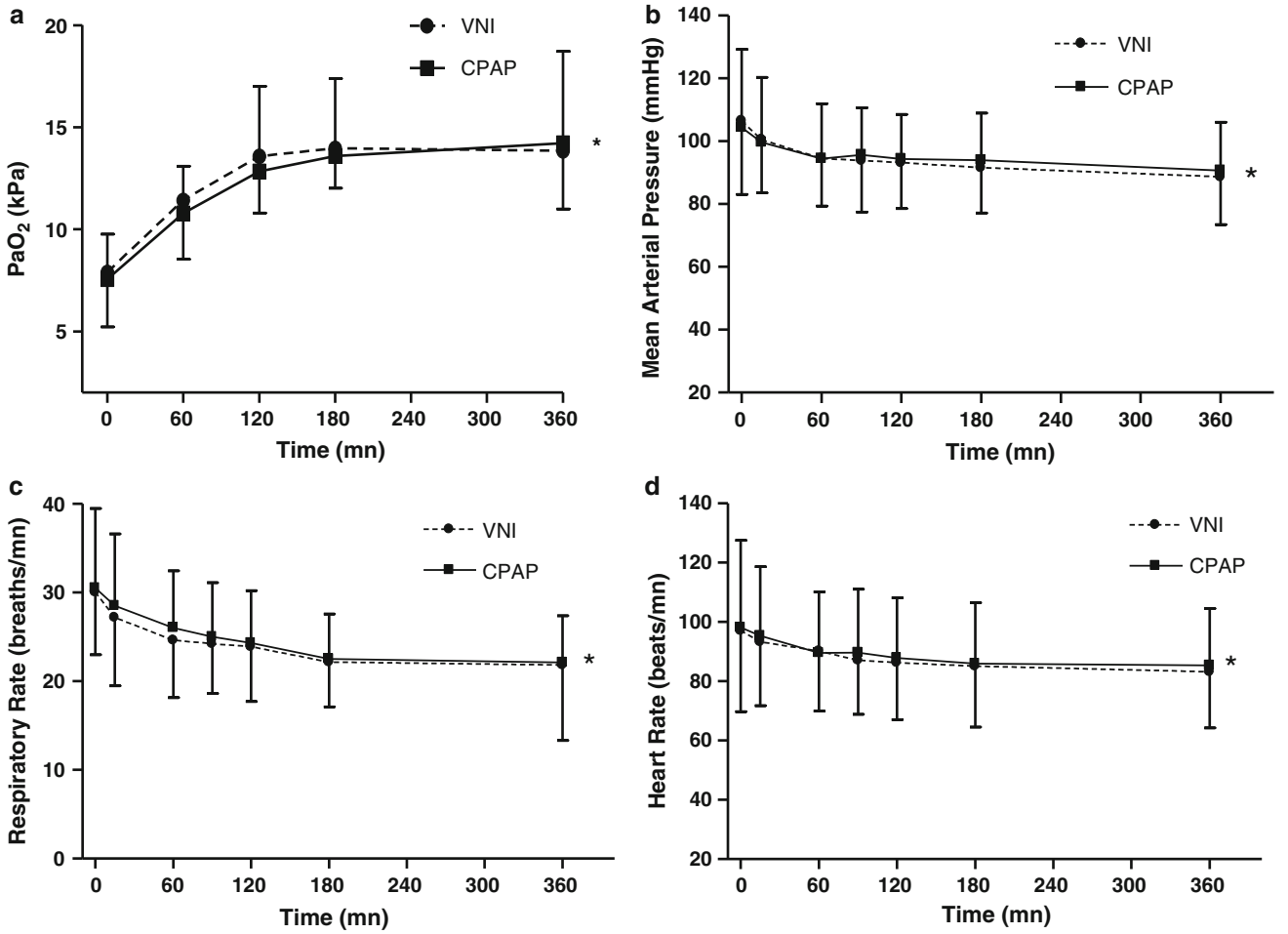

Fig. 2 PaO_2 (**a**), mean arterial pressure (**b**), respiratory rate (**c**), and heart rate (**d**) over time in patients receiving noninvasive pressure support ventilation (NIPSV) or continuous positive airway pressure (CPAP). *$p < 0.05$ for difference between values at baseline and at 360 min

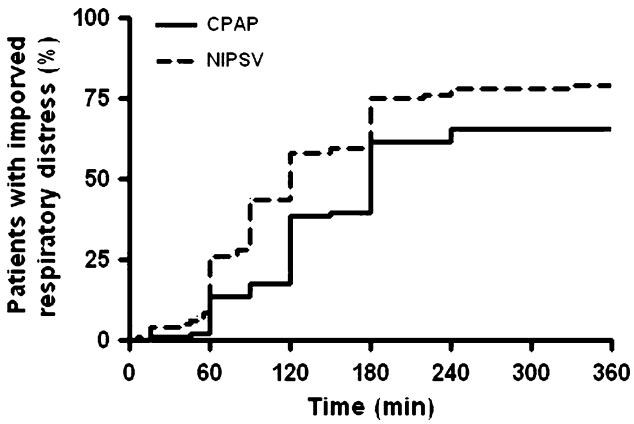

Fig. 3 Cumulative events (resolution time) were significantly higher for the noninvasive pressure support ventilation (NIPSV) group compared to continuous positive airway pressure (CPAP) group (log rank test, $p < 0.01$)

we did not avoid all the potential biases that could alter our results, we should highlight that our study is one of the largest individual randomized controlled trials comparing CPAP and NIPSV in patients with CPE. In addition, we know of no study so far that has compared the effect of NIPSV and CPAP in a selected group of patients with high BNP levels consistent with severe LV dysfunction. In our study we did a separate analysis for these patients, but we did not observe a greater success rate with NIPSV compared to CPAP in this subgroup of patients. Likewise, we did not find that patients with hypercapnia responded successfully to NIPSV more than CPAP [6, 7]. These findings suggest that in CPE, applying an expiratory pressure is probably more relevant than relief of inspiratory workload by inspiratory pressure support. In addition, our study showed that both respiratory supports were well tolerated, and adds support to the lack of relationship between NIPSV and the occurrence of myocardial infarction [24, 25].

Several limitations of this study should be acknowledged. First, retrospectively, our initial estimation of a 30% rate and 15% absolute difference in the combined primary outcomes between NIPSV and CPAP seems excessive. However, considerable variations in clinical outcomes have been reported in the previous studies [12], which highlights important differences in patient characteristics, concomitant therapies, and thresholds for intubation decision. Second, although it is not certain that all patients included in the study presented an acute CPE, we believe that the rate of false diagnosis is low in our study as all patients were examined by at least one emergency physician senior and, when required, by a cardiologist. In addition, we used BNP measurement to improve our diagnostic performance. Third, the protocol treatment was unblinded with the possibility of a bias either on the part of the investigators or clinicians. However, blinding of the investigators in our study was obviously not feasible. In addition, the use of objective clinical parameters such as death and intubation rates as primary outcome could circumvent this potential bias in many respects. Fourth, at the end of the 6-h period, our patients were transferred to general wards, and thus we did not have data on the treatment intensity and the inward decisions to sustain intensive therapies. Finally, the exclusion of patients with chronic lung diseases may not reflect the type of patients with CPE managed in the "real world" as a substantial proportion of patients with CPE have COPD or other chronic respiratory diseases. In our study, only 19 patients (7.7%) had a confirmed COPD, which might reflect a possible underestimation of the true prevalence.

In conclusion, our data can be added to the accumulating evidence underscoring the same effect of NIPSV compared to CPAP on death and intubation rates in CPE, apart from the fact that NIPSV is associated with a more rapid improvement in respiratory failure. The same results were observed in patients with hypercapnia and in those with severe congestive heart failure.

Acknowledgments We thank Miss Hela Souied and Miss Imen Sassi for their help in drafting the manuscript. This study was supported by a grant from the Tunisian State Department of Research.

References

1. Hill NS, Brennan J, Garpestad E, Nava S (2007) Noninvasive ventilation in acute respiratory failure. Crit Care Med 35:2402–2407
2. Peñuelas O, Frutos-Vivar F, Esteban A (2007) Noninvasive positive pressure ventilation in acute respiratory failure. CMAJ 177:1211–1218
3. Ambrosino N, Vagheggini G (2008) Noninvasive positive pressure ventilation in acute care setting: where are we? Eur Respir J 31:874–886
4. Masip J, Betbesé AJ, Páez J, Vecilla F, Cañizares R, Padró J, Paz MA, de Otero J, Ballús J (2000) Non invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary edema: a randomised trial. Lancet 356:2126–2132
5. Park M, Sangean MC, Volpe Mde S, Feltrim MI, Nozawa E, Leite PF, Passos Amato MB, Lorenzi-Filho G (2004) Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. Crit Care Med 32:2407–2415
6. Nava S, Carbone G, DiBattista N, Bellone A, Baiardi P, Cosentini R, Marenco M, Giostra F, Borasi G, Groff P (2003) Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomised trial. Am J Respir Crit Care Med 168:1432–1437
7. Chadda K, Annane D, Hart N, Gajdos P, Raphael JC, Lofaso F (2002) Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. Crit Care Med 30:2457–2461
8. Masip J, Roque M, Sánchez B, Fernández R, Subirana M, Expósito JA (2005) Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. JAMA 294:3124–3130
9. Winck JC, Azevedo LF, Costa-Pereira A, Antonelli M, Wyatt JC (2006) Efficacy and safety of non-invasive ventilation in the treatment of acute cardiogenic pulmonary edema—a systematic review and meta-analysis. Crit Care 10:R69
10. Ho KM, Wong K (2006) A comparison of continuous and bi-level positive airway pressure non-invasive ventilation in patients with acute cardiogenic pulmonary edema: a meta-analysis. Crit Care 10:R49
11. Collins SP, Mielniczuk LM, Whittingham HA, Boseley ME, Schramm DR, Storrow AB (2006) The use of noninvasive ventilation in emergency department patients with acute cardiogenic pulmonary edema: a systematic review. Ann Emerg Med 48:260–269
12. Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD (2006) Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary edema: a meta-analysis. Lancet 367:1155–1163
13. Moritz F, Brousse B, Gellée B, Chajara A, L'Her E, Hellot MF, Bénichou J (2007) Continuous positive airway pressure versus bilevel noninvasive ventilation in acute cardiogenic pulmonary edema: a randomized multicenter trial. Ann Emerg Med 50:666–675
14. Bellone A, Vettorello M, Monari A, Cortellaro F, Coen D (2005) Noninvasive pressure support ventilation vs. continuous positive airway pressure in acute hypercapnic pulmonary edema. Intensive Care Med 31:807–811
15. Mehta S, Al-Hashim A, Keenan S (2009) Noninvasive ventilation in patients with acute cardiogenic pulmonary edema. Respir Care 54:186–195
16. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, 3CPO Trialists (2008) Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 359:142–151

17. Maitre B, Jaber S, Maggiore SM, Bergot E, Richard JC, Bakthiari H, Housset B, Boussignac G, Brochard L (2002) Continuous positive airway pressure during fiberoptic bronchoscopy in hypoxemic patients. A randomized double-blind study using a new device. Am J Respir Crit Care Med 162:1063–1067
18. Koç M, Bozkurt A, Yildiray-Sahin D, Unal I, Acartürk E (2009) Cutoff values of NT-proBNP for the prediction of low functional capacity, decreased ejection fraction and cardiovascular events in patients with heart failure. Cardiol J 16:43–49
19. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP (1992) Cardiac output response to continuous positive airway pressure in congestive heart failure. Am Rev Respir Dis 145:377–382
20. Naughton MT, Raman MK, Hara K, Floras JS, Bradley TD (1995) Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. Circulation 91:1725–1731
21. Lenique F, Habis M, Lofaso F, Dubois-Randé JL, Harf A, Brochard L (1997) Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. Am J Respir Crit Care Med 155:500–505
22. Cross AM, Cameron P, Kierce M, Ragg M, Nelly AM (2003) Non invasive ventilation in acute respiratory failure: a randomized comparison of continuous positive airway pressure and bi-level positive airway pressure. Emerg Med J 20:531–534
23. Potts JM (2009) Noninvasive positive pressure ventilation: effect on mortality in acute cardiogenic pulmonary edema: a pragmatic meta-analysis. Pol Arch Med Wewn 119:349–353
24. Bellone A, Monari A, Cortellaro F, Vettorello M, Arlati S, Coen D (2004) Myocardial infarction rate in acute pulmonary edema: noninvasive pressure support ventilation versus continuous positive airway pressure. Crit Care Med 32:1860–1865
25. Ferrari G, Olliveri F, De Filippi G, Milan A, Aprà F, Boccuzzi A, Converso M, Navalesi P (2007) Nonivasive positive airway pressure and risk of myocardial infarction in acute cardiogenic pulmonary oedema. Chest 132:1804–1809