Abstract. – OBJECTIVE: Noninvasive ventilation (NIV) is an effective treatment in patients with acute exacerbation of COPD (AECOPD). However, it may induce post-hypercapnic metabolic alkalosis (MA). This study aims to evaluate the effect of acetazolamide (ACET) in AECOPD patients treated with NIV.

PATIENTS AND METHODS: Eleven AECOPD patients, with hypercapnic respiratory failure and MA following NIV, were treated with ACET 500 mg for two consecutive days and compared to a matched control group. Patients and controls were non-invasively ventilated in a bilevel positive airway pressure (BiPAP) mode to a standard maximal pressure target of 15-20 cmH₂O.

RESULTS: ACET intra-group analysis showed a significant improvement for PaCO₂ (63.9 ± 9.8 vs. 54.9 ± 8.3 mmHg), HCO₃⁻ (43.5 ± 5.9 vs. 36.1 ± 5.4 mmol/L) and both arterial pH (7.46 ± 0.06 vs. 7.41 ± 0.06) and urinary pH (6.94 ± 0.77 vs. 5.80 ± 0.82), already at day 1. No significant changes in endpoints considered were observed in the control group at any time-point. Inter-group analysis showed significant differences between changes in PaCO₂ and HCO₃⁻ (delta), both at day 1 and 2. Furthermore, the length of NIV treatment was significantly reduced in the ACET group compared to controls (6 ± 8 vs. 19 ±19 days). No adverse events were recorded in the ACET and control groups.

CONCLUSIONS: ACET appears to be effective and safe in AECOPD patients with post-NIV MA.

Key Words: AECOPD, Acetazolamide, Metabolic alkalosis, NIV, Medical ward.

Effect of acetazolamide on post-NIV metabolic alkalosis in acute exacerbated COPD patients

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. The natural history of the disease is marked by exacerbations that strongly influence the prognosis of patients with COPD.

Some patients with severe COPD become chronically hypoxic with or without hypercapnia, as the disease progresses and their prognosis is usually poor. Treatment of chronic hypoxia with supplemental oxygen (O₂) has been shown to improve survival; however, the degree of hypercapnia worsens in some patients during oxygen therapy.

COPD hypercapnia is probably due to a combination of worsened ventilation/perfusion mismatch, carbon dioxide (CO₂) retention with O₂-mediated blunting of the peripheral chemoreceptor drive and the Haldane effect. Furthermore, Foucher et al. found that the rate of death in patients with COPD receiving long-term O₂ therapy was higher in the hypercapnic group compared to the normocapnic group. Hence, hypercapnia itself probably represents an independent prognostic factor of COPD severity.

The use of noninvasive ventilation (NIV), in patients with acute exacerbation of COPD (AECOPD), is increasing over the last decade and appears to be supported by a consistent number of randomized controlled trials. However, in several cases, the NIV beneficial effect in AECOPD might be negatively influenced by the onset of post hypercapnic metabolic alkalosis (MA).

MA is an acid-base disorder frequently occurring in critical ill patients characterized by an elevated serum pH level secondary to increased plasma bicarbonate (HCO₃⁻) retention and often associated with high mortality and morbidity. In fact, MA may depress cardiac output and worsen hypokalemia and hypophos-
phatemia, as well as involve alterations in oxyhemoglobin dissociation and central respiratory drive. All the above mentioned mechanisms induce hypoventilation and may lead to respiratory failure13.

Strong literature evidence supports that MA correction increases both minute ventilation and arterial partial pressure of oxygen (PaO₂)14. Acetazolamide (ACET), an inhibitor of renal carbonic anhydrase, has been used to treat MA in COPD patients demonstrating beneficial effects on the ventilatory drive15,16. ACET decreases proximal tubular HCO₃⁻ reabsorption through carbonic anhydrase inhibition in the luminal borders of renal proximal tubule cells17, as reflected by the consequential alkaline diuresis. On the other hand, the reduction in PaCO₂ can be ascribed to the stimulus on the ventilatory drive, secondary to MA reversal. In fact, the generated metabolic acidosis stimulates peripheral and central chemoreceptors, increasing minute ventilation. Recently, some authors reported a potential usefulness of ACET in mechanical ventilated AECOPD patients18.

To the best of our knowledge there are no previous studies that evaluated the effects of ACET on acid-base balance in patients with COPD undergoing NIV.

**Patients and Methods**

**Study Protocol and Population**

The study assesses data collected over a period of 17 months in a Division of Internal Medicine.

Among all patients with acute respiratory failure, referred to our ward and treated with NIV, those with AECOPD, who developed post-NIV MA, were sequentially evaluated for being included in the study (Figure 1).

Eligible patients fulfilled the following inclusion criteria: both males and females aged ≥18 yrs with a clinical history of COPD, a diagnosis of acute exacerbation (according to the international guidelines www.goldcopd.com), hypercapnic respiratory failure (PaCO₂ ≥ 45 mmHg, PaO₂ < 60 mmHg) and MA (pH ≥ 7.40 and HCO₃⁻ ≥30 mmol/L) following NIV treatment.

![Figure 1. CONSORT diagram.](image-url)
Patients were excluded if one or more of the following conditions were present: relevant concomitant respiratory and neuromuscular diseases, renal failure (glomerular filtration rate < 20 ml/min), potassium serum levels < 3.0 mEq/L, hypersensitivity to acetazolamide or sulfonamides, recent administration of bicarbonates or sedative drugs.

All patients gave their written informed consent. The study was approved by the Institutional Review Board and was performed in accordance with the principles of the Helsinki Declaration.

After enrollment, ACET administration was added to NIV treatment for two consecutive days. ACET was prematurely discontinued when reversal of MA was obtained (arterial pH ≤ 7.38) or hypokalemia occurred (potassium ≤ 3.0).

The following clinical and laboratory parameters were measured at enrollment (day 0) and after 24 (day 1) and 48 hours (day 2): arterial O₂ partial pressure (PaO₂), arterial CO₂ partial pressure (PaCO₂), potassium, chloride, sodium, lactate, bicarbonates (HCO₃⁻), serum and urinary pH.

Enrolled subjects were compared to an age- and sex-matched control group of AECOPD patients with post-NIV MA.

All included subjects were concomitantly treated following international guidelines for COPD exacerbation, with systemic corticosteroids (prednisone 20-40 mg daily) and empirical antibiotic therapy according to the local bacterial resistance pattern, and for related comorbidities.

Clinical and laboratory parameters were collected at the same time points in the two groups.

**Study Procedures**

**Non Invasive Ventilation**

Patients and controls were non invasively ventilated through a device (Vivo 50 Breas, Malmö, Sweden) set in a bilevel positive airway pressure (BiPAP) mode. At first, inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) were set at 10 cmH₂O and 4.5 cmH₂O, respectively. IPAP was then increased by 2.5 cmH₂O each 10 minutes to a standard maximal pressure target of 15-20 cmH₂O until a therapeutic response was achieved or patient tolerability was reached. All subjects underwent NIV 24/24 hours. A full face mask was used for every patient for the first 24 hours followed by a switch to an oro-nasal mask.

O₂ supplementation was administered, when needed, to obtain an arterial oxyhemoglobin saturation (SpO₂) ≥ 90%.

**Arterial Blood Gas Sampling**

Blood was anaerobically drawn from the radial artery via a percutaneous needle puncture and analyzed through a blood gas analyzer (Gem Premier 4000 Instrumental Laboratory, Barcelona – Spain) 30 minutes before daily ACET administration.

**Urine Sampling**

Urine samples were daily collected, in a sterile container and were analyzed in a central laboratory according to standard procedures in order to determine pH values.

**Study drug**

ACET 500 mg (Diamox; Sanofi-Aventis, Paris, France) was orally administered once a day at 8:00 am for two consecutive days by physicians in charge of the patient. The drug was started the morning after MA was found at arterial blood gas sampling (Day 0).

**Study Outcomes**

Outcomes of the study were represented by the effects of ACET on metabolic alkalosis and hypocapnic respiratory failure and were assessed using the following endpoints: PaCO₂, arterial pH, HCO₃⁻, urinary pH. Length of NIV treatment and hospitalization, as well as safety issues, were also recorded.

**Statistical Analysis**

After having checked data distribution, the Student t-test was used to assess intra-group and inter-group variability. All values are reported as mean ± SD, a p-value < 0.05 was considered as statistically significant. Data were analyzed with the SPSS software, version 19.0 (SPSS Inc, Chicago, IL, USA).

**Results**

Out of the 76 patients with acute respiratory failure treated with NIV in our Medical Division, a diagnosis of AECOPD was made in 28 subjects. Those who developed post-NIV MA (n=11) were enrolled in the study for being treated with ACET and were compared to eleven matched controls. Demographic characteristics of the two populations are reported in Table I.
Table I. Demographic characteristics of study population at baseline.

<table>
<thead>
<tr>
<th></th>
<th>ACET group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>11</td>
<td>11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>6/5</td>
<td>7/4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>70.8 ±12</td>
<td>72.7 ±7.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>55.5 ± 8.5</td>
<td>63.3± 13.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>73.8 ± 10.9</td>
<td>73.1 ± 13.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.32 ± 0.05</td>
<td>7.34 ± 0.03</td>
<td>n.s.</td>
</tr>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>137.4 ± 2.9</td>
<td>136.9 ± 3.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>3.7 ± 0.4</td>
<td>4.35± 0.05</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cl⁻ (mEq/L)</td>
<td>97.6 ± 4.0</td>
<td>98.4 ± 5.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>2.0 ± 1.5</td>
<td>1.0 ± 0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>131 ± 11/76</td>
<td>123 ± 24/75</td>
<td>n.s.</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>85 ± 14</td>
<td>91 ± 9</td>
<td>n.s.</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>25 ± 12</td>
<td>24 ± 5</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.06 ± 0.26</td>
<td>0.85 ± 0.34</td>
<td>n.s.</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.80 ± 0.56</td>
<td>1.77 ± 0.48</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.59 ± 0.1</td>
<td>0.49 ± 0.16</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Comorbidities

Cardiovascular (BH, Chronic ischemic heart disease, Chronic heart failure, Atrial fibrillation) 81% 64% \( p < 0.05 \)
Metabolic (Obesity, Hypothyroidism, Dyslipidemia, Osteoporosis, Diabetes mellitus) 54% 54% n.s.
Others 27% 27% n.s.

Figure 2. Primary endpoints in the ACET group. *\( p < 0.05 \) compared to baseline (day 0).
Two patients discontinued ACET after day 1 for reversal of MA.

ACET intra-group analysis at day 1 showed a significant reduction for PaCO₂, serum pH and HCO₃⁻ compared to day 0. In details, PaCO₂ decreased from 63.9±9.8 mmHg to 54.9 ± 8.3 mmHg (p = 0.01), serum pH from 7.46 ± 0.06 to 7.41 ± 0.06 (p = 0.004) and HCO₃⁻ from 43.5 ± 5.9 to 36.1 ± 5.4 mmol/L (p = 0.005). Accordingly urinary pH was significantly increased at day 1 compared to day 0 (6.94 ± 0.77 vs. 5.80 ± 0.82, p = 0.006). Data collected at day 2, despite remaining significantly different, for all endpoints studied compared to baseline conditions (day 0), showed no further significant changes (Figure 2).

No significant changes in all the above blood gas parameters have been observed at the same time points in the control group (data not reported).

As shown in Figure 3, inter-group analysis, performed by comparing changes observed in the ACET and control group at day 1 and at day 2 (Delta), showed significant differences for PaCO₂ and HCO₃⁻ at both time-points.

Among secondary outcomes, the length of NIV treatment was significantly shorter in the ACET group compared with the control group (6 ± 8 vs. 19 ± 19 days, p = 0.03). Length hospitalization was similar in ACET and control patients.

No drug related adverse events, need for intubation or deaths have been reported in the ACET group.

**Discussion**

According to available evidence, there is no consensus on the clinical benefit of ACET on hypercapnic respiratory failure in COPD. In fact, although data support a positive role of ACET in reversing MA, a recent Cochrane systematic review and meta-analysis in stable COPD patients failed in showing improvement of clinical relevance, despite reporting positive effects on pH, PaCO₂ and PaO₂.

To the best of our knowledge this is the first report of a positive clinical effect of ACET on post-NIV MA in AECOPD patients.

Mixed Acid-Base disorders appear to be a relative frequent complication during NIV treatment in AECOPD patients. With this regards, in our study we observed that eleven out of twenty-eight AECOPD patients, with acute respiratory failure and undergoing NIV treatment, developed MA. In this subgroup of patients, we demonstrated that a short treatment with ACET 500 mg once a day can improve both clinical and blood gas parameters. Our results showed that, already 24 hours after the first drug administration, PaCO₂, HCO₃⁻, serum and urinary pH significantly improved.

Recently, Faisy et al demonstrated that in AECOPD mechanically ventilated patients, with mixed or pure MA, ACET administration during the weaning period only moderately diminished serum HCO₃⁻ levels, with no changes either in PaCO₂ levels or in minute ventilation. On the contrary, we observed a simultaneous reduction of HCO₃⁻ levels and PaCO₂ after ACET administration at the end of treatment period. It may be speculated that the above contrasting findings could be due to the different ventilation strategy adopted (NIV vs mechanical ventilation).
Furthermore, differently from the work of Faisy et al.\textsuperscript{18} where patients withdrew ACET after 72 hours, we chose to administer the drug for 48 hours in view of previous observational data gathered in our ward that showed, a reversal of MA after only two administrations. The treatment phase extension to three days could have also increased the risk of reducing the study sample due to the choice of stopping ACET administration after MA reversal.

Oxygen supplementation during NIV treatment was set to maintain a SpO\textsubscript{2} threshold of at least 90\% and was provided through ventilator system, which however did not allow to accurately determine the FiO\textsubscript{2}, making hard to interpret and analyze changes of PaO\textsubscript{2} and PaO\textsubscript{2}/FiO\textsubscript{2} ratio. We, therefore, chose not to report data on these variables during the interventional phase of the study.

In addition to gas analysis results, we observed that the duration of NIV treatment was significantly shorter in ACET compared to control group. These findings are consistent with previous reports demonstrating that MA is an independent predictor of longer duration of NIV treatment in hypercapnic respiratory failure due to AECOPD.

At last, the lack of adverse events (need for intubation or death) supports a reliable safety profile of this therapeutic choice.

The heterogeneity observed in previous studies assessing ACET effectiveness in COPD patients may be related to the concomitant treatment with furosemide or corticosteroids. It’s in fact well known that these drugs lead to MA by stimulating distal tubular H\textsuperscript{+} secretion with different mechanisms. In addition, furosemide may limit the delivery of ACET to renal tubules, since they share the same carriermediate mechanism. Recent evidence revealed that, in presence of concomitant administration of furosemide or corticosteroids, a greater ACET dosage is required to reduce serum HCO\textsubscript{3}– concentration\textsuperscript{18(599,727),(867,746)}\textsuperscript{18}. In our study concomitant treatments with furosemide and corticosteroids were maintained stable throughout the entire study period.

The absence of further statistically significant differences in the ACET group analysis at day 2 compared to day 1 in primary endpoints considered, as well as the lack of significant differences in pH changes in the intergroup analysis, deserve to be disclosed. A possible explanation may be represented by the small sample size evaluated, even less consistent at day 2 due to the two patients who discontinued ACET for MA reversal. A secondary potential reason could be related to the pre-planned study design length, which allowed us to follow-up patients only for 48 hours. Significant differences observed between baseline conditions and day 1 could in fact require more than further 24 hours of NIV to be confirmed.

**Conclusions**

At the best of our knowledge, this is the first study assessing the effects of ACET in AECOPD patients with MA treated with NIV. Our findings showed a positive effect of ACET on PaCO\textsubscript{2}, HCO\textsubscript{3}–, and both arterial and urinary pH. Furthermore, a 48 hours administration of ACET was able to significantly reduce the length of NIV treatment. This interesting result might deserve, however, to be confirmed in future research studies performed in a larger sample size and for a longer follow up period.

**Conflict of Interest**

The Authors declare that there are no conflicts of interest.

**References**


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