

Treatment of acute exacerbations with non-invasive ventilation in chronic hypercapnic COPD patients with pulmonary hypertension

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Abstract. – Background and Objectives: Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive airways disorder characterized by not fully reversible airflow obstruction, often presenting exacerbations of respiratory symptoms requiring hospitalization. Non-Invasive Ventilation (NIV) has been shown to be an effective adjunct to standard medical therapy in the treatment of acute respiratory failure. Secondary pulmonary hypertension leads to a rapid progression of the disease.

Aim: To evaluate the effect of NIV treatment in patients with acute exacerbation of COPD, with or without respiratory acidosis, and its effect in patients with pulmonary hypertension.

Patients and Methods: We enrolled 61 consecutive subjects (M 41; F 20) with COPD admitted to our respiratory ward for acute respiratory exacerbation. Patients were divided into two groups on the basis of arterial pH (group A: 26 individuals with pH <7.35; group B: 35 with pH ≥7.35) and treated with optimal medical therapy (oxygen-therapy, systemic corticosteroids, bronchodilators, antibiotics) and NIV. Moreover, we evaluated functional autonomy through Six Minute Walking Test (6 mWT), and pulmonary arterial pressure (by transthoracic echocardiography).

Results: In group A NIV treatment was associated to a total regression of uncompensated respiratory acidosis (pH 7.36 vs 7.29). In both groups we observed a significant reduction of PaCO₂ (group A: 77.14 ± 10.4 vs 45.1 ± 2.8 mmHg; group B: 70.1 vs 44 ± 3.9 mmHg) and an improvement in PaO₂ (group A: 51.2 ± 10.3 vs 84.2 mmHg; group B: 59 ± vs 87 ± 3.3 mmHg). Total average duration of NIV administration was longer in Group A than in Group B (81.14 hours vs 55.83 hours). At the end of NIV treatment, we observed improvement in the autonomy of walking (175.1 meters vs 118.4 meters) in both groups. Patients with severe pulmonary hypertension (PASP ≥55 mmHg) showed a lower reduction of PaCO₂ (47.8 vs 43.7 mmHg) and a minor improvement of arterial pH (7.37 vs 7.41) compared to patients with a lower value of pulmonary hypertension.

Conclusions: In this study we showed that NIV is useful in patients with or without uncompensated respiratory acidosis, through the improvement of symptoms, blood gases parameters, and walking autonomy. Patients with severe pulmonary hypertension are associated with poorer response to NIV treatment.

Key Words:

Non-invasive ventilation, NIV, COPD, Pulmonary hypertension, Acidosis.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disorder characterized by not fully reversible airflow obstruction. It is associated with chronic inflammation in the airway and lung parenchyma, commonly caused by cigarette smoking and/or exposure to environmental or occupational pollutants¹.

Usually, the progression of COPD is gradual, although the disease often presents exacerbations of respiratory symptoms requiring hospitalization. This leads to greater use of medical resources and increases direct and indirect costs^{2,3}.

Non-Invasive Ventilation (NIV) via nasal or full face mask has been shown to be an effective adjunct to standard medical therapy in the treatment of acute hypoxemic and hypercapnic respiratory failure caused by exacerbations of COPD^{4,5}.

Randomized studies in homogenous populations of COPD patients with acute respiratory failure have provided supporting evidence that the early application of NIV can reduce the length of hospital stay⁴ and the need for endotracheal intubation (ETI), with the associated mor-

tality and morbidity from problems such as pneumonia and/or barotrauma, or the difficulty to wean these patients from invasive ventilation. Furthermore, other advantages are the ability to manage patients in other clinical areas rather than using scarce critical care resources and the added comfort to the patient, becoming able to eat and drink, cough and expectorate, receive physiotherapy and medication by taking breaks from the treatment.

On the other hand, for severe stable disease the data concerning a positive effect of NIV are less convincing. Preliminary evidences suggest that NIV improves gas exchange, sleep quality, and quality of life and might reduce the need for hospitalization. COPD patients with substantial chronic hypercapnia ($\text{PaCO}_2 > 55$ mmHg) and/or nocturnal hypoventilation, and those with repeated exacerbations may profit from NIV⁶.

Previous studies have showed the substantial effectiveness of NIV in patients with COPD exacerbations with a pH of 7.25-7.35⁷⁻¹¹.

Despite this, there are only a few clinical trials in the literature including COPD patients with chronic hypercapnic respiratory failure presenting with acute exacerbations and a pH of 7.35 or higher¹²⁻¹⁴.

The main aim of this study was to evaluate the effectiveness of NIV in COPD patients with acute exacerbation and respiratory failure, with special reference to those with an arterial pH > 7.35 .

In addition, we investigated the correlation between the use of NIV, the increasing exercise capacity, and the effect of the ventilatory treatment on the pulmonary arterial pressure in the same COPD patients. Pulmonary Hypertension (PH) is the hemodynamic manifestation of various pathological processes that result in elevated Pulmonary Artery Pressures (PAP)^{15,16}.

The current hemodynamic definition of PH is a mean PAP > 25 mm Hg with a normal Pulmonary Capillary Wedge Pressure (PCWP) at rest and PAP $>$ than 30 mm Hg with exercise¹⁷.

Pulmonary Arterial Hypertension (PAH) is classified into subgroups, including idiopathic, heritable, and PAH associated with other conditions. Causes of secondary pulmonary hypertension can be divided into three major categories: (1) pulmonary venous pressure elevation, (2) pulmonary vascular occlusion with or without pulmonary parenchymal disease, and (3) hypoxemia¹⁸.

A detailed history, thorough physical examination, and most importantly, a high index of suspicion are essential to diagnosis. Evaluation includes echocardiography and exclusion of other causes of symptoms¹⁸.

PAH is divided into three main classes according to severity: Low (PAP 26-35 mmHg), Moderate (PAP 36-45 mmHg) and Severe (PAP > 45 mmHg)¹⁹. These criteria define PAH associated with multiple other disease processes including COPD. In the current study, we will use this classification to define PAH associated with COPD.

Patients and Methods

Patients

From January 2007 until September 2008, 72 consecutive subjects with a diagnosis of COPD and chronic hypercapnic respiratory failure were admitted to our respiratory ward for acute exacerbation. From the 72 patients, 11 individuals were initially excluded: 2 of them refused the enrolment, and the remaining were not included due to their co-morbidities (3 congestive heart failure, 3 arrhythmia, 1 Obstructive Sleep Apnea Syndrome, OSAS), or due to NIV discontinuation for poor compliance (2 patients). Exclusion criteria were: chronic respiratory diseases other than COPD, important chronic co-morbidities (e.g., chronic heart failure, cancers, chronic renal failure), or significant acute diseases concomitant to COPD exacerbations (arrhythmias, pulmonary embolism, pneumonia, or pneumothorax).

The remaining 61 patients were enrolled in our study. Twenty individuals were females (33%) and 41 males (67%). All were smokers, 38 patients (63%) were affected by systemic arterial hypertension, 9 (15%) by diabetes mellitus and 33 (55%) by pulmonary hypertension.

COPD and its exacerbations were defined according to GOLD guidelines²⁰. Chronic hypercapnic respiratory failure was defined on the basis of arterial blood gas values, i.e., arterial oxygen partial pressure, PaO_2 , < 60 mmHg, arterial carbon dioxide partial pressure, PaCO_2 , > 50 mmHg, and arterial bicarbonate levels, HCO_3^- , > 35 mmol/L, while breathing room air, as previously described by Pastka C et al¹³.

Study Design

All patients were initially treated with optimal medical therapy, including oxygen-therapy (in

order to obtain pulse oximetric saturation (SpO_2) at approximately 88-92%), systemic corticosteroids, bronchodilators, and, when necessary, antibiotics and diuretics, and then they were divided into two groups on the basis of arterial pH (Group A: 26 individuals with $\text{pH} < 7.35$ and Group B: 35 with $\text{pH} \geq 7.35$).

During hospitalization, serial arterial haemogasanalysis were performed in all patients.

In addition to this, at admission and before discharge, all individuals underwent Six Minute Walking Test (6 mWT), in order to evaluate the functional autonomy during a period of walking^{21,22}, and transthoracic echocardiography, in order to obtain data on the pulmonary arterial pressure before and after the ventilatory treatment. We also divided COPD patients in two groups, on the basis of the Pulmonary Artery Systolic Pressure (PASP) measured at admission: in the first group we included patients with $\text{PASP} < 55$ mmHg, in the second one the individuals with $\text{PASP} \geq 55$ mmHg.

Patients received Non-Invasive mechanical Ventilation in Pressure Support mode (PSV)¹⁰.

Ventilatory Setting

NIV was delivered by a BiPAP-ST30 "auto-trak" ventilator (Respironics Inc, Murrysville, PA, USA). Ventilator was set in spontaneous/timed mode, as previously described¹⁰, with the assistance of respiratory therapists and trained nurses. We started with an inspiratory positive airway pressure (IPAP, 12-18 mbar), an expiratory positive airway pressure (EPAP 4-8 mbar), tidal volume (V_t 400-550) and Triggers based on patient's compliance.

The study was approved by the Ethical Committee of our Hospital and all patients provided written informed consent.

Statistical Analysis

All data are expressed as mean \pm standard deviation (SD). Statistical analysis was performed by using Sigmastat software (Jandel Corporation), and all values were analyzed with analysis of variance (ANOVA) followed by Student's *t* test whenever appropriate. Correlations between all parameters (6 mWT, transthoracic echocardiography and haemogasanalysis) and NIV were calculated by using the Pearson coefficient of linear correlation. A *p* value < 0.05 was considered significant.

Results

At admission patients in Group A showed significantly higher values of PaCO_2 compared to Group B (77.14 vs 70.16 mmHg; $p < 0.04$), and significantly lower values of PaO_2 (51.27 vs 59.04 mmHg; $p < 0.05$).

At the end of the first cycle of NIV, performed in emergency regime with an average duration of 13.6 hours, patients of group A had a significant improvement in gas exchange, with a consequent regression of the uncompensated respiratory acidosis (pH 7.36 vs 7.29; $p < 0.001$), and a significant reduction of PaCO_2 (77.14 vs 68.35 mmHg; $p < 0.05$), with an improvement in PaO_2 (62.5 vs 51.27 mmHg; $p = 0.02$). These results were similar to those in the Group B, who were affected by hypercapnic hypoxemic respiratory failure with compensated respiratory acidosis at admission to Hospital (Table I).

Later on, several cycles of NIV were performed in both groups of patients until appropriate levels of PaCO_2 and of PaO_2 were reached, with a similar average total duration in the 2 groups (65.5 vs 55.83 hours) (Figure 1). Total average duration of NIV administration was longer in Group A than in Group B (81.14 vs 55.83 hours; $p < 0.001$).

The assessment of the differences in gas exchange improvement showed that PaCO_2 reduction was closely correlated with the total duration of NIV, either separately for patients of the two groups or for all patients ($r = 0.42$; $p = 0.02$) (Figure 2).

At the end of the therapy, before discharge, we observed an improvement of the autonomy of walking (175.2 vs 118.4 meters; $p < 0.001$) (Figure 3) and also an improvement of the SpO_2 during the recovery stages after the test (96% at rest and 93.1% at the end of 6 mWT vs 93.26% at rest and 91.6% at the end of 6 mWT; $p < 0.001$) (Figure 4).

At admission to our ward, Group A patients presented less walking autonomy compared with Group B patients (82 vs 129.1 meters; $p < 0.05$), while at the end of the courses of NIV we observed a significant improvement of the walking autonomy in both groups without significant differences between them (163.7 vs 179.5 meters) (Figure 5).

There were no significant differences regarding trans-thoracic echocardiography parameters, at admission and before discharge. All patients showed signs of increased pulmonary pressure, as reported in Table II.

Table I. Parameters of the blood gases analysis (BGA) in the 2 groups in all the stages of the study.

BGA in emergency room (I)						
	pH	pCO ₂	pO ₂	HCO ₃	BE	SO ₂
Group A	7.29 ± 0.04*	77.14 ± 10.4*	51.27 ± 10.3*	35.76 ± 6.1*	11.75 ± 5.6*	82 ± 7.7*
Group B	–	–	–	–	–	–
Group A/B <i>p</i>	NC	NC	NC	NC	NC	NC
BGA at the admission to ward (II)						
	pH	pCO ₂	pO ₂	HCO ₃	BE	SO ₂
Group A	7.36 ± 0.03°	68.35 ± 7.8°	62.5 ± 8.2°	37 ± 5.2°	13.5 ± 5.7°	88 ± 5.7°
Group B	7.40 ± 0.05°	70.16 ± 9.5°	59 ± 8.1°	38.93 ± 7.8°	14.35 ± 6.6°	90.41 ± 3.1°
Group A/B <i>p</i>	NS	NS	NS	NS	NS	NS
BGA at the moment of hospital discharge (III)						
	pH	pCO ₂	pO ₂	HCO ₃	BE	SO ₂
Group A	7.42 ± 0.03	45.14 ± 2.8	84.21 ± 6.6	28.71 ± 2.6	10.5 ± 1.8	95.21 ± 1.7
Group B	7.40 ± 0.01	44 ± 3.9	87 ± 3.3	26.33 ± 2.1	7.53 ± 2.1	95.79 ± 0.8
Group A/B <i>p</i>	NS	NS	NS	NS	NS	NS

NC = not computable; NS = not significant; *vs BGA II; *p* < 0.001; °vs BGA III; *p* < 0.001.

At the end of the ventilatory treatment, patients with severe pulmonary hypertension (PASP ≥ 55 mmHg) had a lower reduction of PaCO₂ (47.8 vs 43.7 mmHg; *p* = 0.03) (Figure 6) and less improvement of arterial pH (7.37 vs

7.41; *p* < 0.05) compared to patients with a lower stage of PAH.

Furthermore, in patients with severe pulmonary hypertension, oxygen saturation measured during the 6 mWT, at the end of the NIV treatment, was significantly reduced compared with patients with moderate pulmonary hypertension (Figure 7).

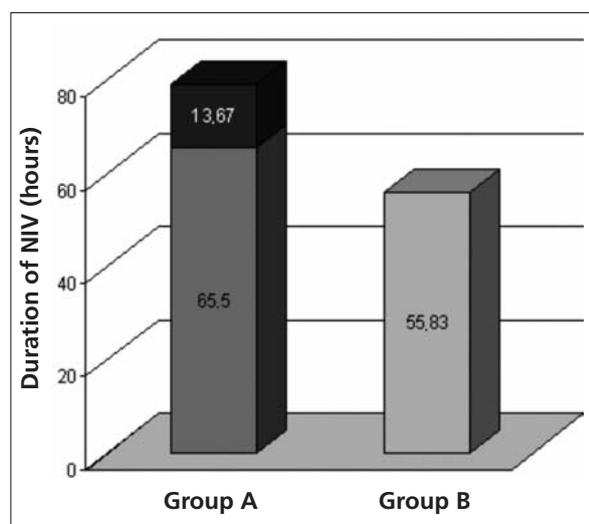


Figure 1. Total duration of NIV in the two groups.

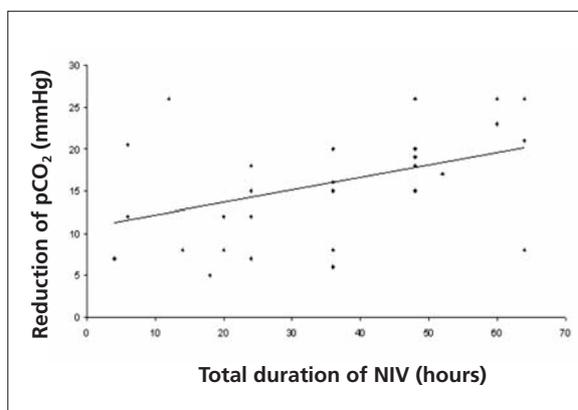


Figure 2. Correlation between total duration of NIV and the reduction of pCO₂.

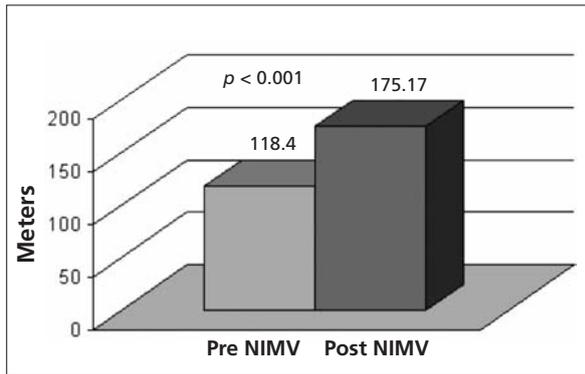


Figure 3. Meters at the end of 6 mWT at admission (pre) and at discharge (post) NIMV treatment in all patients.

Discussion

In 1989, Meduri et al were the first to use NIV during a non randomized study with 10 patients affected by acute ventilatory failure²³. Six of them were affected by COPD. In all of the patients, NIV showed an improvement of arterial blood gases (ABG) even though 3 of them needed intubation because of complications during the study. During the following years more studies demonstrated the benefits of NIV in COPD, especially in patients with respiratory acidosis.

The European Respiratory Society and The American Thoracic Society Guidelines, pub-

lished in 1995, described the following indications for NIV: presence of acidosis ($\text{pH} < 7.35$), hypercapnia ($\text{paCO}_2 > 45\text{-}60$ mmHg), and a respiratory rate of > 24 breaths/min^{24,25}. The British Thoracic Society Guidelines in 2002²⁶, confirmed these indications. NIV showed benefits not only on pH values between 7.25-7.35 but also for pH values < 7.25 ²⁷.

In 1995, Brochard et al.²⁸ published the results of an european multicentre study demonstrating the advantage of early use of NIV with respect of the traditional therapy in chronic respiratory failure during COPD, associated with respiratory acidosis. In 2003, the same Authors²⁹, confirmed the validity of the therapy in reducing pCO_2 , increase of pO_2 , pH stability, shorter hospital stay periods, a decrease of intubation rate, and a mortality decrease. On the contrary, Bardi et al¹², analyzing the possible benefits of NIV in patients with COPD exacerbations with a pH value between 7.3 and 7.4, didn't show any significant benefit in decreasing intubation rate or hospital stay period.

Afterwards, other studies analyzed these parameters³⁰. Pastaka and Gourgoulianis¹³ described benefits in patients with chronic respiratory failure exacerbations with pH values ≥ 7.35 . The patients were divided in 2 groups: control and NIV group. The control group used the standard therapy of COPD mean, while the other group used NIV. The results showed an improvement of all arterial gas analysis parameters, especially pCO_2

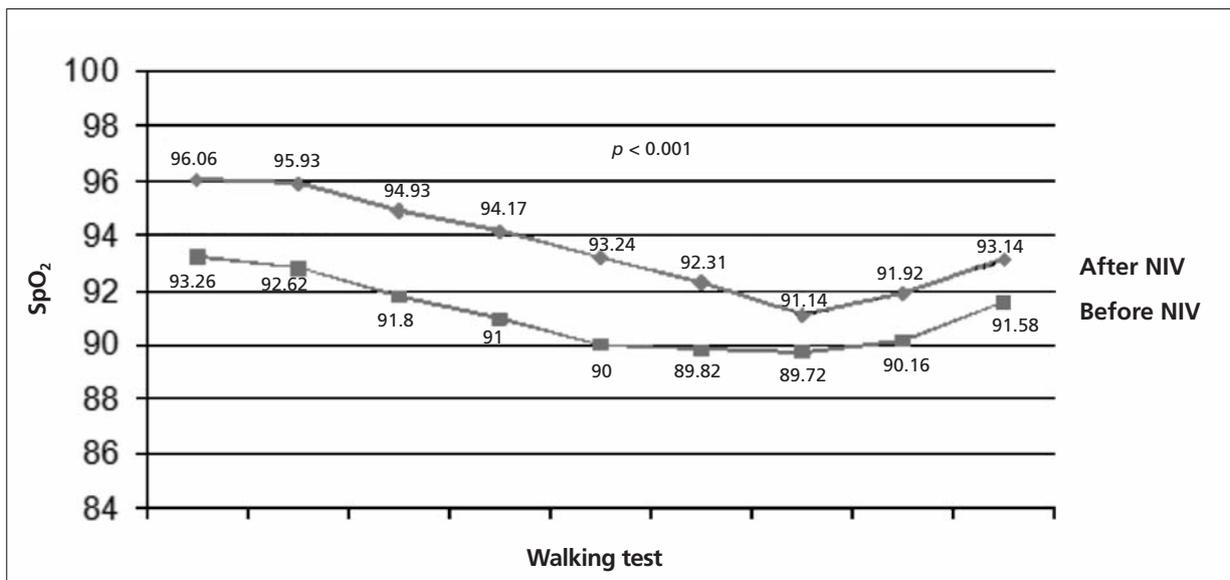


Figure 4. Trend of the O₂ saturation during 6 mWT in patients at admission (before NIV) and at discharge (after NIV).

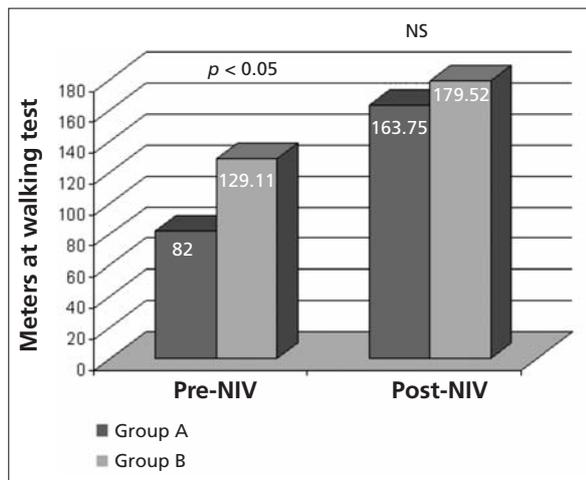


Figure 5. Meters walked at the end of walking test at admission (Pre) and at discharge (Post) NIV in the 2 groups.

in NIV group. However, there was no statistically significant improvement in bicarbonate values. These results confirm the benefits of NIV in treatment of hypercapnic hypoxemic chronic respiratory failure without acidosis.

Results of our study were partially similar, where we described a group of hospitalized patients with chronic respiratory failure without acidosis (initial values: pH 7.4, pCO₂ 70.16; pO₂ 59; HCO₃ 40; BE 14.35; SpO₂ 90%) and a group with uncompensated respiratory acidosis (initial pH 7.29) before NIV treatment. We obtained significant statistically improvements in all parameters of the blood gas examination, bicarbonates as well. At the moment of the discharge from

hospital, patients of the 2 groups showed similar values of blood gas examination. The only difference was the duration of the treatment with NIV.

In literature only few studies reported data on this topic: it is important to consider how our study demonstrated that the use of NIV is effective also in patients affected by hypercapnic and hypoxiemic respiratory failure with compensated respiratory acidosis.

Diaz and Lisboa³¹ reported that mechanical ventilation is effective also for improving walking autonomy, measured by the Six Minute Walking Test. Our study highlighted the great increase of the distance covered when the test was performed at the end of the therapy. This distance was significantly longer than 60 meters. We also stressed the difference between performances at 6 mWT in a group with uncompensated acidosis and in a group with pH >7.35 at the moment of the admission to Hospital. Considering 6 mWT before and after NIV, we observed an improvement of O₂ saturation also in the post-test recovery period. As reported by Paciocco et al³², oxygen desaturation on the 6 mWT is also correlated with mortality in untreated primary pulmonary hypertension.

Original data of our study was the negative correlation between PASP measured with echocardiography in patients affected by average-severe pulmonary hypertension and NIV treatment. It is not known whether long term nocturnal mechanical ventilation reduces pulmonary hypertension in patients with chronic respiratory failure. Literature reported few studies analyzing both NIV and PAH.

Table II. Trans-thoracic echocardiography parameters in Group A and Group B.

		Gruppo A	Gruppo B	p
DDVs	mm	49.90 ± 4.9	49.75 ± 4.9	ns
DSVs	mm	31.45 ± 4.2	32.05 ± 4.1	ns
SIV	mm	11.09 ± 1.2	11.2 ± 1.3	ns
PP	mm	10.45 ± 1.1	10.4 ± 0.8	ns
ASx	mm	44.67 ± 5.6	41.05 ± 7.6	ns
DPmax	mmHg	44.67 ± 8.2	44.07 ± 6.1	ns
DDVdx	mm	28 ± 3.3	29.89 ± 5.3	ns
PASP	mmHg	46.22 ± 6.9	50.76 ± 5.3	ns
FA	%	36.16 ± 4.4	34.66 ± 5.3	ns
M	g	206.60 ± 23.5	196.66 ± 17.9	ns
M-i	g/m ²	106.1 ± 20.3	104.5 ± 19.1	ns
FE	%	55.84 ± 6.5	53.63 ± 5.1	ns

NS = not significant.

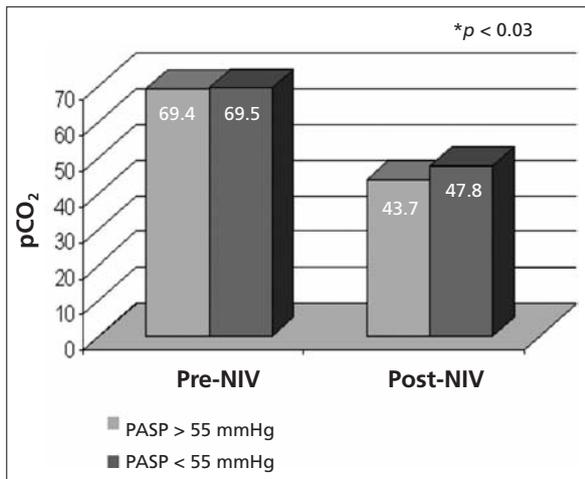


Figure 6. Levels of pCO₂ at admission (Pre) and at discharge (Post) NIV in patients divided by stage of pulmonary hypertension evaluated by the values of systolic pressure measured in pulmonary artery (PASP).

Schönhofer et al³³ have shown that after 1 year of NIV there was a substantial reduction on mean PAP in patients with thoracic restriction but not in patients with COPD. We demonstrated that at the end of NIV therapy there is only a slight improvement of the blood gases examination parameters and the 6 mWT parameters in patients with PASP > 55 mmHg compared with PAH < 55 mmHg. Moreover, in these patients hypoxaemia and hypercapnia both increase pulmonary vasculature tone and induce pulmonary hypertension.

Mechanical factors may also have an important effect on the pulmonary circulation. A dated study³⁴ found that longitudinal muscularisation of larger vessels resulted from mechanical distortion in the lungs, caused by progressive airway obstruction. Therefore, PAH in COPD would not be expected to be changed by NIV.

Finally, treatment of PAH³⁵ is continuously refined on the base of new data reported in the recent years; anyway, studies on the effect of NIV on PAH in COPD are still lacking.

Conclusions

There is evidence in using non invasive techniques of mechanical ventilation in patients with chronic hypercapnic hypoxiemic respiratory failure. Efficacy of NIV in COPD patients with uncompensated respiratory acidosis (pH < 7.35), and less frequently in patients with chronic respiratory failure with compensated respiratory acidosis, is poorly reported in literature. The early use of NIV in these cases can reduce the number of the admissions to hospital, their lasting and it can avoid endotracheal intubation. In our study, we demonstrated that treatment with NIV is useful in patients with uncompensated respiratory acidosis and also that there is a great improvement in blood gases parameters and in walking autonomy (measured by 6 mWT) in patients with compensated respiratory acidosis.

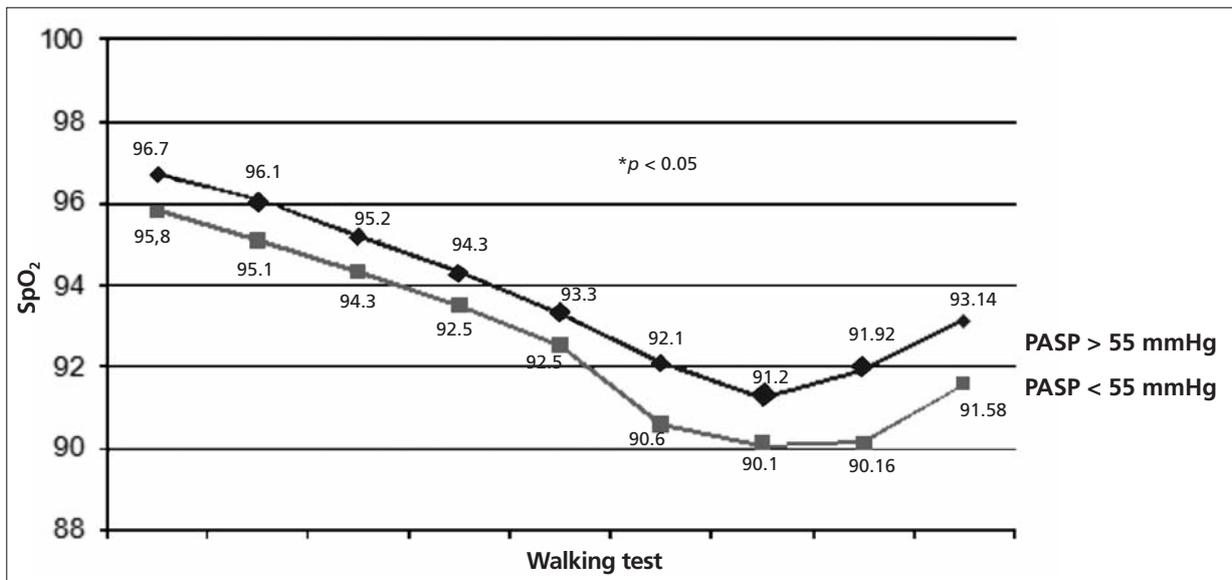


Figure 7. Trend of O₂ saturation (SpO₂) during 6 mWT in pulmonary hypertensive patients submitted to NIV.

However, O₂ saturation during 6 mWT and the improvement of PaCO₂ in patients with severe pulmonary hypertension at the end of NIV was significantly lower than patients with moderate pulmonary hypertension.

Patients with severe pulmonary hypertension (PASP ≥55 mmHg) showed a lower reduction of PaCO₂ and a minor improvement of arterial pH compared to patients with a lower value of PAH.

The stage of PAH characterizes the response to NIV in COPD patients. Our study highlights the importance to assess pulmonary pressure in order to predict the effect of NIV on respiratory failure with acidosis. In future, pathophysiological features of correlation between PAH and NIV treatment have to be deepened in further studies, understanding the real advantage on prognosis and on its synergy with new pulmonary antihypertensive drugs.

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