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# Noninvasive pressure support ventilation vs. continuous positive airway pressure in acute hypercapnic pulmonary edema

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**Abstract** *Objective:* This study compared noninvasive pressure support ventilation (NIPSV) and continuous positive airway pressure (CPAP) in patients with acute hypercapnic pulmonary edema with regard to resolution time. *Design and setting:* Randomized prospective study in an emergency department. *Patients and participants:* We randomly assigned 36 patients with respiratory failure due to acute pulmonary edema and arterial hypercapnia ($PaCO_2$ >45 mmHg) to NIPSV ($n$=18) or CPAP through a face mask ($n$=18). *Measurements and results:* Electrocardiographic and physiological measurements were made over 36 h. There was no difference in resolution time defined as clinical improvement with a respiratory rate of fewer than 30 breaths/min and $SpO_2$ of 96% or more between CPAP and NIPSV groups. Arterial carbon dioxide tension was significantly decreased after 1 h of ventilation (CPAP, 60.5±13.6 to 42.8± 4.9 mmHg; NIPSV, 65.7±13.6 to 44.0±5.5 mmHg); respective improvements were seen in pH (CPAP, 7.22±0.11 to 7.37±0.04; NIPSV, 7.19±0.11 to 7.38±0.04), $SpO_2$ (CPAP, 86.9±3.7% to 95.1±2.6%; NIPSV, 83.7±6.6% to 96.0±2.9%), and respiratory rate (CPAP, 37.9±4.5 to 21.3±5.1 breaths/min; NIPSV, 39.8±4.4 to 21.2±4.6 breaths/min). No significant differences were seen with regards to endotracheal intubation and in-hospital mortality. *Conclusions:* NIPSV proved as effective as CPAP in the treatment of patients with acute pulmonary edema and hypercapnia but did not improve resolution time.

**Keywords** Noninvasive pressure support ventilation · Acute hypercapnic pulmonary edema · Continuous positive airway pressure · Resolution time

## Introduction

Acute pulmonary edema is one of the most important clinical problems in patients presenting to emergency departments. Management has traditionally focused on reducing ventricular filling pressures, principally with nitrates, loop diuretics, and oxygen at high flow rates. Over the past 15 years noninvasive ventilation (NIV) has been shown to reduce the need for endotracheal intubation and mechanical ventilation, length of stay in an intensive care unit (ICU), and mortality in patients with decompensated chronic obstructive pulmonary disease [1, 2, 3]. NIV can be delivered by continuous positive airway pressure (CPAP) or bilevel noninvasive positive-pressure support ventilation (NIPSV). The former maintains a positive airway pressure during spontaneous ventilation throughout the respiratory cycle whereas the latter is a mode of partial ventilatory assistance in which the ventilator supports the patient's triggered inspiration combining inspiratory pressure support and positive end-expiratory pressure. CPAP delivered by face mask has been shown to improve gas exchange and vital signs and to

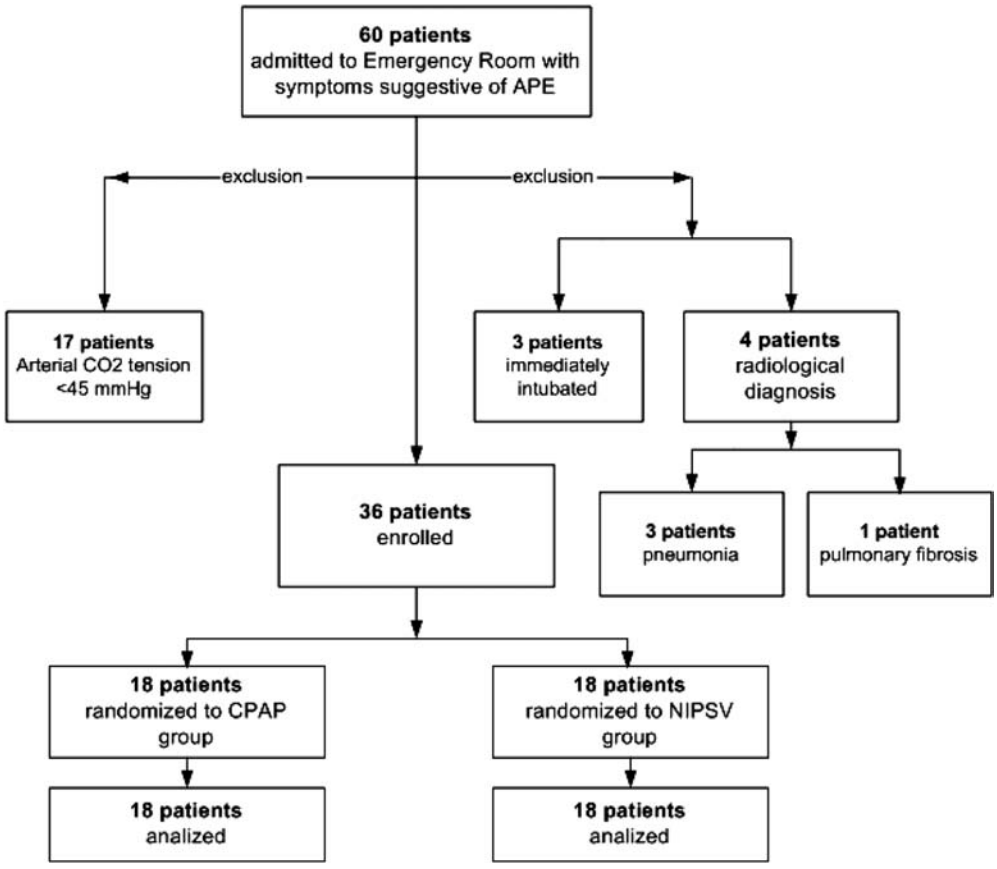


**Fig. 1** Trial profile

reduce the need for intubation and mechanical ventilation in patients with acute pulmonary edema (APE) [4, 5, 6, 7, 8]. The possible benefits of CPAP include improvement in oxygenation, decrease in respiratory work, and decrease in left ventricular afterload [9, 10]. More recently NIPSV has become increasingly used in combination with pharmacological treatment for APE as reported in these patients [11, 12, 13, 14, 15, 16].

A recent study bilevel found NIPSV superior to CPAP in unloading the respiratory muscles when patients were studied after at least a 24 h stabilization period [17]. A study comparing NIPSV and conventional therapy in APE has also shown NIPSV superior [14]. Another study of NIPSV vs. conventional therapy observed a reduced intubation rate in patients with hypercapnia [16]. Our controlled prospective randomized study compared NIPSV with CPAP in patients with acute hypercapnic pulmonary edema using the resolution time as the primary end-point.

## Patients and methods

The study design was approved by our institutional ethics committee. Written consent was obtained from the patients' relatives at the start of the protocol because of the severe condition of patients enrolled. Patients were recruited from the Niguarda Hospital Emergency Department in whom APE was diagnosed based on peripheral oxygen saturation ($SpO_2$) below 90% with more than 5 l/min oxygen via reservoir face mask, acute respiratory distress as evidenced by severe dyspnea, breathing frequency greater than 30 breaths/min, and use of accessory respiratory muscles or paradoxical abdominal motion in association with tachycardia (heart rate of >100 beats/min), cardiac gallops, bilateral rales, and typical findings of congestion on chest radiography, without a history suggesting pulmonary aspiration or evidence of pneumonia. Since hypercapnic patients were expected, according to literature, to benefit more from NIPSV treatment, we excluded patients with $PaCO_2$ less than 45 mmHg. We also excluded patients requiring endotracheal intubation immediately or already intubated, presenting a respiratory or cardiac arrest, cardiogenic shock (systolic blood pressure <90 mmHg), severe chronic renal failure (serum creatinine concentration >265 μmol/l), or presenting clinical and history findings of chronic obstructive pulmonary disease. Moreover patients were excluded if they were unresponsive, agitated, and unable to cooperate, or if they had any condition that precluded the application of a face mask. Patients previously enrolled in other studies were also excluded. Patients who were initially enrolled in the study but subsequently found not to have had APE on initial radiography were excluded from randomization.

Of the 60 patients admitted to our Emergency Room between January 2001 and January 2002 with acute respiratory distress suggestive of APE 36 were randomized to receive either CPAP ($n$=) or NIPSV ($n$=18; Fig. 1). Baseline characteristics of the patients, their history, and causes of APE (Table 1) were similar in the two groups, as were arterial blood gases, respiratory rate, heart rate, and blood pressure at study entry (Table 2). Multiple measure comparison (analysis of variance) showed no statistically significant

**Table 1** Baseline characteristics of the patients and causes of acute pulmonary edema (*APE*) (APACHE II Acute Physiology and Chronic Health Evaluation II)

| | CPAP (*n*=18) | NIPSV (*n*=18) | *p* |
|---|---|---|---|
| Age (years) | 76.8±6.9 | 76.8±6.6 | 0.99 |
| Males/females | 6/12 | 6/12 | |
| APACHE II score | 17.4±2.6 | 18.9±4.6 | 0.23 |
| History | | | |
| Heart failure | 7 (38.8%) | 10 (55.5%) | 0.50 |
| Acute myocardial infarction | 6 (33.3%) | 11 (61.1%) | 0.18 |
| Hypertension | 8 (44.4%) | 8 (44.4%) | >0.99 |
| Diabetes | 5 (27.8%) | 7 (38.8%) | 0.72 |
| Causes of APE | | | |
| Respiratory infections | 4 (22.2%) | 2 (11.1%) | 0.66 |
| Hypertension | 11 (61.1%) | 9 (50%) | 0.74 |
| Tachyarrhytmia | 2 (11.1%) | 4 (22.2%) | 0.66 |
| Myocardial infarction | 0 (0%) | 2 (11.1%) | 0.48 |
| Other | 3 (16.7%) | 3 (16.7%) | >0.99 |

difference between CPAP group and NIPSV group with regards to PaCO2 profile or pH profile.

Randomization used a computer-generated random number sequence, and assignments were placed in closed envelopes with identification numbers that were stored in the Emergency Room. Each patient's assignment was made on admission to the Emergency Room by the attending physician. Masking of treatment allocation was not possible. At the time of randomization patients were promptly fitted with an oronasal mask (Respironics, Murrysville, USA) and were connected to NIPSV or CPAP. Patients were managed according to our protocol for APE. Initial medical treatment consisting of the following: oxygen therapy via Venti-mask adjusted to obtain $SpO_2$ of 90% or more, 60 mg furosemide intravenously, 3 mg morphine sulfate intravenously (in patients without impaired consciousness), and continuous infusion of glyceryl trinitrate at an initial rate of 1–5 mg/h. Further doses of morphine (2 mg), furosemide (60 mg), and l glyceryl trinitrate were unrestricted and administered according to clinical response. Patients with fast atrial fibrillation received digoxin. Sodium nitroprusside (starting dose 0.1 μg/kg per minute) could be given to patients not immediately responsive to nitrate therapy and to those whose pulmonary edema was largely attributable to severe mitral or aortic valvular regurgitation or marked systemic hypertension. The dose was adjusted as required to improve the patient's overall clinical and hemodynamic status, using a systemic systolic pressure of 85–90 mmHg as the usual lower limit for a dose increment in patients previously normotensive and as long as adequate perfusion of vital organs was maintained. Patients were monitored by continuous pulse-oximetry and electrocardiography; urinary output was monitored through a Foley catheter. Patients were intubated and transferred to the ICU when the criteria of Brochard et al. [1] for treatment failure were met: respiratory arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation making nursing care impossible and requiring sedation, heart rate below 50 bpm with loss of alertness, and hemodynamic instability with systolic arterial blood pressure below 70 mmHg. Those who survived the acute phase were transferred to the Emergency Ward where echocardiography was performed.

To administer NIV a ventilator (Vela, Viasys; Critical Care Division, Calif., USA) was connected to a face mask. In the NIPSV group the degree of pressure support was initially set at 15 $cmH_2O$ and then adjusted to obtain a tidal volume of more than 400 ml, without leakage. A positive end expiratory pressure of 5 $cmH_2O$ was delivered to all patients. In the CPAP group 10 $cmH_2O$ was the selected pressure level. According to the protocol the duration of NIV was 3 h, but if a patient responded very rapidly, the treatment could be stopped earlier. Fraction of inspired oxygen ($FIO_{2)}$ was delivered to achieve $SpO_2$ of 90% or more. When the goal of $SpO_2$ between 90% and 92% was reached, $FIO_2$ was maintained constant. Heart rate, breathing frequency, and $SpO_2$ were monitorized continuously; arterial blood pressure was measured every 5 min; arterial blood gases were recorded at the time of study entry and 15, 30, 60, and 180 min later. Chest radiograph and routine blood samples were obtained at the time of study entry, when the acute physiology component of the Acute Physiology and Chronic Health Evaluation II score was also determined.

Resolution of APE was defined as evident clinical improvement with both a respiratory rate of less than 30 breaths/min and $SpO_2$ of 96% or more with oxygen ($FIO_2$=0.28). The time for these criteria to be met was called the resolution time [14]. Noninvasive ventilation was stopped when clinical improvement was evident with both a respiratory rate less than 24 breaths/min and $SpO_2$ of 96% or more. NIV was resumed if the following concomitant conditions appeared within 60 min of spontaneous ventilation: respiratory rate greater than 25/min and $SpO_2$ less than 90%. Patients were weaned after meeting the criteria for NIV stopping by gradually reducing pressure support or CPAP to 8 cmH2O.

The primary end-point was the resolution time comparing two different modalities of noninvasive ventilation, NIPSV vs. CPAP. For a statistical power of 80% we calculated that a sample size of 36 patients would allow us to detect, at $p$=0.05, a difference of 10 min (arbitrarily chosen) in resolution time between the two groups of patients. Secondary objectives included intubation rate, in-hospital mortality rate, and gas exchange response. We compared physiological measurements in the CPAP and NIPSV groups using the unpaired *t* test for data obtained at study entry. The paired *t* test was employed for within-group comparisons of variables at study entry and 1 h later. Multiple comparisons were made using analysis of variance for repeated measures. Fisher's exact test was employed to compare the rates of intubation and in-hospital mortality in the two groups.

**Table 2** Physiological measurements at baseline and after 1 h; differences between the groups at baseline were not statistically significant

| | CPAP | | | NIPSV | | |
|---|---|---|---|---|---|---|
| | Baseline | After 1 h | *p* | Baseline | After 1 h | *p* |
| $PaO_2/FIO_2$ ratio | 183±64 | – | – | 159±53 | – | – |
| Bicarbonate (mEq) | 24±4 | – | – | 25±6 | – | – |
| Heart rate (beats/min) | 110±20 | – | – | 113±23 | – | – |
| Systolic BP (mmHg) | 186±42 | – | – | 182±34 | – | – |
| Diastolic BP (mmHg) | 100±19 | – | – | 98±21 | – | – |
| Respiratory rate (bpm) | 37.9±4.5 | 21.3±5.1 | <0.001 | 39.8±4.4 | 21.2±4.6 | <0.001 |
| Arterial pH | 7.22±0.11 | 7.37±0.04 | <0.001 | 7.19±0.11 | 7.38±0.04 | <0.001 |
| $PaCO_2$ (mmHg) | 60.5±13.6 | 42.8±4.9 | <0.001 | 65.7±13.6 | 44.0±5.5 | <0.001 |
| $SpO_2$ (%) | 86.9±3.7 | 95.1±2.6 | <0.01 | 83.7±6.6 | 96.0±2.9 | <0.01 |

**Table 3** Patient outcomes

| | CPAP ($n$=18) | NIPSV ($n$=18) | $p$ |
|---|---|---|---|
| Endotracheal intubation | 1 (5.5%) | 2 (11.1%) | 0.5 |
| In-hospital death | 1 (5.5%) | 0 (0%) | 0.5 |
| Resolution time | 29±18 | 30±16 | 0.87 |

## Results

After 1 h of ventilation both groups showed a decrease in arterial carbon dioxide tension and in respiratory rate and an improvement in pH and $SpO_2$. There was no difference in resolution time between the groups (Table 3). Ventilation was resumed in one patient in the CPAP group and none of the NIPSV patients. Endotracheal intubation rate and in-hospital mortality did not differ significantly between the groups (Table 3). CPAP was applied for a mean of 220±82 min and NIPSV for a mean of 205±68 min). One patient in the CPAP group and two in the NIPSV group required additional doses of nitroprusside because of arterial hypertension not responsive to nitrates. The intention-to-treat analysis to assess the effect the results based on radiological criteria therefore added four patients previously excluded (two in each group). The unpaired $t$ test revealed no significant differences in resolution time between the groups showed (CPAP, 34±22 min; NIPSV, 33±20; $p$=0.97).

## Discussion

In this study NIPSV and CPAP both proved effective modalities of treating patients with APE associated with hypercapnia. Our study is the first to compare NIPSV and CPAP and their effectiveness in these patients with regards to resolution time, which was found to be similar in the two groups. Previously, Wysocki et al. [18] observed that the application of NIPSV entailed no benefit in a selected group of patients without hronic obstructive pulmonary disease compared to medical therapy, except in patients with $PaCO_2$ higher than 45 mmHg. A recent randomized controlled study [14] showed NIPSV superior to conventional oxygen therapy, especially in patients with severe signs of alveolar edema on chest radiography and those with impaired functional class or high arterial pressure of carbon dioxide. Nava et al. [16] observed hypercapnic patients that NIPSV improved $PaCO_2$ significantly more rapidly and reduced the intubation rate compared to medical therapy. Masip et al. [19] found that patients with pH less than 7.25 or systolic blood pressure less than 180 mmHg associated with hypercapnia should be promptly considered for NIV to prevent endotracheal intubation. Previously only a single study [11] has compared NIPSV and CPAP in patients with APE, but the authors interrupted their trial when a high proportion of patients with acute myocardial infarction was detected in the NIPSV group; the relationship between mode of ventilation (CPAP vs. NIPSV) and the occurrence of acute myocardial infarction remains unclear.

Our aim was to compare the effectiveness of CPAP and NIPSV in a subgroup of patients with APE associated with hypercapnia. It is well known that continuous positive airway pressure in patients with left ventricular failure increases functional residual capacity, improves respiratory mechanics, and thus improves oxygenation and potentially decreases left ventricular afterload [9, 10]. Chadda and colleagues [17] have recently demonstrated that NIPSV is more effective than CPAP in unloading respiratory muscles in APE. Therefore in hypercapnic patients with signs of respiratory distress such as patients with APE the addition of a pressure support ventilation to the CPAP may improve the impairment of the respiratory pump and alveolar ventilation leading to the rapid reduction in respiratory frequency and subsequently a more pronounced improvement in $PaCO_2$ than with CPAP alone.

Surprisingly, CPAP and NIPSV had similar resolution times and similar gas exchange responses (as shown by analysis of variance), suggesting that the mechanism responsible for improvement in hypercapnic patients with APE is more likely related to the application of a positive airway pressure. The main pathophysiological mechanism of ventilatory pump failure in patients with pulmonary edema is related to an increase in inspiratory muscle energy demands [20]. Work of breathing is may be held responsible for increasing energy demands when the elastic load (alveolar congestion and consequently a decreased lung compliance) and hyperventilation imposed on the inspiratory muscles are increased. Therefore we suggest that in patients with APE and hypercapnia the positive airway pressure improves the pulmonary congestion and subsequently gas exchange, respiratory mechanics, and finally respiratory pump. Consequently the addition of pressure support to the CPAP would add no advantage in the treatment of these patients. Although we cannot be sure that intrathoracic pressures using 15/5 $cmH_2O$ would be similar to that of 10 $cmH_2O$ CPAP, these specific pressure values were selected because (a) they are common settings used in patients with acute respiratory failure in a previous study [11], and (b) they should provide mean airway pressures close to those levels obtained with a CPAP of 10 $cmH_2O$.

A limitation of our study that must be underlined is the used of resolution time as an indirect index of the effectiveness of NIV treatment, based mainly on noninvasive measured parameters. In our study population APE was mainly secondary to ischemia, hypertension and consequent diastolic heart failure, or cardiac arrhythmia, respiratory tract infections, or all of the above. Both NIV modalities produced significant improvements in $PaCO_2$,

pH, heart rate, and respiratory rate within 1 h after the initiation of treatment.

In conclusion, the results of our preliminary study a subgroup of hypercapnic patients demonstrate that NIPSV is as effective as CPAP in treating of APE, and that the two ventilation modalities lead to similar benefits.

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