Short-term Noninvasive Pressure Support Ventilation Prevents ICU Admittance in Patients With Acute Cardiogenic Pulmonary Edema

Matteo Giacomini, Gaetano Iapichino, Marco Cigada, Aldo Minuto, Rebecca Facchini, Andrea Noto and Elena Assi

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http://chestjournal.chestpubs.org/content/123/6/2057.full.html
**Study objectives:** Noninvasive ventilation, although effective as treatment for patients with acute cardiogenic pulmonary edema when prolonged for hours, is of limited use in the emergency department (ED). The aim of the study was to determine whether a short attempt at noninvasive pressure support ventilation avoids ICU admittance and to identify lack of response prediction variables.

**Design:** Prospective inception cohort study.

**Setting:** ED of a university hospital.

**Patients:** Fifty-eight consecutive patients with cardiogenic pulmonary edema who had been unresponsive to medical treatment and were admitted between January 1999 and December 2000.

**Interventions:** Pressure support ventilation was instituted through a full-face mask until the resolution of respiratory failure. A 15-min “weaning test” was performed to evaluate clinical stability. Responder patients were transferred to a medical ward. Nonresponding patients were intubated and were admitted to the ICU.

**Main outcome measures:** The included optimal length of intervention, the avoidance of ICU admittance, the incidence of myocardial infarction, and predictive lack of response criteria.

**Results:** Patients completed the trial (mean ± SD duration, 96 ± 40 min). None of the responders (43 patients; 74%) was subsequently ventilated or was admitted to the ICU. Two new episodes of myocardial infarction were observed. Thirteen of 58 patients died. A mean arterial pressure of < 95 mm Hg (odds ratio [OR], 10.6; 95% confidence interval [CI], 1.8 to 60.8; p < 0.01) and COPD (OR, 9.4; 95% CI, 1.6 to 54.0; p < 0.05) at baseline predicted the lack of response to noninvasive ventilation.

**Conclusions:** A short attempt at noninvasive ventilation is effective in preventing invasive assistance. A 15-min weaning test can identify patients who will not need further invasive ventilatory support. COPD and hypotension at baseline are negative predictive criteria.

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cessful or not. Noninvasive respiratory assistance is usually applied for hours. As a result, ICU facilities are required, and possibly unavoidable invasive ventilation can be delayed.\textsuperscript{7,10,17,18}

Of note, predictive criteria for lack of response to NIPSV for ACPE are lacking\textsuperscript{13,16,17} and higher incidences of acute myocardial infarction (AMI)\textsuperscript{10} and mortality\textsuperscript{10} were reported in patients who had been treated with NIPSV in contrast to those receiving continuous positive airway pressure or conventional treatment.

This uncontrolled prospective trial was performed in the ED on patients with pure ACPE who were unresponsive to full medical treatment. The primary objectives were as follows: (1) to determine the optimal duration of NIPSV (ie, whether it can be short enough to be performed in the ED, yet effective in avoiding intubation and ICU admittance); (2) to identify specific criteria that are predictive of lack of response; and (3) to evaluate the effect of NIPSV on patients with AMI and its role in the presence of AMI.

Secondary objectives were hospital length of stay and mortality.

### Materials and Methods

The setting was the ED of a university hospital. This study was performed in accordance with the Declaration of Helsinki. Informed consent was given by the patients in the study or by their next of kin. All consecutive patients affected by ACPE who required respiratory assistance after the institution of conventional medical treatment (defined as therapy with morphine oxygen via face mask, diuretics, and vasoactive drugs) had proven to be ineffective were eligible for the study.

The inclusion criteria were as follows: (1) pulmonary edema confirmed by rales over both lungs and signs of pulmonary congestion on chest radiographs within the first hour after presentation to the ED; (2) a pulse oximetric saturation ($\text{SpO}_2$) of $< 95\%$ despite oxygen administration at 10 L/min via a reservoir mask; and (3) severe respiratory distress with dyspnea and use of accessory muscles, severe cyanosis, oligoanuria, and signs of peripheral hypoperfusion.

The exclusion criteria were life-threatening conditions (eg, bradycardia or malignant tachyarrhythmias with severe hemodynamic impairment), end-stage renal or liver disease, severe neurologic impairment (ie, Glasgow coma scale, $< 7$), and concomitant pneumonia. Demographic and anamnestic data were collected. A gastric tube was placed to avoid stomach distension.

NIPSV was applied (Respipac SC ventilator; Dräger Medi-zintechnik GmbH; Lübeck, Germany) through a full-face mask. PEEP and pressure support were initially set at 5 and 10 cm H\textsubscript{2}O (over PEEP), respectively. This setting then was modified in the attempt to obtain a tidal volume between 5 and 7 mL/kg. The fraction of inspired oxygen ranged between 0.8 and 1.

Noninvasive BP, $\text{SpO}_2$, heart rate, and respiratory rate were monitored continuously. Arterial blood gas levels and ECG were recorded at baseline (on a reservoir oxygen mask before the onset of NIPSV) and just before the termination of NIPSV.

NIPSV was considered to be effective if dyspnea disappeared and if respiratory and hemodynamic parameters improved together with peripheral perfusion (ie, skin temperature and diuresis). The reporting of a subjective impression of “getting better” by the patient was also mandatory.

In the first 10 months of the study, the decision to stop NIPSV treatment and to perform a weaning test was left to the clinical judgment of the intensivist in charge, once the NIPSV efficacy criteria were met. After an interim analysis, which was intended to further reduce the duration of treatment, we decided to perform a weaning test within 90 min of the initiation of NIPSV.

The weaning test was conducted as follows. NIPSV was discontinued, and the patient was allowed to breathe spontaneously on a reservoir oxygen mask for 15 min. If the patient remained clinically stable (ie, $\text{SpO}_2$ of $> 95\%$, absence of dyspnea, and stable hemodynamic parameters), the patient was discharged to the ward (defined as the responder group). The wards were defined medical wards with cardiologic expertise in which at least some beds were equipped with ECG and $\text{SpO}_2$ monitoring equipment. If the patient did not respond to weaning, we proceeded to invasive ventilation, and the patient was transferred to the ICU (defined as the failure group).

The need for invasive ventilation, new episodes of AMI, hospital length of stay, and mortality were analyzed. AMI was diagnosed when two of the following three criteria were met: chest pain; increase in creatine phosphokinase concentration; and ECG signs of myocardial necrosis.

### Statistical Analysis

The data were reported as the mean ± SD and interquartile range. The Student $t$ test was used for statistical comparison. A $p$ value of $< 0.05$ was considered to be significant. A logistic regression model, built using a backward stepwise approach, was carried out to identify the independent variables at hospital admission that could predict failure (the dependent variable). Age, the presence of COPD on hospital admission, AMI, heart and respiratory rate, mean arterial pressure of $< 95$ mm Hg, Pa$_2$, pH, and PaCO$_2$ were considered to be independent variables and were introduced into the model only if they were associated with the dependent variable in the bivariate analysis at a permissive significance level (ie, $p < 0.1$ [$\chi^2$ test]) or if the odds ratio (OR) was $> 1.5$ or $< 0.67$. Variables that did not meet at least one of these conditions were not included in the final logistic model.

### Results

Between January 1999 and December 2000, 58 consecutive patients with ACPE were enrolled in the study. The underlying diseases were as follows: ischemic heart disease (34 patients); COPD (16 patients); hypertension (15 patients); diabetes (7 patients); chronic renal failure (8 patients); and patent ductus (1 patient). Seven patients (12\%) had signs of AMI at the time of hospital admission. Baseline hemodynamic and respiratory parameters, the data for which were collected before the onset of NIPSV, are reported in Table 1. Four patients could not be treated with NIPSV because of mask intolerance or refusal, five patient progressively worsened despite receiving NIPSV, and six patients failed the weaning test. All of these 15 patients were invasively ventilated and transferred to the ICU. NIPSV was
applied with a mean pressure support level of 14 ± 3 cm H2O10–16 (responder group, 14.1 ± 3.2 cm H2O; failure group, 14.1 ± 4.1 cm H2O) with a PEEP of 8 ± 2 cm H2O8–10 (responder group, 8.4 ± 1.8 cm H2O; failure group, 8.4 ± 1.8 cm H2O). NIPSV significantly improved hemodynamic and respiratory parameters in the 43 patients in the responder group who were discharged from the ED. A positive but nonsignificant trend was found also in the failure group, 14.1 – 105 to 143 min) in the first study period (19 patients) and 77 ± 22 min (range, 60 to 90 min) in the second study period (35 patients). In the responder group, 6 patients had AMIs on hospital admission and 37 did not. Only one patient who was admitted to the hospital with a diagnosis of AMI. Two of the patients who died were in the responder group (one died of ventricular fibrillation on the ward 20 h after undergoing NIPSV, and the second patient died on day 19), and one patient in the failure group died on day 9. Two patients developed AMIs during their hospital stay (1 patient in the failure group on day 4, and 1 of 43 patients in the responder group on day 5). The latter patient died on the 25th day of the hospital stay. The mean hospital length of stay did not differ between the patients in the responder group and those in the failure group (mean length of hospital stay, 17 ± 12 days [range, 9.5 to 19.5 days] vs 19 ± 10 days [range, 9.5 to 28 days], respectively; p = 0.4).

**DISCUSSION**

The great majority of patients with ACPE are initially managed in the ED. When patients do not respond to conventional medical treatment, ventilator assistance is needed. We tested the hypothesis that a short NIPSV run in the ED may avoid the use of invasive ventilation and admittance to the ICU. In the present study, critically ill patients were selected for treatment on the basis of the NIPSV protocol used at the ED. Logistic regression analysis in 54 patients identified two risk factors for lack of response to NIPSV. Patients with a mean BP of < 95 mm Hg at hospital admission had a 10-fold increased risk of failing the NIPSV trial (OR, 10.6; 95% confidence interval, 1.6 to 60.8; p < 0.01). The presence of COPD was also significantly associated with the need for invasive ventilation (OR, 9.4; 95% confidence interval, 1.6 to 54.0; p < 0.05). Twenty-two percent of the patients died (13 of 58 patients), 26.7% of those (4 of 15 patients) in the failure group and 20.9% of those (9 of 43 patients) in the responder group. Of the 13 patients who died, 3 had been admitted to the hospital with a diagnosis of AMI. Two of the patients who died were in the responder group (one died of ventricular fibrillation on the ward 20 h after undergoing NIPSV, and the second patient died on day 19), and one patient in the failure group died on day 9. Two patients developed AMIs during their hospital stay (1 patient in the failure group on day 4, and 1 of 43 patients in the responder group on day 5). The latter patient died on the 25th day of the hospital stay. The mean hospital length of stay did not differ between the patients in the responder group and those in the failure group (mean length of hospital stay, 17 ± 12 days [range, 9.5 to 19.5 days] vs 19 ± 10 days [range, 9.5 to 28 days], respectively; p = 0.4).

**Table 1—Demographic Characteristics and Baseline Clinical Parameters (During Oxygen Therapy) in the 58 Enrolled Patients***

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>74.1 ± 13.0 (69–84)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>60.0</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>36.8 ± 4.2 (35–40)</td>
</tr>
<tr>
<td>Arterial blood pH</td>
<td>7.20 ± 0.11 (7.14–7.28)</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>65.0 ± 34.8 (48–70)</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>63.7 ± 20.7 (47–76)</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>80.6 ± 13.7 (75–90)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>112.8 ± 24.4 (100–130)</td>
</tr>
<tr>
<td>Mean arterial BP, mm Hg</td>
<td>112.6 ± 29.6 (88–136)</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD (interquartile range).

**Table 2—Effects of NIPSV on Hemodynamic and Respiratory Parameters***

<table>
<thead>
<tr>
<th>Variables</th>
<th>Responder Group (n = 43)</th>
<th>Failure Group (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End-NIPSV</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>36.2 ± 6.0 (35–40)</td>
<td>24.5 ± 5.7 (20–28)†</td>
</tr>
<tr>
<td>Arterial blood pH</td>
<td>7.21 ± 0.10 (7.16–7.28)</td>
<td>7.38 ± 0.10 (7.3–7.4)†</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>67.7 ± 39.1 (51–70)</td>
<td>114.4 ± 52.0 (82–119)†</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>62.3 ± 20.0 (48–75)</td>
<td>43.7 ± 10.5 (36–47)†</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>82.0 ± 13.7 (70–91)</td>
<td>97.5 ± 2.0 (96–99)‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>114.6 ± 24.1 (100–131)</td>
<td>92.3 ± 16.6 (80–104)†</td>
</tr>
<tr>
<td>Mean arterial BP, mm Hg</td>
<td>118.6 ± 27.2 (102–138)</td>
<td>95.1 ± 14.1 (83–106)‡</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD (interquartile range).

†p < 0.05 compared to baseline.

‡p < 0.05 compared to responder patients at baseline.
by their need for ventilatory support after undergoing ineffective conventional medical therapy for ACPE (eg, morphine, oxygen mask, diuretics, and nitrates) [Table 1]. Patients with severe concomitant illnesses were excluded. Pneumonia was an exclusion criterion because in patients with pneumonia NIPSV already had proven to be a less effective therapy, and the patients probably needed a longer period of assistance. We did not perform a randomized trial since NIPSV has already proven to be effective in the treatment of ACPE and because our primary end point was the time needed to treat respiratory failure and to avoid ICU admission.

The duration of treatment is a critical issue when treating patients with ACPE outside the ICU. Prolonged ventilatory assistance is impractical in an environment like the ED, which is frequently understaffed, has limited space, and has a high turnover of patients. Moreover, NIPSV may dangerously delay, in some patients, unavoidable tracheal intubation and invasive mechanical ventilation. Despite the fact that most authors have reported a significant improvement of clinical parameters after 15 to 60 min, NIPSV is usually administered for a considerable length of time, ranging from 2 to 24 h in patients who already have been admitted to the ICU or are transferred there soon after the beginning of NIPSV. As described by other authors, invasive respiratory support is avoided in a large percentage of patients, but we have shown that adequate clinical stability can be obtained in a much shorter time. A 90-min NIPSV trial applied in the ED with patients who had ACPE resulted in a rapid assignment to the best treatment, medical or invasive support, without inappropriate delay and use of ED resources. The weaning test identified patients who, although their condition improved during NIPSV, did not reach a sufficient clinical stability to be assigned to pure medical treatment. Patients in the failure group were invasively treated and transferred to the ICU, while patients in the responder group were discharged in a short time and transferred to the ICU, or are transferred there soon after the beginning of NIPSV. We did not perform a randomized trial since NIPSV has already proven to be effective in the treatment of ACPE and because our primary end point was the time needed to treat respiratory failure and to avoid ICU admission.

We do not confirm the reported high incidence of AMI that has been associated with NIPSV. During their hospital stays, only two patients developed new episodes of AMI, days after undergoing NIPSV and too late to be attributed to it. Moreover, at variance with another report, six of seven patients with AMI at baseline were responders. In accordance with the results of other trials, NIPSV thus may be used with reasonable safety in patients with AMI. The overall mortality rate was in the range that has been reported by other authors (ie, 7 to 25%), even if many studies have included patients before medical treatment was defined to be ineffective, thus enrolling a less critical population.

Moreover, it is reasonable to affirm that deaths were related to the pathology itself rather than to the type of respiratory treatment. This finding is supported by the fact that the only death potentially related to treatment (which occurred during the first day in a responder patient who had AMI at baseline) was actually due to a sudden and unexpected malignant arrhythmia while the patient was on the ward. All the other deaths occurred days after NIPSV was performed in those who were not candidates for intensive treatment and probably were the result of concomitant terminal disease.

Finally, only two baseline conditions, mean arterial pressure < 95 mm Hg and a history of COPD, significantly predicted the failure of NIPSV. The latter condition could be at least partially explained by the sum of long-term and short-term increases in the work of breathing, resulting in an excessive respiratory workload that could not be rapidly managed by NIPSV alone. However, other concomitant factors, such as chronic tracheobronchitis, malnutrition, or obesity, cannot be excluded. The absence of arterial hypertension at baseline is probably consistent with a decreased left ventricular function with decreased cardiac reserves, selecting a group of patients with more severe conditions. The use of a NIPSV in ACPE patients with a mean arterial pressure of < 95 mm Hg at hospital admission cannot thus be encouraged. In COPD patients with ACPE, NIPSV may be effective, but the predictable need for prolonged respiratory assistance suggests caution in using it in the ED.

ACKNOWLEDGMENTS: We thank Luca Bigatello for discussing our results, and Bruno Simini for his precious advice and suggestions in preparing and editing the manuscript.

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Pulmonary Embolism in Pernicious Anemia and Hyperhomocysteinemia

To the Editor:

We read with great interest the article of Caldera et al1 about pulmonary embolism in a patient with pernicious anemia and hyperhomocysteinemia (October 2002). This case report illustrates the potential role of a cobalamin deficiency, here related to pernicious anemia, in the pathogenesis of venous thrombosis, especially in case of preexistent thrombophila status, herein a G20210A prothrombin gene mutation.

We have previously reported a similar observation in a 40-year-old woman with splenic venous infarction and thrombosis, hyperhomocysteinemia associated with a cobalamin deficiency related to celiac disease, and a preexistent thrombophilic disease: a C677T methyltetrahydrofolate reductase gene mutation.2 In our opinion, the question as to whether cobalamin deficiency may favor the onset of venous thrombosis remains questionable. We have previously reported a retrospective study of a cohort of patients (n = 120) with moderate hyperhomocysteinemia (20 ± 9 μmol/L, extreme, 13 to 42 μmol/L) related to cobalamin deficiency (145 ± 37 pmol/L, extreme, 45 to 200 pmol/L).3 In our study, we have observed 2.5% of venous thrombosis (all deep venous thrombosis and pulmonary embolism) in the group of patients with hyperhomocysteinemia related to cobalamin deficiency vs 2.6% in a control group (p value not significant).4 We suggest that future studies should be undertaken to definitively link hyperhomocysteinemia and cobalamin deficiency to venous thrombosis.

Emmanuel André’s, MD
Jean-Emmanuel Kurtz, MD, PhD
Hôpitaux Universitaires de Strasbourg
Strasbourg, France

Correspondence to: Emmanuel André’s, MD, Service de Médecine Interne, Clinique Médicale B, Hôpital Civil, Hôpitaux Universitaires de Strasbourg, 1 place de l’Hôpital à 67 091 Strasbourg Cedex, France; e-mail: emmanuel.andres@chru-strasbourg.fr

REFERENCES

Errata

In the July 2003 issue, the article, “What Is Sarcoidosis” (CHEST 2003; 124:367–371) by Jerome Reich, contained an error introduced during production. On page 368, the last sentence in the left column should read as follows: “In the remaining 12, a more gradual response developed, characterized by close associations of phagocytic macrophages and helper T cells, some of which were also Tac+; dendritic Langerhans cells were not seen.”

In the June 2003 issue, the article, “Short-term Noninvasive Pressure Support Ventilation Prevents ICU Admittance in Patients With Acute Cardiogenic Pulmonary Edema” (CHEST 2003; 123:2057–2061) by Giacomini et al, contained an error introduced during copy editing. On page 2059, the first sentence of the first full paragraph should read “Invasive mechanical ventilation was avoided in 76% (16 of 21) and 73% (27 of 37) of patients in the two periods, respectively.”
Short-term Noninvasive Pressure Support Ventilation Prevents ICU Admittance in Patients With Acute Cardiogenic Pulmonary Edema
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