Objective: To compare the effects of oxygen, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (bilevel-PAP) on the rate of endotracheal intubation in patients with acute cardiogenic pulmonary edema.

Design: Randomized, controlled trial.

Setting: Tertiary hospital emergency room.

Patients: We randomly assigned 80 patients with severe cardiogenic acute pulmonary edema into three treatment groups. Patients were followed for 60 days after the randomization.

Interventions: Oxygen applied by face mask, CPAP, and bilevel-PAP.

Measurements and Main Results: The rate of endotracheal intubation as well as vital signs and blood gases was recorded during the first 24 hrs. Mortality was evaluated at 15 days, at 60 days, and at hospital discharge. Complications related to respiratory support were evaluated before hospital discharge. Treatment with CPAP or bilevel-PAP resulted in significant improvement in the Pao2/Fio2 ratio, subjective dyspnea score, and respiratory and heart rates compared with oxygen therapy. Endotracheal intubation was necessary in 11 of 26 patients (42%) in the oxygen group but only in two of 27 patients (7%) in each noninvasive ventilation group \((p = .001)\). There was no increase in the incidence of acute myocardial infarction in the CPAP or bilevel-PAP groups. Mortality at 15 days was higher in the oxygen than in the CPAP or bilevel-PAP groups \((p < .05)\). Mortality up to hospital discharge was not significantly different among groups \((p = .061)\).

Conclusions: Compared with oxygen therapy, CPAP and bilevel-PAP resulted in similar vital signs and arterial blood gases and a lower rate of endotracheal intubation. No cardiac ischemic complications were associated with either of the noninvasive ventilation strategies. (Critic Care Med 2004; 32:2407–2415)

Key Words: pulmonary edema; respiratory failure; artificial respiration; congestive heart failure; mechanical ventilators; respiratory therapy.
here have precluded the inclusion of noninvasive ventilation as first-line therapy for acute pulmonary edema (7). Mehta et al. (4) and Masip et al. (5) also pointed out the need for a simultaneous comparison among oxygen, CPAP, and bilevel-PAP. In the current study, we prospectively randomized and compared the effects of standard oxygen therapy, CPAP, and bilevel-PAP promptly delivered in the emergency room to patients with severe acute cardiogenic pulmonary edema.

MATERIALS AND METHODS

Study Population. Between January 1999 and August 2000, 83 consecutive patients with severe acute cardiogenic pulmonary edema were prospectively enrolled. The study was conducted in the emergency department, with the approval of our institutional ethics committee. Written, informed consent was obtained from patients' next-of-kin.

The patients diagnosed with acute cardiogenic pulmonary edema in the emergency room were promptly recruited and enrolled. The patients met all the following criteria: age >16 yrs, acute onset of severe respiratory distress (breathing rate >25 breaths/min, associated tachycardia and diaphoresis, and findings of pulmonary congestion on physical examination. A chest radiograph was obtained to confirm the diagnosis up to 2 hrs after the randomization. Patients were excluded if they had impaired level of consciousness at presentation; intractable vomiting; acute myocardial infarction with persistent ST segment elevation; systolic pressure <90 mm Hg or hypertension; systolic pressure <90 mm Hg, left ventricular dysfunction, and/or a systolic pressure <90 mm Hg or hypertension; hypotension; acute respiratory failure; acute MI, or chronic obstructive pulmonary disease.

All enrolled patients were evaluated by an investigator on call, who was responsible for the implementation of respiratory support, whereas the medical staff was responsible for other medical interventions including the decision about endotracheal intubation.

Initial Procedures and Randomization. Arterial blood pressure, electrocardiogram, and peripheral oximetry were monitored continuously. A Venturi mask with FiO₂ of 0.5 was applied. After these procedures, vital signs were taken; 5 mg of isosorbide dinitrate was given sublingually and if necessary titrated up to 15 mg. After the initiation of the Venturi mask, we waited 6 mins for patients to reach the threshold breathing rate for oxygen therapy (25), and after that time heart and respiratory rates, arterial blood pressure, and an arterial blood sample were collected. The patients were randomized with sealed envelopes (nine patients per envelope), using a 3:3:3 assignment scheme, and then the ventilatory support was applied according to randomization. The CPAP and the bilevel-PAP were applied by BIPAP Vision system (Respironics, Murrysville, PA) with FiO₂ of 0.5 delivered by a face mask. CPAP was initially adjusted to 10 cm H₂O. In the bilevel-PAP group, the initial inspiratory pressure (PEAP) was also adjusted to 10 cm H₂O, and inspiratory pressure (IPAP) was adjusted to 15 cm H₂O. For the oxygen group, the Venturi mask was used with PFO₂ 0.5 to reach a peripheral oxygen saturation >90%.

An electrocardiogram and creatine kinase MB isoenzyme activity were obtained at entry. An electrocardiogram was repeated after 1 hr, and both were repeated after 6 and 12 hrs.

Subsequent Procedures. Physiologic variables (heart and respiratory rate, arterial blood pressure) and dyspnea score were assessed at 10, 30, 60, 180, and 360 mins as well as 12 and 24 hrs after the randomization. Arterial blood samples were collected at 30, 60, 180, and 360 mins after the randomization. Dyspnea score was evaluated by an analogical verbal scale with levels from 0 (no dyspnea) to 10 (maximal dyspnea). The patients rated the sensibility of dyspnea in reference to the randomization time, when dyspnea score was considered maximal, that is, level 10.

After randomization, the following standardized ventilatory support algorithm was used: In all groups, the primary target was to maintain SpO₂ at >90%. In the oxygen group, if SpO₂ <90%, the Venturi mask was changed to a nonrebreathing mask providing nearly 1 of FIO₂. In the CPAP and bilevel-PAP groups, the following adjustments, if needed, were made in 2- to 5-min steps: PFO₂ was increased by 0.1 with a concomitant 2-cm H₂O increment of CPAP or EPAP up to 16 cm H₂O. After that, only PFO₂ was increased in 0.1 steps. During bilevel-PAP, whenever EPAP was increased by 2 cm H₂O, IPAP was also increased by 2 cm H₂O to maintain the same level of inspiratory assistance. Additionally, if the respiratory rate was >30 breaths/min or a marked respiratory distress was present, despite an SpO₂ >90%, only IPAP was increased in steps of 2 cm H₂O. Respiratory pressures could be lowered in 2 cm H₂O steps each 2–5 mins if the respiratory rate was <20 breaths/min. After stabilization, no further changes in ventilator variables were made until 60 mins after randomization. Afterward, if the respiratory variables allowed, weaning from respiratory support was initiated. Drug therapy followed the advanced cardiac life support (7).

After 24 hrs of study enrollment, all patients were followed for up to 60 days after the randomization or up to death. Medical interventions and complications were recorded.

Weaning From Respiratory Support. Weaning from respiratory support was initiated after 60 mins of randomization, only if the patient had a) absence of respiratory distress; b) SpO₂ >95%; and c) respiratory rate <25 breaths/min. These three criteria were also used to move the patients forward through the weaning steps. Each weaning step took 10 mins. If SpO₂ fell below 90%, the patient was moved backward to the previous step. The reduction of PFO₂ in the oxygen group was made by changing the nonrebreathing mask (when it was used) to a Venturi mask with PFO₂ = 0.5 and to a mask with PFO₂ = 0.4. In the CPAP group, the PFO₂ was lowered in steps of 0.1 until a PFO₂ of 0.4 was reached, followed by reductions of 2 cm H₂O in the CPAP until 6 cm H₂O was reached. After 30 mins, IPAP was changed to a Venturi mask with PFO₂ = 0.4. In the bilevel-PAP group, weaning started with PFO₂ similar to that of CPAP group and subsequently IPAP and then EPAP. IPAP was lowered in steps of 2 cm H₂O until the pressure support (IPAP – EPAP) was 5 cm H₂O. After this step, the EPAP and IPAP were lowered together until EPAP was 6 cm H₂O. Weaning from positive pressure was considered successful if the patients remained stable at these variables for 30 mins.

Endotracheal Intubation Criteria. Endotracheal intubation was performed according to the judgment of the medical staff on duty, without input from the researchers, based on the following criteria: Glasgow coma scale ≤13, persistent respiratory distress, PacO₂ <60 torr (8 kPa) or SpO₂ <90% despite maximal therapy, or an increase in PacO₂ >5 torr (0.7 kPa) from the baseline value (measured at study admission).

Statistical Analysis. The primary end point was the intubation rate. We estimated that a sample of 93 patients was required based on a pilot study and others' findings (2–6). We accepted a type 1 error of 5%, a statistical power of 85%, and an estimated intubation rate in the CPAP or bilevel-PAP group four times lower than that in the control group (2–6). Two interim analyses were programmed, after enrollment of 50 and 80 patients. To counterbalance the increased chances of prematurely stopping the study because of type 1 error, we used a nominal significance level of ≤.001 for any interim analysis (26). The effect of positive pressure on the need for endotracheal intubation was analyzed with the chi-square test, considering an intention-to-treat analysis, as for any other secondary end point represented by categorical variables. Secondary end points were in-hospital mortality and survival at 15 and 60 days, estimated by Kaplan-Meier curves and the log-rank test. The analysis at 15 days was considered in order to reduce the interference of late events on mortality to hospital discharge.

All data were classified as normal or non-normal comparing the tested data distribution with the Gaussian distribution through the Kolmogorov-Smirnov distance analysis. Parametric data were analyzed by two-way analysis of variance and Tukey post hoc pairwise analysis. Nonparametric data were analyzed using the Kruskal-Wallis test, and Dunn post hoc pairwise analysis was applied to individualize the different groups. The Bonferroni continuity correction was used in multiple comparisons.
RESULTS

The study included 83 patients; three patients were excluded, one in the oxygen group due to acute myocardial infarction with persistent elevation of the ST segment at entry and two in the bilevel-PAP group due to chronic obstructive disease and pneumonia (Fig. 1). The study was stopped during the second interim analysis after 80 patients had been studied, because of a significant difference in endotracheal intubation rates among the groups. Only 20% of the patients with acute pulmonary edema were enrolled because the majority did not fulfill the inclusion criteria and had mild forms of acute pulmonary edema (Fig. 1).

The baseline characteristics and the causes of acute cardiogenic pulmonary edema are shown in Table 1. Table 2 shows the treatment characteristics of the study groups. The mean $F_{O_2}$, the medications, and the dosages used during the protocol were similar among the study groups. The ejection fraction, measured after the stabilization of the patients and without positive pressure support, was similar in the three groups: $0.52 \pm 0.16$ in the oxygen group, $0.56 \pm 0.15$ in the CPAP group, and $0.58 \pm 0.15$ in the bilevel-PAP group ($p = .356$).

During the first 24 hrs after randomization, CPAP and bilevel-PAP groups had identical rates of intubation, two in each group of 27 patients (7%). In contrast, 11 of 26 patients (42%) were intubated in the oxygen group ($p = .001$). No significant differences existed in medical interventions and complications. The survival at 15 days was lower in the oxygen group (Fig. 2). All the in-hospital fatalities were related to refractory septic or cardiogenic shock. Septic shock predominated as the cause of late deaths (>72 hrs). No patient died after cardiac surgery. No significant differences occurred in mortality to hospital discharge ($p = .061$; Table 3). No patients had adverse events, such as mask intolerance and vomiting. Mild gastric distension occurred in 13 patients, five in the CPAP group and eight in the bilevel-

Figure 1. Flow diagram illustrating the progress of patients throughout the trial. CPAP, continuous positive airway pressure; bilevel-PAP, bilevel positive airway pressure; AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease.
Table 1. Baseline characteristics, etiologies of pulmonary edema, and previous significant events of the study groups

<table>
<thead>
<tr>
<th>Characteristic at randomization</th>
<th>Oxygen (n = 26)</th>
<th>CPAP (n = 27)</th>
<th>Bilevel-PAP (n = 27)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs, mean ± SD</td>
<td>65 ± 15</td>
<td>61 ± 17</td>
<td>66 ± 14</td>
<td>.416</td>
</tr>
<tr>
<td>Gender, M/F, no. (%)</td>
<td>14/12</td>
<td>9/18</td>
<td>11/16</td>
<td>.312</td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>19 ± 3</td>
<td>19 ± 6</td>
<td>20 ± 2</td>
<td>.319</td>
</tr>
<tr>
<td>Etiology of pulmonary edema, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>11 (42)</td>
<td>9 (32)</td>
<td>10 (37)</td>
<td>.795</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>.389</td>
</tr>
<tr>
<td>Hypertensive emergency</td>
<td>8 (31)</td>
<td>9 (33)</td>
<td>6 (22)</td>
<td>.641</td>
</tr>
<tr>
<td>Progressive heart failure</td>
<td>4 (15)</td>
<td>8 (30)</td>
<td>8 (30)</td>
<td>.387</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>—</td>
</tr>
<tr>
<td>Characteristic at randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time until medical support, mins</td>
<td>129 ± 161</td>
<td>169 ± 138</td>
<td>110 ± 97</td>
<td>.161</td>
</tr>
<tr>
<td>Thoracic pain at enrollment, no. (%)</td>
<td>12 (46)</td>
<td>10 (37)</td>
<td>10 (37)</td>
<td>.738</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL, mean ± SD</td>
<td>30 ± 13</td>
<td>28 ± 12</td>
<td>37 ± 18</td>
<td>.060</td>
</tr>
<tr>
<td>Creatinine, mg/dL, mean ± SD</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.7</td>
<td>2.1 ± 1.8</td>
<td>.226</td>
</tr>
</tbody>
</table>

CPAP, continuous positive airway pressure; bilevel-PAP, bilevel positive airway pressure; APACHE, Acute Physiology and Chronic Health Evaluation.

*Patients with non-5T elevation myocardial infarction; p < .05, oxygen group had more previous myocardial infarctions than bilevel-PAP group; p < .05, bilevel-PAP and CPAP groups had more previous cardiogenic pulmonary edema than oxygen group; time from the start of symptoms up to arrival in the emergency room.

Table 2. Respiratory support characteristics and drugs used in the study groups

<table>
<thead>
<tr>
<th>Use Characteristics</th>
<th>Oxygen (n = 26)</th>
<th>CPAP (n = 27)</th>
<th>Bilevel-PAP (n = 27)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of mask use, mins</td>
<td>—</td>
<td>102 ± 41</td>
<td>124 ± 62</td>
<td>.040*</td>
</tr>
<tr>
<td>Mean ± so CPAP/EPAP</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
<td>.673</td>
</tr>
<tr>
<td>Mean IPAP</td>
<td>51 ± 17</td>
<td>52 ± 15</td>
<td>52 ± 15</td>
<td>.858</td>
</tr>
<tr>
<td>Drugs used, no. (%) all doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate, mg</td>
<td>26 (100)</td>
<td>27 (100)</td>
<td>27 (100)</td>
<td>.614*</td>
</tr>
<tr>
<td>Methylene, mg</td>
<td>5 ± 0</td>
<td>5.2 ± 0.96</td>
<td>5.26 ± 0.96</td>
<td>—</td>
</tr>
<tr>
<td>Methylene, mg</td>
<td>21 (81)</td>
<td>23 (85)</td>
<td>23 (85)</td>
<td>.645*</td>
</tr>
<tr>
<td>Furosemide, mg</td>
<td>3.14 ± 1.31</td>
<td>3.82 ± 2.46</td>
<td>3.04 ± 1.55</td>
<td>.530*</td>
</tr>
<tr>
<td>Nitroprusside, μg/kg/min</td>
<td>65.38 ± 33.25</td>
<td>67.40 ± 42.66</td>
<td>60.74 ± 42.05</td>
<td>.320*</td>
</tr>
<tr>
<td>Nitroglycerin, μg/min</td>
<td>1.14 ± 1.12</td>
<td>3.06 ± 1.78</td>
<td>3.00 ± 1.41</td>
<td>.693*</td>
</tr>
<tr>
<td>31.69 ± 29.87</td>
<td></td>
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</tbody>
</table>

CPAP, continuous positive airway pressure; bilevel-PAP, bilevel positive airway pressure; EPAP, expiratory pressure; IPAP, inspiratory pressure.

*Data were not collected because the Venturi mask was used in all groups after respiratory support discontinuation; †nonpairwise t-test with Welch's correction was used; ‡FIO2 values are the mean of the maximal value used within the first hour; no. is the number of patients who used the reported drug; p values were calculated about the mean doses of the drug; ‡doses are the mean of the higher doses used during the protocol.

The evolution of vital signs is shown in Figure 3. Respiratory rate declined in all groups during the protocol. However, at 10, 30, and 60 mins, the values in CPAP and bilevel-PAP groups were similar and significantly lower than those in the oxygen group (p = .001). Mean arterial blood pressure and the double product declined equally in all groups. The bicarbonate, pH, and PaO2 also improved comparably in all groups (Fig. 4).

Although the instantaneous values for cardiac rate and PaO2/FIO2 were not statistically different among the groups, the decreased heart rate and the increase in the PaO2/FIO2 ratio within the first 10 and 30 mins, respectively, were more pronounced in the CPAP and bilevel-PAP groups than in the oxygen group (Fig. 3). The dyspnea score was significantly lower in the CPAP and bilevel-PAP groups during the initial 30 mins when compared with that in the oxygen group. At 60 mins, only the bilevel-PAP group had a statistically lower dyspnea score when compared with that in the oxygen group (Fig. 4).
Sixteen patients (20%) had had hypercapnia (\(\text{PaCO}_2 > 45 \text{ mm Hg}\)) and 33 patients (41%) had had hypocapnia (\(\text{PaCO}_2 < 35 \text{ mm Hg}\)) at the time of randomization. Among the patients with hypercapnia, seven were in the oxygen group, five in the CPAP group, and three in the bilevel-PAP group (\(p = .07\)). The mean \(\text{PaCO}_2\) was 57 ± 2 mm Hg (8.8 kPa) in the oxygen group, 59 ± 4 (9 kPa) in the CPAP group, and 55 ± 3 (8.5 kPa) in the bilevel-PAP group (\(p = .826\)). After 30 mins, only one patient in the oxygen group and none in the other groups remained with hypercapnia. Of those patients with hypercapnia at randomization, two were intubated in the oxygen group, one in the CPAP group, and two in the bilevel-PAP group, all within the first 30 mins.

**DISCUSSION**

In this study, CPAP and bilevel-PAP were similar and clearly superior to oxygen therapy, decreasing the need for endotracheal intubation and invasive mechanical ventilation (\(p = .001\)). The treatment with CPAP or bilevel-PAP resulted in a faster improvement in the \(\text{PaCO}_2/\text{FiO}_2\) ratio, subjective dyspnea score, and respiratory and heart rates compared with oxygen. This physiologic benefit was not accompanied by any serious adverse effect related to CPAP or bilevel-PAP. Our study also showed that the oxygen group had a significantly higher mortality rate at 15 days compared with the CPAP and the bilevel-PAP groups (\(p = .006\)) according to the actuarial survival curve (Fig. 2). It must be stressed, however, that a nonsignificant decrease occurred in inhospital mortality (\(p = .061\)) in the CPAP and bilevel-PAP groups compared with the oxygen group (Table 3). Although this was not our primary objective, to our knowledge, this is the first study to show differences in mortality in the treatment of acute cardiogenic pulmonary edema.

The patients were prospectively randomized and were similar in relevant characteristics as the incidence of acute myocardial ischemia (Table 1). It is difficult to ascribe the better outcome of bilevel-PAP and CPAP groups to bias related to uncontrolled and unrecognized factors, because our staff was much more used to the oxygen support approach. In addition, a strict protocol resulted in a

![Figure 2. Actuarial 15-day survival among 80 patients with acute cardiogenic pulmonary edema assigned to oxygen, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (bilevel-PAP) therapy. At 15 days, the cumulative survival was significantly lower in the oxygen group compared with the CPAP (\(p = .007\)) and bilevel-PAP (\(p = .043\)) groups. The \(p\) value shown in the graph is the significance taken into account all the three groups. The data are based on an intention-to-treat analysis. The \(p\) value indicates the effect of ventilatory treatment as estimated by log rank test.](image)

<table>
<thead>
<tr>
<th>Table 3. General outcomes of the study groups</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Intubation rate, no. (%)</td>
</tr>
<tr>
<td>Time until intubation, mins, mean ± sd</td>
</tr>
<tr>
<td>Intubation cause, no. (%)</td>
</tr>
<tr>
<td>Impaired level of consciousness</td>
</tr>
<tr>
<td>Unrelenting respiratory distress</td>
</tr>
<tr>
<td>Time to hospital discharge, days, mean ± sd</td>
</tr>
<tr>
<td>Procedures after 12 hrs, no. (%)</td>
</tr>
<tr>
<td>Surgical myocardial revascularization</td>
</tr>
<tr>
<td>Angioplasty</td>
</tr>
<tr>
<td>Cardiac valvular surgery</td>
</tr>
<tr>
<td>Complications, no. (%)</td>
</tr>
<tr>
<td>Cause of in-hospital death, no. (%)</td>
</tr>
<tr>
<td>Refractory septic shock</td>
</tr>
<tr>
<td>Refractory cardiacogenic shock</td>
</tr>
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</table>

**CPAP, continuous positive airway pressure; bilevel-PAP, bilevel positive airway pressure.**

*These significant differences are between CPAP and oxygen groups and between bilevel-PAP and oxygen groups; † one patient was intubated 135 mins after randomization due to hypotension and impaired conscience level. Despite the hypotension by hypovolemia, this patient was considered as intubated by intention-to-treat analysis; ‡ percentages were calculated based on the total number of patients intubated and died, respectively; § complications as acute renal failure, stroke, gastrointestinal hemorrhage, and infections.
similar doses of medications among the
groups (Table 2). Despite the higher
number of previous myocardial infarc-
tions in the oxygen group, the ventricular
function measured by echocardiography
was similar among the three groups. In
addition, the CPAP and bilevel-PAP
groups had a higher number of previous
episodes of pulmonary edema of any de-
gree (Table 1).

Several studies have investigated the
effects of noninvasive ventilation on the
treatment of acute cardiogenic pulmo-
nary edema, by comparing oxygen vs.
CPAP (1–3), CPAP vs. bilevel-PAP (4), and
oxygen vs. bilevel-PAP (5). We considered
that the inclusion of oxygen, CPAP, and
bilevel-PAP in the same trial was manda-
tory. Pulmonary edema has a wide spect-
rum of severity, and few patients have
severe respiratory distress at entry. In our
study, as in others (5), only 20% of the
patients evaluated were enrolled with se-
vere pulmonary edema. Therefore, it is
likely that the effects of noninvasive ven-
tilation are not uniform across the whole
spectrum of cardiogenic pulmonary
edema (24). In our study, the presence of
a control group treated with oxygen al-
lowed us to estimate the expected out-
come for the particular population se-
lected.

The assumption that CPAP and bi-
level-PAP are equivalent therapies could
not be made without closer examination.
By protocol design, different airway pres-
sure profiles in both strategies could re-
sult in very dissimilar effects on the car-
diovascular system (17). When adding
inspiratory assistance during bilevel-PAP,
the intrathoracic pressure is not propor-
tionally increased according to inspira-
tory pressures, but it depends on unpredictable factors, such as patient inspiratory time and effort, as well as the patient-ventilator synchrony, all of which can change over time (25). Concerned about potential hemodynamic problems, previous studies have tested relatively low (5 cm H$_2$O) EPAP during bilevel-PAP application (4–6). On the contrary, we decided to use exactly the same level of end-expiratory pressure (10 cm H$_2$O) during both CPAP and bilevel-PAP for the following two reasons: a) Previous studies showed near-optimum physiologic effects associated with 10 cm H$_2$O end-expiratory pressure (1–3); and b) provided that a good patient-ventilator synchrony is achieved, inspiratory support represents a very short portion of the respiratory cycle (25). This decision was also supported by a previous pilot study showing that a CPAP of 5 cm H$_2$O did not prevent endotracheal intubation in comparison with oxygen in the treatment of acute pulmonary edema (6). Therefore, this study design allowed us to determine the effect of adding inspiratory assistance over the well-known benefits of CPAP. One could argue that the initial setting of pressure support (5 cm H$_2$O) used in our study was low and could be insufficient to show the benefits provided by bilevel-PAP. However, evidence in the literature indicates that this level of pressure support is effective in patients with congestive heart failure. Philip-Joët et al. (13) showed that 5 cm H$_2$O pressure support in addition to EPAP of 10 cm H$_2$O is safe and superior in terms of oxygenation to CPAP of 10 cm H$_2$O in patients with heart failure. Chadda et al. (21) showed that 5 cm H$_2$O of pressure support added to 5 cm H$_2$O of EPAP significantly reduced the respiratory load when compared with 10 cm H$_2$O of CPAP in patients with acute cardiogenic pulmonary edema (21). Furthermore, in our study, it was possible to increase the IPAP up to 30 cm H$_2$O, ac-
Compared with oxygen therapy, continuous positive airway pressure and bilevel positive airway pressure resulted in similar vital signs and arterial blood gases and a lower rate of endotracheal intubation.

cording to the level of respiratory distress. Despite this possibility, the mean level of pressure support in this study was 5.3 cm H$_2$O and the maximum was 7 cm H$_2$O. The rapid improvement in respira- tory distress associated with both CPAP and bilevel-PAP is the most likely expla- nation for the low pressure support re- quirements. On the other hand, 10 cm H$_2$O of pressure support can overventi- late patients with acute cardiogenic pulmo- nary edema (4). One possible limitation of our study is that the sample did not provide sufficient power to confirm that CPAP is equal to bilevel-PAP, and we cannot exclude a type 2 error. However, the similarities in the outcome of both treatments suggest that if differences do exist between the two groups, they would probably be of little clinical significance.

In our study, 35 patients had acute ischemic heart disease as the cause of pulmonary edema (Table 1), and the number of myocardial infarctions was low and similar in oxygen, CPAP, and bilevel-PAP groups (Table 1). No myocar- dial infarctions were diagnosed after the randomization. In contrast to our find- ings, Mehta et al. (4) found an increased incidence of acute myocardial infarction in patients treated with bilevel-PAP com- pared with those treated with CPAP. The pathophysiologic mechanism by which bilevel-PAP rather than CPAP was harm- ful to patients in Mehta’s study remains unclear and unconfirmed (24). One pos- sible explanation for Mehta’s results is that patients treated with bilevel-PAP had a decrease in mean arterial blood pres- sure associated with an early decrease in PaCO$_2$. Another possibility raised by the authors is an unbalanced number of myocar- dial infarctions at entrance. Our re- sults are in accordance with the more recent study of Masip et al. (5), who found no increased incidence of acute myocardial infarction when comparing bilevel- PAP with oxygen.

The longer time of mask use during bilevel-PAP than CPAP (Table 2) was likely related to more complex weaning procedures in the former. Despite the inspi- ratory assistance provided by bilevel- PAP, we did not observe a different evo- lution in PaCO$_2$ levels. The majority of patients in our study were not hypercap- nic at entry, and this fact can explain the small effect of bilevel-PAP on PaCO$_2$ re- duction. Our result is similar to those in some recent studies (5), demonstrating that a significant impact of bilevel-PAP on arterial carbon dioxide levels can only be detected in a subgroup of patients with hypercapnia. It is possible that the impact of respiratory assistance provided by bilevel-PAP would be more important in patients with acute cardiogenic pulmo- nary edema and hypercapnia. Masip et al. (5), when comparing bilevel-PAP to oxy- gen in patients with acute cardiogenic pulmonary edema, found hypercapnia in 50% of patients. It must be stressed that in that study, noninvasive ventilation was only initiated after intensive care unit admission, several hours after the onset of respiratory distress. A delay in initiat- ing noninvasive ventilation is a possible explanation for hypercapnia in these pa- tients. According to the results of our study, the use of bilevel-PAP with a mod- erately high EPAP (≥ 10 cm H$_2$O) and relatively low IPAP (≥ 15 cm H$_2$O) nei- ther offered additional benefits nor caused harm compared with CPAP ther- apy in patients with acute cardiogenic pulmonary edema and no hypercapnia.

CONCLUSIONS

Our study showed that noninvasive ventilation applied by CPAP or bilevel- PAP had similar effects and was effective in preventing endotracheal intubation in patients with respiratory distress of car- diac origin. Our results support the con- cept that positive intrathoracic pressure must be seen as a nonpharmacologic form of treatment of acute pulmonary edema rather than a supportive measure.

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REFERENCES

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**ACCM Guidelines on SCCM Website**

The Guidelines and Practice Parameters developed by the American College of Critical Care Medicine are now available online at http://www.sccm.org/professional_resources/guidelines/index.asp. The printed version of the Guidelines, provided in a binder, is also available through the SCCM Bookstore, located at http://www.sccm.org/pubs/sccmbookstore.html. Please watch the Website to stay updated on the ACCM Guidelines and Practice Parameters.