Evolution of acute chronic obstructive pulmonary disease treated with non-invasive ventilation

Evolución de la enfermedad pulmonar obstructiva crónica agudizada tratada con ventilación no invasiva

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ABSTRACT

Introduction: Non-invasive ventilation is a new modality of respiratory support therapy in patients with acute chronic obstructive pulmonary disease.

Objective: To describe the factors related to failure of non-invasive ventilation treatment in the population of patients with exacerbated chronic obstructive pulmonary disease.

Methods: An observational, descriptive and cross-sectional study was carried out in the intensive care units of Saturnino Lora Hospital, between January, 2011 and January, 2019.

Results: The presence of leaks, the start time of the treatment longer than 24 hours, the decrease in the average values of pH and Glasgow, the increase in respiratory and heart rates and PaCO2, are associated with failure of non-invasive ventilation.
**Conclusions:** Alterations of typical clinical and hemogasometric variables of ventilation, structure the failure in this patients population.

**Key words:** noninvasive ventilation; chronic obstructive pulmonary disease; acute respiratory failure.

**RESUMEN**

**Introducción:** La ventilación no invasiva es una nueva modalidad de terapia de soporte respiratorio en los pacientes con enfermedad pulmonar obstructiva crónica agudizada.

**Objetivo:** Describir los factores relacionados con el fracaso en la población de enfermos con enfermedad pulmonar obstructiva crónica agudizada, tratados con ventilación no invasiva.

**Métodos:** Se realizó un estudio observacional, descriptivo y transversal en las unidades de atención al grave del Hospital Provincial “Saturnino Lora”, entre enero de 2011 and enero de 2019.

**Resultados:** La presencia de fugas, el tiempo de inicio del tratamiento mayor de 24 horas, la disminución de los valores promedios del pH y el Glasgow, el incremento de las frecuencias respiratoria y cardiaca y la PaCO2, se asocian con el fracaso de la ventilación no invasiva.

**Conclusiones:** Alteraciones de variables propias de la ventilación, clínicas y hemogasométricas estructuran el fracaso en esta población de enfermos.

**Palabras clave:** Ventilación no Invasiva; Enfermedad Pulmonar Obstructiva, Crónica. Insuficiencia respiratoria aguda.

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**Introducción**

Acute respiratory failure (ARF) is a condition that can appear in patients with healthy lungs or with a history of lung disease and chronic obstructive pulmonary disease (COPD), which is the most prevalent among these conditions.\(^{[1,2]}\)
More than 52 million people in the world suffer from COPD. It is estimated that there are currently about 16 million people that have been diagnosed with the disease in the United States, and many others have the disease without being diagnosed.[3]

Non-invasive ventilation (NIV) is one of the therapeutic alternatives that has shown the best benefits for acute COPD and this scientific evidence has been found in multiple studies carried out with a higher level of quality over conventional oxygen therapy and orotracheal intubation in hypercapnic ARF.[4,5,6,7]

Brochard’s work in 1995[1] showed a faster clinical-gasometric improvement with NIV therapy than with conventional therapy and considered NIV in acute COPD as a therapeutic element of no doubt, it was supported by 12 randomized controlled studies that compared NIV therapy to usual care, as the object of three meta-analyzes, a reduction in hospital mortality was also established with the use of this technique.[8,9,10,11]

COPD was considered acute according to the criteria of the Clinical Guide for the diagnosis and treatment of Chronic Obstructive Pulmonary Disease of the Working Group of the Spanish Society of Pneumology and Thoracic Surgery.[12,13]

Due to the international scientific evidence, the use of NIV therapy has been incorporated in Cuba. Acute COPD is one of the main causes of admission to care units. This investigation is carried out with the objective of describing patients with acute chronic obstructive pulmonary disease treated under NIV therapy according to epidemiological, clinical, ventilatory and hemogasometric variables of interest.

**Methods**

An observational, descriptive and cross-sectional study was carried out in patients diagnosed with acute COPD ventilated in a non-invasive way in the emergency intensive care unit (ICU), intermediate care unit (ICU) and in the intensive care unit (ICU) of Saturnino Lora Hospital, in the period from January, 2011 to January, 2019, according to the following criteria:

Inclusion criteria: Patients with a diagnosis of acute COPD who received NIV.
Exclusion criteria:

- Patients with disorders which contraindicated NIV.
  - Cardiac or respiratory arrest
  - Non-respiratory organic dysfunction
- Upper gastrointestinal bleeding
- Hemodynamic instability
  - Facial surgery, trauma or facial deformity
  - Upper airway obstruction or Orotracheal secretions obstructing the upper airway
  - Glasgow Coma Scale ≤ 8
- Deceased patients with less than 2 hours, as the short time limits the adequate collection of the necessary information.

The sample was selected by simple random sampling, a minimum sample size of 95 patients was calculated, with a final sample size of 118 patients. The following variables were studied: age, sex, NIV result, leaks, duration, modality, time of onset of symptoms, frequency of application, average level of pressure on PEEP (positive pressure at the end of expiration), level of PEEP, triggers, comorbidity, evolutionary and basal average values of respiratory rate, heart rate, mean blood pressure, Glasgow coma scale, PaO2 / FiO2 ratio, pH and PaCO2

The non-invasive ventilation protocol was applied to all the patients included in the study.

For the analysis of the information, the absolute numbers and the percentage were used. The middle and its standard deviation, the average and the range were calculated. 95 % confidence intervals were computed. The t-Student technique was applied for the comparison of mean differences, as well as the Chi squared test (X²) for the difference in proportions.

**Ethical aspects**

The research was submitted for consideration and approval by the Scientific Council of the Hospital and the Research Ethics Committee. Adherence to
International Conventions on ethical principles for research in human beings was taken into account. This research respected the principles promulgated in the Declaration of Helsinki, (particularly in the last revision: Helsinki VI, Edinburgh, 2000), which contains the ethical principles for research in human beings, and the international ethical guidelines for research and Biomedical experimentation in human beings, from the Council of International Organizations of Medical Sciences (CIOMS), 2002.

**Results**

The current research shows a failure rate of 65.3 %, CI: 95 % (56.2; 74.2). The 85.7 % of the patients in whom non-invasive ventilation failed were over 60 years of age. Male sex predominated for 65.3 % (table 1).

<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics and outcome of non-invasive ventilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age median (years)</strong></td>
</tr>
<tr>
<td><strong>72± 9.4</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>NIV result</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
</tbody>
</table>

When the ventilatory characteristics analysis was performed, 81.8 % (72.5; 91.0) of the cases that failed had significant leaks, with a high association between the variables. The highest percentage of patients in the present investigation used pressure support as the ventilatory modality (98.7 %), (CI: 92.9; 99.9) without being statistically significant the selected modality and the probability to fail. The duration of NIV of more than 24 hours, the highest frequency in its application or a higher average level of positive pressure at the end of expiration (PEEP) or pressure on PEEP was also not found to be related to the probability of failure. Regarding the time in which NIV treatment was started with respect to respiratory symptoms, in this investigation the failure was related to the initiation of therapy after 24 hours (77.9 %), CI: (68.0; 87.8) (table 2).
Table 2. Ventilatory characteristics and outcome of NIV in exacerbated COPD

<table>
<thead>
<tr>
<th></th>
<th>Success n=41</th>
<th>Failure n=77</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
</tr>
<tr>
<td>Leaks</td>
<td>6(14.6)</td>
<td>63 (81.8)</td>
<td>0.00</td>
</tr>
<tr>
<td>Duration&gt; 24 hours</td>
<td>36(87.8)</td>
<td>54(70.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Modality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure Support</td>
<td>38 (92.6)</td>
<td>76 (98.7)</td>
<td>0.93</td>
</tr>
<tr>
<td>BIPAP (double pressure level)</td>
<td>3 (7.3)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Symptom onset time &gt; 24 hours</td>
<td>2(4.9)</td>
<td>60(77.9)</td>
<td>0.00</td>
</tr>
<tr>
<td>Frequency greater than every 2 hours</td>
<td>39(95.1)</td>
<td>59(76.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Average PEEP level greater than 5 cm / H2O</td>
<td>17 (41.5)</td>
<td>36 (46.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Average P / PEEP level greater than 10 cm / H2O</td>
<td>26 (59.1)</td>
<td>51 (66.2)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Respiratory infection for 83.1 %, CI: (71.0; 90.0) was the most frequent triggering cause in this study. No statistically significant relationship between the presence of this trigger factor and the response to the ventilatory technique was found. The presence of other factors such as heart failure and pulmonary thromboembolism were equally distributed. The associated comorbidity related to the probability of failure was not relevant (table 3).

Table 3. Triggers, comorbidities and outcome of NIV in exacerbated COPD.

<table>
<thead>
<tr>
<th></th>
<th>Success n=41</th>
<th>Failure n=77</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>36 (87.8)</td>
<td>62 (80.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5 (12.2)</td>
<td>8 (10.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (4.9)</td>
<td>3 (3.9)</td>
<td>1.23</td>
</tr>
<tr>
<td>Presence of comorbidity</td>
<td>32 (78.0)</td>
<td>58 (75.3)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

When the variation of the clinical and hemogasometric parameters is analyzed (Table 4), it is observed that the differences in the respiratory frequencies (Fr.) at
the beginning were not significant among the patients with success or failure, however in the evaluation at two hours there were significant differences among the patients who were successful (28.2 breaths per minute) and those who failed (34.5 breaths per minute).

Regarding heart rate (Fc.), the lowest average values at baseline were related to success (105.3 beats per minute) and higher values (120.5 beats per minute) were found in those that failed. The course of the heart rate at two hours was also representative with a heart rate in successful patients with an average of 99.6 beats per minute, and 128.2 beats per minute in those who failed, so the presence of tachycardia at baseline and no improvement or increase after two hours was related to failure of the technique. The mean arterial pressure did not show significant variations. Low Glasgow at baseline (11.9) and drop at two hours (9.1) were associated with failure.

Regarding pH values close to normality, upon admission they corresponded to the success of the technique; while low values, on average 7.20; were associated with failure. In the course at two hours, normal pH values successfully related (7.40) were found, and patients with an average pH of 7.22 were associated with failure. The mean PaCO2 at baseline of 57.2 mmHg was associated with success, higher values (64.5 mmHg) were associated with failure of the technique. After two hours, those patients who progressed to success had average PaCO2 values of 54.9 mmHg, and those with a mean value of 66.1 mmHg failed. Therefore, the decrease in pH and the increase in PaCO2 at two hours and low pH values at baseline were related to the failure of NIV. PaO2 / FiO2 did not present significant changes in relation to the failure of the technique. X
Table 4. Baseline and evolutionary mean values of clinical and hemogasometric parameters of NIV in exacerbated COPD.

<table>
<thead>
<tr>
<th></th>
<th>Beginning of NIV</th>
<th>2 Hours of NIV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success</td>
<td>Failure</td>
</tr>
<tr>
<td>Fr.</td>
<td>31.3</td>
<td>32.5</td>
</tr>
<tr>
<td>Fc.</td>
<td>105.3</td>
<td>120.5</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>103.3</td>
<td>106.6</td>
</tr>
<tr>
<td>Glasgow</td>
<td>13.3</td>
<td>11.9</td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>250.3</td>
<td>218.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.33</td>
<td>7.20</td>
</tr>
<tr>
<td>PaCO2</td>
<td>57.2</td>
<td>64.5</td>
</tr>
</tbody>
</table>

NIV failure was directly related to mortality (79.2 %), CI: (69.5; 88.9), being these results significant (table 5).

Table 5. Frequency distribution according to state at discharge and outcome of NIV

<table>
<thead>
<tr>
<th>State upon discharge</th>
<th>Success NIV</th>
<th>Failure NIV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>dead</td>
<td>2</td>
<td>4.9</td>
<td>61</td>
</tr>
<tr>
<td>Alive</td>
<td>39</td>
<td>95.1</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100.0</td>
<td>77</td>
</tr>
</tbody>
</table>

\(X^2=59.4\ p<0.001\)

Discussion

There are no doubts about the effectiveness in the use of NIV, during the exacerbation of patients affected by chronic obstructive respiratory disease, however within this group, failure of this form of mechanical ventilation can also be seen and in these cases mortality is higher.\(^{(12,13,14)}\)

In previous studies at the center where the research is carried out, a high failure rate was already observed compared to other national and international research. The series by Navarro Rodriguez\(^{(15)}\), obtained in the intensive care unit of the
Provincial Hospital "Saturnino Lora", of patients with acute respiratory failure treated with non-invasive ventilation showed a 29.5% failure rate. The literature includes as a percentage of permissible failure the range between 7 and 30%, which is highly variable. As it can be observed the problem of the unfavorable evolution with non-invasive ventilation becomes more important when it is related to an increase in mortality, the objective is to eliminate or minimize all the factors that could lead to failure of the technique due to the fatal outcome entails.\textsuperscript{(1,6,9,16)}

In the series by Suárez Domínguez\textsuperscript{(4)} a 63.3% of the cases presented an unfavorable evolution and in a subsequent study by Navarro Rodríguez\textsuperscript{(15)} in this same center, the failure occurred in 19.5% of the patients studied. Brochard\textsuperscript{(1)} and Meduri\textsuperscript{(6)} show in their investigations a success rate of NIV between 75 and 85%.

Patients older than 60 years are more susceptible to exacerbations when they have COPD, due to the physiological changes that occur during aging, and it has been proven that an older age favors intolerance to NIV, secondary to the mismatch with the interface, patients without teeth, loss of facial muscle tone, fear and anxiety.\textsuperscript{(7,18,19,20)}

As for the frequency of its application, it is suggested to use it as long as possible, especially in the first hours. Honrubia et al.\textsuperscript{(20)} examined the efficacy of NIV in 64 patients undergoing NIV intensification, the authors demonstrated a reduction in the relative risk of intubation. During the first 12-24 hours, it should be continuous, interspersing only the periods to eat, aspirate secretions, administer nebulized medication or short breaks that improve tolerance to ventilation. This guideline can be modified based on needs and tolerance.\textsuperscript{(8,12)}

In the present series, no statistically significant relationship between the duration of non-invasive ventilation and the evolution to failure or not of the patients was found. The duration of NIV does not determine the success or failure of the technique, only clinical and blood gas monitoring allows determining the most appropriate moment to convert to conventional ventilation, this moment is independent of the time the patient has been under treatment.\textsuperscript{(3,4,7)}

The frequency and duration of NIV sessions depend on the patient’s clinical situation, his tolerance to the treatment and the place where it is applied. Different
NIV protocols have been published with similar results, although no comparative study has been carried out to date.\(^{(3,17,18)}\) When the time elapsed between the onset of symptoms and the introduction of NIV is analyzed, it shows beneficial effects as a first-line intervention for the management of ARF together with standard medical treatment in appropriate patients with hypercapnic respiratory failure and respiratory acidosis.\(^{(5)}\)

In the analysis of the ventilatory modality, the superiority of one ventilatory mode over another has not yet been verified. However, BiPAP is a mode with great potential, not generalized in the present study due to the lack of fans with this modality. Esquinas\(^{(19)}\) indicates that non-invasive mechanical ventilation in the BIPAP ventilation modality was used in cases of hypercapnic respiratory failure and there were no complications and no patient was intubated or transferred to the ICU.

Another study that shows the BIPAP modality as promising in the treatment of patients with NIV in exacerbation of COPD was the one carried out at the Hospital de Cabueñas in Asturias, after applying this modality, obtained effectiveness levels of 67.3 % in the studied patients.\(^{(19,20)}\)

There is no superiority of one ventilatory mode over another (proportional assisted ventilation, pressure support, BiPAP) in exacerbated COPD that has determined a lower rate of endotracheal intubation, although the double level of pressure mode prevails by epidemiological studies.\(^{(16,17)}\)

In the Meduri review\(^{(6)}\), 31 published works were analyzed, covering 633 cases; success was demonstrated in 78 % of the patients, regardless of the modality used, as long as it was used correctly.

When the presence of leaks is analyzed, it is observed that it is a factor with a high statistical relationship with respect to failure. Leaks result in poor tolerance to the technique and patient asynchrony ventilator. The type of mask also plays an important role. Sometimes a variety of interfaces are not available, they are not ideal for the patient's anatomy and predispose to flight, asynchrony and failure.\(^{(11,17)}\)

The presence of pneumonia is a factor associated with failure of the technique in most investigations.\(^{(18)}\)
An investigation carried out in Santiago de Cuba by Torres Maceo\(^{(11)}\) the main cause of the exacerbation was an infection of the bronchial tracheo tree. However, no statistically significant relationship was demonstrated between the presence of this triggering factor and the favorable or unfavorable evolution of these patients\(^{(3,9)}\).

In the present series, the improvement of clinical parameters in patients with favorable evolution was verified. In almost all studies, a recovery of heart rate, respiratory rate and blood pressure is reported in patients with a successful outcome of the technique. In Navarro Rodríguez's research\(^{(15)}\), the elevation of the Glasgow score was established as a predictor of NIV success.

Clinical and hemogasometric parameters are analyzed in multiple investigations as predictors of failure. Several studies show that the improvement of blood gas parameters (especially pH) during this initial period, predict the success of the therapy, and therefore they propose to perform a control blood gas within one to two hours after the start of NIV\(^{(12,15,17,18)}\).

An adequate level of consciousness at the beginning of NIV and the improvement in pH, PaCO\(_2\) and Glasgow after one hour of NIV are related to a good response in hypercapnic ARF in patients with COPD\(^{(11)}\).

There is evidence that supports the risk of using NIV in exacerbated COPD with greatly decreased pH values, which is an expression of the severity of the clinical picture, this is considered to have influenced the unfavorable evolution of the patients in this series\(^{(16)}\).

Confalonieri's work\(^{(8)}\) indicates that patients with a pH equal to or less than 7.25 on admission and after two hours of NIV have a risk greater than 70 and 90 %, respectively of poor prognosis. In a study carried out at the Intensive Medicine Service in Palma de Mallorca in 2013, they concluded that the improvement in pH, PaCO\(_2\) and level of consciousness after the first to second hour of NIV are related to a good response, in patients with exacerbated COPD\(^{(3)}\).

In other research, they showed that when patients with a very low pH below 7.19 and PaCO\(_2\) above 65 mmHg are chosen, failure of NIV is certain\(^{(19)}\).

The failure of NIV is directly related to an increase in mortality as Moretti\(^{(9)}\) and Antonelli\(^{(10)}\) have suggested in their research, so avoiding it and identifying the
factors related to the failure of the technique in this population of patients is essential for the best evolution of these patients.

NIV decreases in-hospital mortality. The Brochard NIV group\(^{(1)}\) has an in-hospital mortality of 9 % compared to 29 % in the standard therapy group and Jabier Jacob\(^{(2)}\) has a 10 % mortality in the NIV group compared to 20 % in the group of standard therapy. In general, a mortality of 9 % is recorded in 206 patients with NIV versus 22 % in 205 patients on standard therapy. Multiple studies have shown that failure to increase mortality, the selection of patients tributary to this therapy is essential\(^{(6,7,12,14)}\).

Scope of results:

This research provides useful and necessary theoretical support for scientific knowledge when describing the population of patients with exacerbated chronic obstructive pulmonary disease treated with non-invasive mechanical ventilation according to variables of interest, and increase the preparation of the personnel to treat patients with exacerbated COPD, which unifies criteria in relation to the evolution of these patients treated with this ventilatory technique.

**Conclusions**

Alterations of specific variables to ventilation, as well as clinical and hemogasometric variables structure the failure in the population of patients with acute chronic obstructive pulmonary disease treated with non-invasive ventilation, with a marked burden of mortality in patients in which this ventilatory technique fails.

**Bibliographical references**


Conflict of interests

The authors of the work declare no conflict of interests.

Authoral contribution

Zadis Navarro Rodríguez: Conceptualization and investigation, formal analysis, project administration, supervision, validation and verification (40 %).
Lázaro Ibrahim Romero García: Development and methodological design (20 %).
Niger Guzmán Pérez: Redaction and reviewing (20 %).
Franklin Brito Lacerra: Translation of the draft work (20 %).