

# Bi-level Versus Continuous Positive Airway Pressure in Acute Cardiogenic Pulmonary Edema: A Randomized Control Trial

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**Abstract:** This study was to compare the efficacy of continuous, bi-level positive airway pressure (CPAP, Bi-PAP) and oxygen therapy on detailed observation of time-course change in blood gases, physiological parameters and rate of endotracheal intubation in patient with acute cardiogenic pulmonary edema (ACPE). Sixty-six patients with ACPE were randomly assigned to receive standard oxygen (O<sub>2</sub>) therapy (n=23), CPAP (n=21), and Bi-PAP (n=22). Blood gases (PaCO<sub>2</sub>, PaO<sub>2</sub>, SaO<sub>2</sub>, pH, and HCO<sub>3</sub>), and physiological parameters (HR, RR, SBP, and DBP) were collected at baseline (T0), immediately after 60 minutes (T60), and after 30 minutes of discontinuation (T90). A significant improvements (p<0.05) in PaCO<sub>2</sub>, PaO<sub>2</sub>, SaO<sub>2</sub> and vital signs were observed immediately after CPAP and Bi-PAP when compared to O<sub>2</sub> therapy. After 30 minutes of disconnection, Bi-PAP revealed significant improvement (p<0.05) in PaO<sub>2</sub>, SaO<sub>2</sub>, and respiratory rate. No differences on intubation and death rate detected among treatment groups. Both methods of noninvasive ventilations are effective treatment for ACPE. However, Bi-PAP should be considered as first line of treatment due to faster and continuous improvement in oxygenation and respiratory rate.

**Keywords:** Continuous Positive Airway Pressure, Bi-level Positive Airway Pressure, Acute Cardiogenic Pulmonary Edema

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## 1. Introduction

Acute cardiogenic pulmonary edema (ACPE) is one of the most common conditions presenting to the emergency department. It is associated with higher rate of death, especially when it is coupled with acute myocardial infarction [1-3].

Standardized medical treatment with oxygen therapy, diuretics, and vasodilators could improve the symptom of most of the patients with ACPE. However, a significant number of patients required endotracheal intubation and mechanical ventilation, with its associated potential complications [4]. Consequently, may prolong intensive care unit (ICU) and hospital stay.

Over the past three decades, application of noninvasive ventilation (NIV) either with continuous positive airway

pressure (CPAP) or Bi-level positive airway pressure (Bi-PAP) has been used with the standardized medical treatment as an effective therapeutic approach to treat ACPE [5-10].

The goals of NIV use in the treatment of ACPE are to improve oxygenation, reduce the effort of breathing and increase cardiac output and decreased left ventricular pre- and after-load [5-8].

Many studies revealed that, CPAP improved arterial oxygenation (PaO<sub>2</sub>), and reduces endotracheal intubation rate [9-11] and mortality rate in ACPE [12, 13]. However, other studies failed to show these effects [14-16]. As compared with CPAP, and oxygen therapy, Bi-PAP reduces the work of breathing and improves gas exchange, dyspnea and respiratory distress more effectively [17, 18]. However, the role of Bi-PAP in patients with ACPE remains controversial. In a comparison of CPAP with Bi-PAP, the latter demonstrated more rapid recovery of respiratory and

hemodynamic parameters [19], but Bi-PAP associated with an increased incidence of acute myocardial infarction [14]. Recently, Nour et al., [20] showed that Bi-PAP improves respiratory failure, while, Masip et al., [21] showed a decrease in intubation rate in Bi-PAP group when compared with CPAP. However, other studies [10, 22] failed to demonstrate significant differences in vital signs, blood gases, and rate of myocardial infarction between two modes of ventilations and between Bi-PAP and oxygen therapy [23]. Moreover, Gray et al., [24] did not find the difference in intubation or mortality rates with either CPAP or Bi-PAP compared to oxygen therapy. In contrast, previous trials [21, 25] found that Bi-PAP reduced the need for invasive mechanical ventilation, and endotracheal intubation when compared with oxygen therapy.

In spite of the potential advantages of NIV for the management of ACPE, there appears to be a lack of high-quality clinical evidence to support the use of these interventions. Additionally, there is only one study [26] that investigated the role of NIV on ACPE in emergency departments in Egypt. Therefore, the purpose of this study was to compare the efficacy of CPAP, Bi-PAP, and standard oxygen therapy on detailed observation of time-course change in blood gases and physiological parameters in patients with ACPE. Furthermore, to investigate whether either CPAP or Bi-PAP would cause improvement in endotracheal intubation and death rates.

## 2. Material and Methods

### 2.1. Study Design and Participants

This study was a single blinded, randomized controlled trial with repeated measurement analysis. Patients who attend the emergency department at National Heart Institute, Imbaba, Giza, Egypt, with clinical evidence of ACPE were eligible for enrollment in this study. Inclusion criteria were: severe dyspnea, bilateral rales on auscultation, and typical findings of congestion on chest radiography without evidence of pulmonary aspiration or pneumonia. In addition, respiratory rate of  $\geq 30$  breaths per minute, hypoxemia ( $\text{PaO}_2 \leq 80\text{mmHg}$ ) with a fraction of inspired oxygen ( $\text{FiO}_2$ ) of 60% via a Venturi mask, and  $\text{PaCO}_2 \geq 45\text{mmHg}$  [14, 20, 27, 28].

Exclusion criteria were: requirement for a life-saving or emergency intervention, such as primary percutaneous coronary intervention, or chronic obstructive pulmonary diseases, hemodynamic instability (systolic BP  $\leq 90\text{mmHg}$ ), or life-threatening arrhythmia, acute myocardial infarction and/ or unstable angina, recent facial trauma, and esophageal/gastric surgery, gastrointestinal bleeding, or pregnant [22, 28].

Postgraduate ethics committee at faculty of physical therapy, Cairo university approved this study. The trial registration code of this study was ACTRN12614001208695. Depending on the severity of the illness, the patients or their relative gave written informed consent.

The estimated sample size was 60 patients in all groups

and would be increased to 69 for possible dropout. This sample size was estimated to detect 5mmHg difference in  $\text{PaCO}_2$  among groups; with the probability level was set at 0.05 and power of 80% [14]. Then, the patients were randomly assigned into CPAP-group ( $n=23$ ), Bi-PAP-group ( $n=23$ ) and standard oxygen therapy ( $\text{O}_2$ -group) ( $n=23$ ). Randomization was performed within one hour of arrival using an opaque envelope, which was further concealed within another. Once enrolled within the study it was impossible to mask treatment allocation.

### 2.2. Intervention

All patients received the standard medical treatment, according to the emergency department protocol, at the National Heart Institute [29]. These included: 1) supplementary oxygen therapy was supplied at a rate of up to 15 liters per minute via a reservoir mask to maintain oxygen saturation  $\geq 90\%$ ; 2) nitroglycerine 0.4mg sublingual if systolic BP  $> 100\text{mmHg}$ -excluding patients receiving potential drug interaction preparations, doses can be repeated every 5 minutes; 3) furosemide IV starts with 40 mg and in incremental doses if required; 4) morphine sulfate 2 mg IV, may be repeated once. If BP less than 100 mmHg dopamine is given starting at 2.5 mcg/Kg/min and increase dose every 10 minutes if BP remains low. Patients were continuously monitored using pulse oximetry, and electrocardiography to detect changes in vital signs. In addition, urinary output was checked using a Foley's catheter.

NIV was delivered through a full-face mask by a Respironics Synchrony ventilator (Model RTX Inodes, 10 Downage RespiCare, Drager, London). In the CPAP group, a continuous pressure of 10  $\text{cmH}_2\text{O}$  was generated. Patients in Bi-PAP group received IPAP (15 $\text{cmH}_2\text{O}$ ) and EPAP (5 $\text{cmH}_2\text{O}$ ) [10, 13, 14]. All patients received their assigned treatment for 1 hour. After NIV mask removed, the patients continued to receive standard  $\text{O}_2$  facemask.

Criteria for termination of noninvasive ventilation therapy were: inability to tolerate the tightness of the mask or pressure, abundant secretion or met the criteria for intubation according to Brochard et al [30]. In those who could not tolerate the NIV, it was stopped and standard facemask  $\text{O}_2$  applied. After the study period (90 minutes), the patients were transferred to medical ward or admitted to an intensive care unit (ICU) if they required intubation or did not improve.

### 2.3. Outcome Measures

The primary outcome measures were physiological parameters concerning blood gases ( $\text{PaCO}_2$ ,  $\text{PaO}_2$ ,  $\text{SaO}_2$ , pH, and  $\text{HCO}_3^-$ ), and physiological parameters (HR, RR, SBP, and DBP). These parameters were collected before entry of the study ( $T_0$ ), after 60 minutes ( $T_{60}$ ), of NIV application and after 30 minutes ( $T_{90}$ ) of NIV discontinuation. Secondary outcomes were rate of endotracheal intubation, and the rate of death that reported at the time of discharge. Therapist recorded the adverse events of NIV (mucosal pain, nasal

bridge erythema, or ulcerations, eye irritation, vomiting & gastric distension) during applications.

Blinded laboratory investigator drawn blood samples through an arterial cannula from radial artery using heparin rinsed plastic syringe, then analyzed it immediately using the acid–base analyzer (Model ABL 3075R 24NB, and Manufactured by Radiometer A/S Copenhagen) to detect the level of (PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, HCO<sub>3</sub> and SaO<sub>2</sub>).

#### 2.4. Statistical Analysis

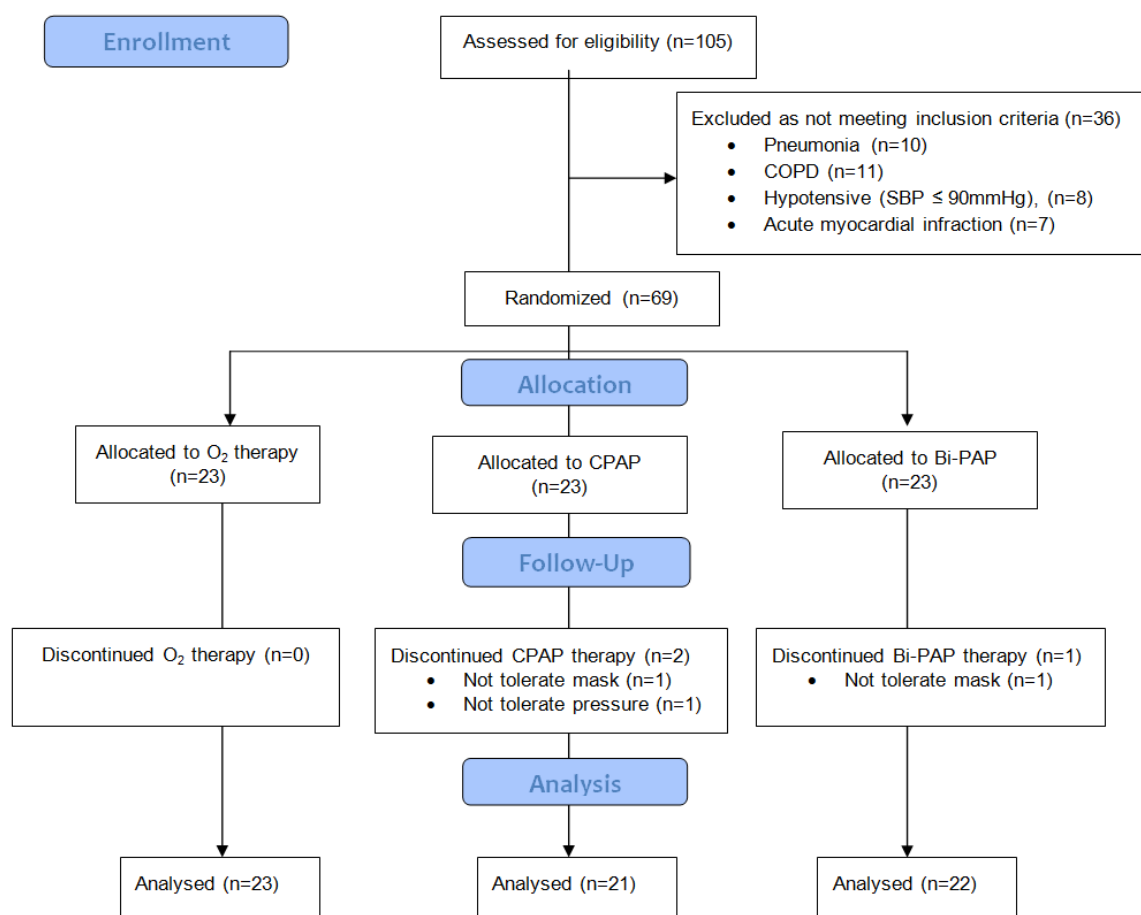
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0. Kolmogorov-Smirnov test was used to determine the normality of data distribution. Normally distributed data were described as mean and standard deviation; otherwise, the data were presented as frequency, median and range and analyzed non-parametrically. A one way repeated measure analysis of variance (ANOVA), with the Scheffe test for repeated comparison was used to identify specific differences within and between groups at each time point. Variables without

normal distribution and homogeneous variance were analyzed with the Kruskal-Wallis test. All statistical analysis was two-tailed with significant differences was assumed at  $p < 0.05$ .

### 3. Results

#### 3.1. Baseline Demographic and Clinical Characteristics of the Patients

Figure 1 shows the flow chart of patient enrollment. 105 patients with acute pulmonary edema were admitted to the emergency department at National Heart Institute, Giza, Egypt, from May 2007- to November 2008. Among those, 69 patients were met the inclusion/exclusion criteria; three patients were excluded (two on CPAP-group, and one on Bi-PAP-group). Therefore, 66 patients (27 males and 39 females) completed the study procedures and were included in the final analysis.



**Figure 1.** Flow of participants through the study.

Table 1 represents the baseline demographic and clinical characteristics of all patients. All groups were comparable in baseline characteristics ( $P > 0.05$ ) and physiological measurements ( $p > 0.05$ ). Pulmonary edema was confirmed in all patients by portable radiography, and developed

secondary to ischemic cardiomyopathy, 37 patients (56%) or dilated cardiomyopathy, 29 patients (44%). Adverse events such as mucosal pain, nasal bridge ulcerations, eye irritation, vomiting & gastric distension were not reported during applications of NIV. Only mild nasal bridge redness was

observed in 10 patients, 6 in CPAP group and 4 in Bi-PAP group.

**Table 1.** Baseline demographic and clinical characteristics of three treatment groups.

Variables	Treatment Groups		
	Control (n=23)	CPAP (n=21)	Bi-PAP (n=22)
Age (years)	57±5.3	58.4±6.53	56.6±5.12
Genders n (%)			
Males	9(39.1%)	8(38.1%)	10(45.45%)
Females	14(60.9%)	13(61.9%)	12(54.54%)
Etiology of ACPE n (%)			
Ischemic cardiomyopathy	13(56.53%)	12(57.14%)	12(54.54%)
Dilated cardiomyopathy	10(43.47%)	9(42.86%)	10(45.45%)
Physiological measurements			
HR(bpm)	127±9.51	123±17.21	127±9.82
RR (brpm)	38±3.04	38±5.8	36±4.98
SBP (mmHg)	150±12.01	149±9.3	147±8.01
DBP (mmHg)	99±11.57	94±9.98	94±9.63
PaO <sub>2</sub> (mmHg)	67.75±5.3	64.04±6.83	63.83±7.23
PaCO <sub>2</sub> (mmHg)	48.22±1.86	48.05±2.77	49.23±3.21
SaO <sub>2</sub> (%)	86.15±3.88	88.14±3.19	86.23±4.94
HCO <sub>3</sub> (mmol/l)	22.57±2.5	22.95±2.71	22.45±2.27
pH	7.4±0.03	7.39±0.02	7.38±0.05
Medical treatment-n (%) of patients			
Vasodilators	23(100%)	20(95%)	20(91%)
Diuretics	23(100%)	21(100%)	22(100%)
Opioids	13(56.5%)	11(52.38%)	12(54.5%)
Inotropic	2(8.7%)	2(9.5%)	2(9%)

Bi-PAP= Bi-Level Positive Airway Pressure, bpm= Beat per minute, brpm= Breath per minute CPAP= Continuous Positive Airway Pressure, DSP =Diastolic blood pressure, (HCO<sub>3</sub>)=Arterial Blood Bicarbonate, HR= Heart rate, (PaCO<sub>2</sub>)= Arterial Carbon Dioxide Pressure, (PaO<sub>2</sub>)=Arterial Oxygen Pressure, (pH)= Hydrogen Ion Concentration, mmHg= Millimeter mercury pressure, mmol/L= Milimole per liter, RR= Respiratory rate, (SaO<sub>2</sub>)=Oxygen Saturation, SBP= Systolic blood pressure, %=Percentage, <sup>†</sup> = significant differences (p<0.05) among the three groups.

### 3.2. Primary Outcomes

Table 2 shows physiological measurements during the study periods. The mean values of PaO<sub>2</sub> and SaO<sub>2</sub> were significantly increased in CPAP and Bi-PAP groups compared to oxygen therapy after 60 minutes of intervention (T60). After 30 minutes of discontinuation (T90) of intervention, the mean values of PaO<sub>2</sub> and SaO<sub>2</sub> were significantly lowered in CPAP and Bi-PAP groups compared to 60 minutes of intervention, except for oxygen therapy, there were non-significant increase in PaO<sub>2</sub> and SaO<sub>2</sub> compared to 60 minutes of intervention. However, the Bi-PAP-group remained had significantly increased in PaO<sub>2</sub> and SaO<sub>2</sub> compared to oxygen therapy (86.75±6.51 vs 80.6±8.09, P<0.05 and 94.47±2.96 vs 92.05±1.96, P<0.05) and CPAP-group (86.75±6.51 vs 75.57±6.47 ± 6.47, P<0.01 and 94.47±2.96 vs 89.94±3.72, P<0.01), respectively.

The percentage increase of PaO<sub>2</sub> and SaO<sub>2</sub> was primarily higher in Bi-PAP-group (81.76% and 14.18%) compared to CPAP-group (72.25% and 10.77%) and oxygen therapy (7.13% and 1.98%) immediately after 60minutes of

intervention (T60). While after 30 minutes of discontinuation (T90), percentage increase of PaO<sub>2</sub>, and SaO<sub>2</sub> was predominately in the oxygen therapy (19.97% and 6.85%), while for CPAP and Bi-PAP groups, the percentages decreased to (18%, 35.9% and 2.04%, 9.56%) respectively.

**Table 2.** Blood gases measurements during 90 minutes of study period in three groups.

	Study Period Measurements		
	Baseline(T0)	60 minutes(T60)	90 minutes(T90)
PaO <sub>2</sub> (mmHg)			
Control	67.75±5.3	72.58±5.75	80.6±8.09*
CPAP	64.04±6.83	110.31±25.61 <sup>††</sup>	75.57±6.47
Bi-PAP	63.83±7.23	116.02±23.96 <sup>††</sup>	86.75±6.51 <sup>††</sup>
PaCO <sub>2</sub> (mmHg)			
Control	48.22±1.86	47.01±3.26	46.43±2.01
CPAP	48.05±2.77	42.39±3.68 <sup>††</sup>	40.34±2.33 <sup>††</sup>
Bi-PAP	49.23±3.21	42.21±5.67 <sup>††</sup>	38.66±2.88 <sup>††</sup>
SaO <sub>2</sub>			
Control	86.15±3.88	87.86±3.63	92.05±1.96*
CPAP	88.14±3.19	97.63±1.44 <sup>††</sup>	89.94±3.72
Bi-PAP	86.23±4.94	98.46±2.8 <sup>††</sup>	94.47±2.96 <sup>††</sup>
pH			
Control	7.4±0.03	7.41±0.02	7.42±0.03
CPAP	7.39±0.02	7.4±0.03	7.41±0.03
Bi-PAP	7.38±0.05	7.4±0.04	7.41±0.04
HCO <sub>3</sub> (mmol/L)			
Control	22.57±2.52	23.28±3.55	24.03±1.91
CPAP	22.95±2.71	23.99±3.01	24.44±2.8
Bi-PAP	22.45±2.27	23.19±3.22	23.93±2.53

Bi-PAP= Bi-Level Positive Airway Pressure, CPAP= Continuous Positive Airway Pressure, (HCO<sub>3</sub>)=Arterial Blood Bicarbonate, (PaCO<sub>2</sub>)= Arterial Carbon Dioxide Pressure, (PaO<sub>2</sub>)=Arterial Oxygen Pressure, (pH)= Hydrogen Ion Concentration, mmHg= Millimeter mercury pressure, mmol/L= Milimole per liter, (SaO<sub>2</sub>)=Oxygen Saturation, \* = significant differences (p<0.05) within group compared to baseline, <sup>†</sup> = significant differences (p<0.05) between groups compared to control group.

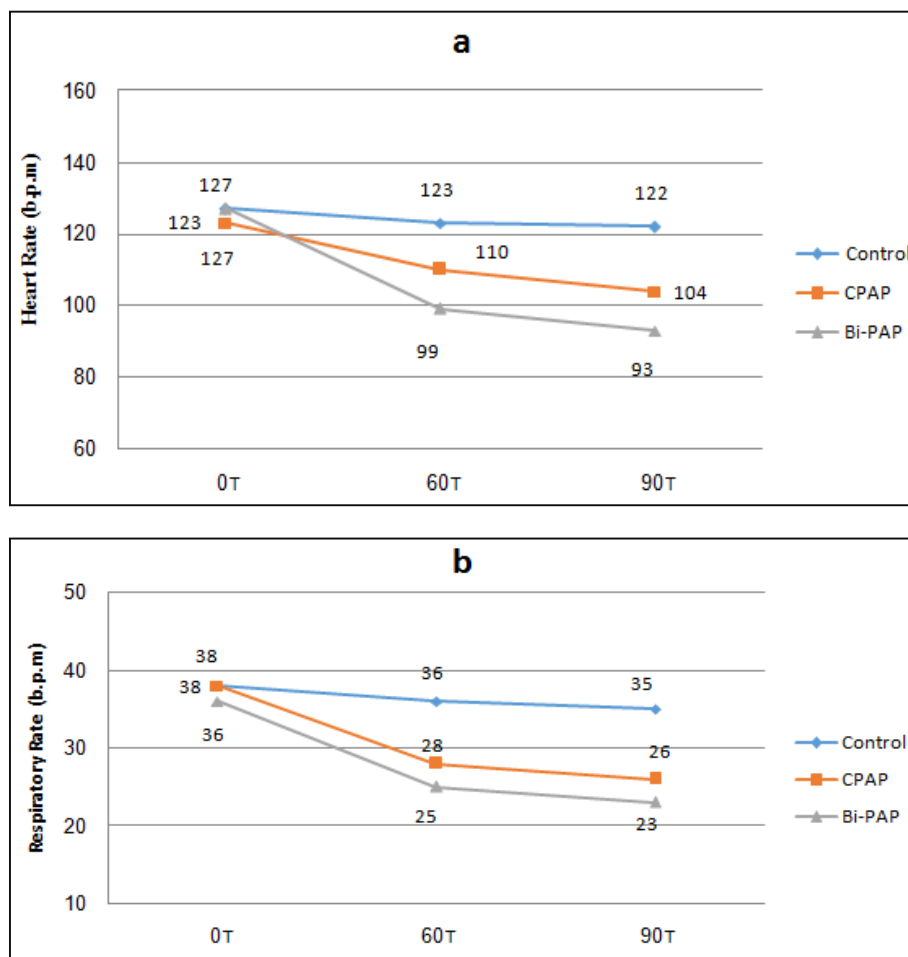
The PaCO<sub>2</sub> was significant (P<0.01) lower in CPAP and Bi-PAP groups compared to the oxygen therapy group with no differences between CPAP and Bi-PAP groups through the study period. There no difference between the three groups, regards to HCO<sub>3</sub> and at any other time point.

As presented in (Figures 2 and 3), time-related changes in heart rate, respiratory rate, and blood pressure were significantly (p<0.01) lowered in CPAP and Bi-PAP groups at each time point compared to baseline. In the Oxygen therapy group, there were no significant differences in heart rate, and respiratory rate. However, significant differences were detected in blood pressure after 30 minutes of discontinuation of intervention (T90).

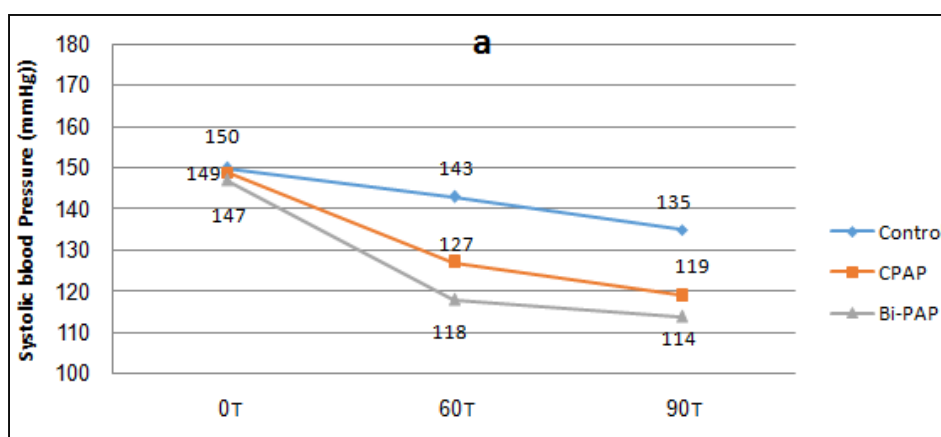
Group-related differences showed statistically significant (P<0.01) differences in percentage of reductions in the heart rate (22.33%, versus 10.26% and 3.14%, p = 0.05), respiratory rate (29.86%, versus 25.23% and 4.63%, P = 0.05), for Bi-PAP group compared to the CPAP and oxygen therapy respectively, after 60 minutes (T60) of intervention. Except for systolic blood pressure and diastolic blood pressure significant differences detected between Bi-PAP-

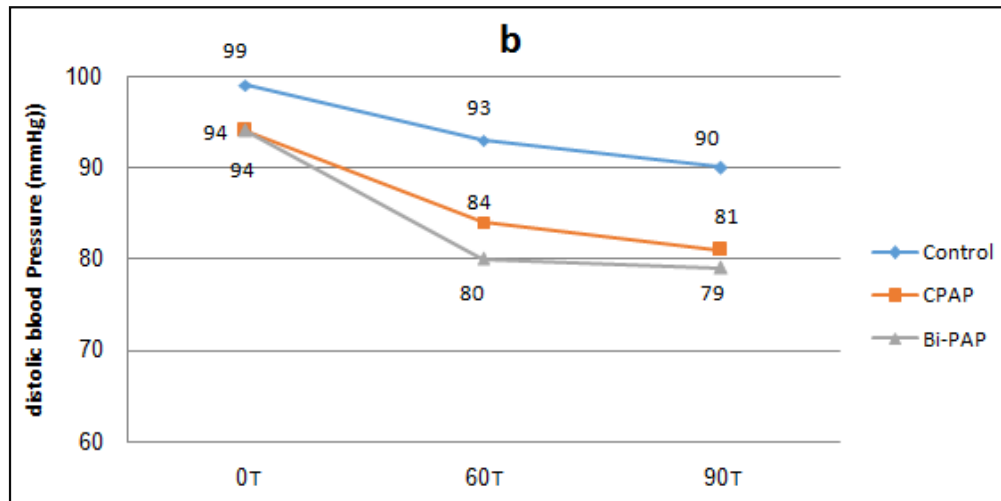
group compared to oxygen therapy (SBP: 19.73% versus 5.32%,  $p>0.05$  and DBP; 14.86% versus 6.1%,  $P>0.05$ ). However, no significant differences detected between Bi-PAP-group and CPAP-group (SBP: 19.73% versus 15.05%,  $p>0.05$  and DBP; 14.86% versus 10.93%,  $P>0.05$ ) after 60 minutes of interventions. The percentage of reduction in physiological parameters observed after 30 minutes of therapy discontinuation revealed a continuous and greater percentage of reduction in Bi-PAP-group (26.69% versus 14.85%, and

3.93%), for heart rate, (36.25% versus 30.72%, and 5.31%) for respiratory rate compared to CPAP-group and oxygen therapy. There were no significant differences detected between Bi-PAP and CPAP groups regards to systolic blood pressure (22.1% versus 20.4%,  $p>0.05$ ) and diastolic blood pressure, (16.71% versus 13.87%,  $p>0.05$ ). However, marked significant differences were observed between both Bi-PAP and CPAP groups compared to oxygen therapy.



**Figure 2.** Changes in physiological parameters heart rate (a) and respiratory rate (b) at baseline of study (T0), after 60 minutes of intervention (T60) and after 30 minutes (T90) of discontinuation of intervention for Bi-PAP, CPAP, and Oxygen therapy groups.





**Figure 3.** Changes in physiological parameters systolic and diastolic blood pressure (SBP-a) and (DBP-b) at baseline of study (T0), after 60 minutes of intervention (T60) and after 30 minutes (T90) of discontinuation of intervention for Bi-PAP, CPAP, and Oxygen therapy Groups..

### 3.3. Secondary Outcomes

There was no significant difference in the hospital death, and intubations rates between both Bi-PAP and CPAP groups compared to oxygen therapy. As 22 (95%) of the control group patients survived to hospital discharge (one patient died due to ventricular dysrhythmias), compared with 21(100%) in the CPAP group and 22(100%) in the Bi-PAP-group. There was no difference in hospital stay among groups and all patients discharged within 24 hours after the study. However, one patient (4.3%) was intubated because of worsening of gas exchange in the control group.

## 4. Discussion

To our knowledge, this study is the first single blinded, randomized trial designed to compare the potential effectiveness of Bi-PAP, CPAP and standard oxygen therapy on blood gases and physiological parameters in patients with ACPE at the emergency department in Egypt. In addition, this study investigates whether there was a difference between Bi-PAP and CPAP with regrading rate of endotracheal intubation, and the rate of death reported at the time of discharge.

In this study, the effects of CPAP and Bi-PAP were superior to the oxygen therapy group regarding improvement of blood gases ( $\text{PaO}_2$ ,  $\text{PaCO}_2$  and  $\text{SaO}_2$ ) and physiological parameters (HR, RR, SBP, and DBP). The effects of Bi-PAP and CPAP were similar except in heart rate and respiratory rate within 60 minutes of application. In addition, patients receiving Bi-PAP had significant improvement in  $\text{PaO}_2$ ,  $\text{SaO}_2$ , and HR and RR within 90 minutes of initiation of therapy. These physiologic benefits did not accompany by a difference in endotracheal intubation and death rates ( $P > 0.05$ ) among groups. There were no serious adverse effects related to application of CPAP or Bi-PAP.

The results of current study are supported by several studies [9, 21, 24]. The authors revealed that, both Bi-PAP

and CPAP had marked effect when compared with standardized oxygen therapy regarding gas exchange, and heart rate, with no adverse events. However, Gray et al., [24] did not report significant differences between NIV compared to standard oxygen therapy regarding to RR, SBP, and DBP. This may be due to differences in the values of applied pressure and in patient characteristics.

The current significant reduction in RR observed in Bi-PAP group compared to CPAP group might be attributed to the effect of Bi-PAP in unloading respiratory muscles. This agrees with finding of Chadda et al., [17] who concluded that, addition of a pressure-supported ventilation of Bi-PAP might improve the respiratory pump, and alveolar ventilation leading to rapid reduction in respiratory rate than with CPAP alone. Similarly, Nouria and colleagues [20] reported significant increase in  $\text{PaO}_2$  and decrease in HR, and RR in both Bi-PAP and CPAP groups. However, Bi-PAP accelerated the improvement of respiratory failure compared to CPAP.

An improvement in RR and symptoms of respiratory fatigue (improved breathing pattern, decreasing intercostal suprasternal retraction and subjective respiratory distressed) when coupled with improved oxygenation, and lower  $\text{PaCO}_2$  is considered as indirect objective evidence of decrease work of breathing, dyspnea, and alveolar hypoventilation [15, 31]. These confirm that the therapeutic intervention in our study was delivered successfully and appropriately.

In contrast to our findings, Levitt [23] demonstrate no significant effect of Bi-PAP compared to oxygen therapy on vital signs, blood gases. These results may be attributed to the low pressure applied and baseline differences between the groups. Our study failed to show a major difference to improve blood gases between CPAP and Bi-PAP techniques within 60 minutes of application. These findings are in agreement with those reported in previous studies [10-12, 20, 28, 32-34] In addition, there was an apparent drop in the  $\text{PaO}_2$  and  $\text{SaO}_2$  after 30 minutes of discontinuation of NIV. This drop was significant in CPAP compared to Bi-PAP group. There is no treatment failure attributed to worsening

hypoxia and the improvement in the Bi-PAP group might produce faster than CPAP group. These findings showed that, the changes in blood gases were owing to the effect of NIV rather than other factors such as medication.

Our results showed no difference in the proportion of patients who underwent endotracheal intubation and the rate of death among groups. These results were similar to previous studies [24, 35]. Moreover, systematic review and meta-analysis conducted by Hui *et al.*, [36] reported no differences in mortality, intubation rate, and length of stay in the hospital between Bi-PAP and CPAP. However, some studies [33, 37] reported (47%) reduction in mortality rate [33] and no endotracheal intubation [37] among ACPE patient who treated with NIV.

Contrast, to our findings Mehta *et al.*, [14] prematurely completed their trial comparing CPAP with Bi-PAP because of increased rate of MI and mortality in Bi-PAP group, with higher incidence of chest pain in Bi-PAP group at the entry of the study which suggested non-homogeneity between the groups.

The specific pressure values of CPAP and Bi-PAP in this study selected based on previous studies [10, 13, 14, 38]. This pressure (15/5Cm H<sub>2</sub>O) of Bi-PAP provided mean airway pressures close to those levels obtained with a CPAP of 10 Cm H<sub>2</sub>O, although we cannot be sure that intrathoracic pressures result from these selected pressure values would be similar.

The limitations of this study were; the physicians who decided when it started endotracheal intubation or to cease NIV were not blinded. This increase the possibility of a bias, however, blinding in our study was not feasible; Further NIV studies should consider blinding physician to the mode of NPPV used. Moreover, small sample size, and long-term results are not available, so additional large international Multicenter study comparing three treatment arms is required to investigate long-term improvement.

## 5. Conclusion

Both CPAP and Bi-PAP are safe, well-tolerated adjunctive therapy in patients with ACPE. The Bi-PAP therapy had faster and continuous improvement in RR, with rapid improvement in PaO<sub>2</sub> and SaO<sub>2</sub> compared to both CPAP and standardized oxygen therapy. However, there were similar reductions in death and intubation rates among groups. Because of its immediate efficacy, and lack of serious side effects, Bi-PAP should be encouraged as a first-line therapy in a patient with ACPE in emergency setting.

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