

Hypercapnic COPD patients and NIV at home: is there any benefit? Using the CAT and BODE index in an effort to prove benefits of NIV in these patients

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Introduction: The benefits of long-term noninvasive ventilation (NIV) in stable COPD with chronic hypercapnic respiratory failure (CHRF) have been debated for many years due to the conflicting results observed in these patients.

Materials and methods: We investigated the effects of domiciliary NIV in stable hypercapnic COPD patients for a period of 1 year using COPD Assessment Test (CAT), BODE Index, and the number of acute exacerbations. NIV was administered in 57 stable COPD patients with CHRF in the spontaneous/timed mode. Spirometry, 6 minute walk test, Medical Research Council dyspnea scale, arterial blood gases, number of acute exacerbations, BODE Index, and CAT were assessed. Study participants were reassessed in the 1st, 6th, and 12th months after the initial evaluation.

Results: There was a significant improvement in COPD exacerbations ($p < 0.001$), CAT ($p < 0.001$), PO_2 ($p < 0.001$), PCO_2 ($p < 0.001$), and Medical Research Council dyspnea scale ($p < 0.001$) in 1 year of follow-up. BODE Index was improved in the first 6 months (5.8 ± 2.2 vs 4.8 ± 2.4 , $p < 0.001$), but the improvement was not maintained.

Conclusion: In conclusion, domiciliary NIV in stable COPD patients with CHRF has beneficial effect on CAT, arterial blood gases, and number of acute exacerbations in a year of NIV use at home. A significant improvement in BODE Index from baseline to 12 months was found in patients aged >70 years, while for those aged <70 , the improvement was not maintained after the sixth month.

Keywords: hypercapnic COPD, domiciliary, improvement, BODE Index, CAT

Introduction

COPD is currently one of the leading causes of morbidity and mortality worldwide in the adult population and will be the third most frequent cause of death in the world by the year 2030.¹ COPD is a chronic, progressive disease and many patients, especially those at stage III and IV,² will eventually develop chronic hypercapnic respiratory failure (CHRF). These patients are more likely to develop more often exacerbations, worsening their prognosis.^{3,4}

Short-term noninvasive ventilation (NIV) has become an accepted management approach for patients with acute respiratory failure.⁵ It has been shown that NIV in acute settings can prevent intubation and invasive ventilation, while it can reduce hospital mortality.^{6,7} Nevertheless, the role of NIV in long-term management of stable COPD with CHRF is still debated.⁸⁻¹⁰ There are a number of clinical trials that have reported improvement in blood gasses,^{3,11-13} functional status reporting both forced vital capacity

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(FVC) and forced expiratory volume in 1 second (FEV_1),^{3,14,15} and an improvement of survival in stable COPD,^{16,17} but at the cost of worsening of quality of life.¹⁶ On the other hand, there are several clinical trials that have reported an improvement of quality of life.^{3,13,15,18–21} Therefore, it is necessary to select subgroups of COPD patients, who will respond to the use of NIV. The difficulty in finding these subgroups probably lies on the fact that COPD is a systematic disease, and therefore, many parameters must be taken into consideration.

The necessity to understand a complicated disease such as COPD gave birth to a multidimensional predictor factor known as BODE Index. BODE Index was reported to be superior to FEV_1 in reflecting the severity of COPD and effective in predicting the mortality in patients with COPD.²² Furthermore, the recently developed COPD Assessment Test (CAT) is a potentially useful instrument to assess the efficacy of treatments following COPD exacerbations²³ and to quantify the impact of COPD in routine practice.²⁴

The purpose of our study is to investigate the influence of NIV on BODE Index, CAT, and the number of acute exacerbations in COPD patients with CHRF in long-term NIV use at home. Our secondary target is to define in advance the characteristics of patients who will respond to the use of NIV at home.

Materials and methods

Seventy-eight COPD patients from the outpatient clinic of a tertiary university hospital, while in stable conditions, were enrolled in the trial. COPD was diagnosed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines,²⁵ smoking history of >20 pack-years, $FEV_1 < 50\%$ predicted, and $FEV_1/FVC < 70\%$ on stable conditions.

Patients' inclusion criteria were: age ≤ 75 years, ex-smokers (≥ 20 pack-years), and CHRF constant for at least 4 weeks ($PO_2 < 60$ mmHg, $PCO_2 > 50$ mmHg, and $pH > 7.35$ while breathing room air). All patients received long-acting bronchodilators. Some also received inhaled corticosteroids. All patients received long-term oxygen therapy. Our patients' therapy was in accordance with ATS/ERS guidelines.²⁵ During enrollment, all patients were free of exacerbations for the last 4 weeks and domiciliary NIV was offered to all our patients who agreed to receive it as an additional therapy. The study protocol was approved by the ethics committee of the University Hospital of Larissa, and written informed consent was obtained from all study participants.

Patients' exclusion criterion was presence of other severe comorbidities that could interfere with the outcome of our study, such as bronchiectasis, asthma, post-tuberculosis

sequelae, rib and thoracic cage deformities, neuromuscular disorders, lung cancer, and chronic heart failure. To rule out the coexistence of moderate and severe obstructive sleep apnea, patients were screened with Epworth Sleepiness Scale (ESS) and polysomnography (PSG) study (Alice 4 Diagnostic Device OBS/G7829, Respiromics). In fact, patients were excluded from the study when the PSG study gave a result of apnea-hypopnea index (AHI) > 15 /hour or when AHI was > 5 /hour in combination with ESS > 12 . We also excluded patients with a body mass index (BMI) > 35 kg/m² in order to exclude the coexistence of obesity – hypoventilation syndrome.³ We also excluded patients with BMI < 19 kg/m² as they were small in number, had more than three exacerbations with long hospitalization period time in 1 year, and thus, their period of stable condition and domiciliary NIV use was really short. Probably these patients must be followed up for longer than a year to have more reliable results.

Patients were hospitalized for 2–3 days during the initial application of NIV, in order to ensure the optimal compliance of the patients. NIV was administered in the spontaneous/timed mode via a full-face mask using a bi-level positive airway pressure system (VPAP III ST; ResMed, Sydney, Australia). This mode was chosen for the ability to set inspiratory and expiratory time and has been proven effective in COPD patients.¹⁷ Supplement oxygen was added in order to obtain 88%–92% saturation. Inspiratory positive airway pressure and expiratory positive airway pressure were adjusted according to the patients' comfort and synchrony with the ventilator. Twenty-four hours before patients' return at home, patients and their relatives were trained in the hospital in order to be able to use the ventilator properly. Technically skilled personnel installed the ventilator at patients' homes and provided full technical support when required.

Home NIV was offered eventually to 65 patients. Patients were reassessed after 1 month to establish their compliance. In fact, 1 month later, eight of our patients were excluded from our study because of their poor compliance with the ventilator (intermittent use, use < 4 hours/day). Patients were examined at M6 (6 months after the initial NIV application) and at M12 (a year after the initial NIV application) with new spirometry test, blood gasses analysis, BODE Index, CAT, and the number of acute exacerbations.

Physiological measurements and questionnaires

Spirometry was performed with a dry spirometer (KoKo Legend; Ferraris Respiratory, Louisville, CO, USA) according

to the ATS guidelines.²⁶ Arterial blood gases were measured with the patient at rest, patient in sitting position, while breathing room air, and before submitting our patient to 6 minute walk test (6MWT). Dyspnea was assessed with the Medical Research Council (MRC) dyspnea scale.²⁷ Subjective daytime sleepiness was evaluated with the ESS²⁸ that has been validated for the Greek language.²⁹ CAT is a short, simple questionnaire that is easily completed by the patient and is used for assessing and monitoring COPD;²⁴ it has been also validated for the Greek language. BODE Index, a composite marker of disease taking into consideration the systemic nature of COPD,³⁰ was evaluated at any appointment for every patient.

Study protocol

Patients enrolled in our study were re-evaluated in the NIV outpatient clinic on the 1st, 6th, and 12th months after the initial evaluation. If the patient had an exacerbation at any of these time points, measurements were obtained 1 month after the event. As a COPD exacerbation, we define an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-on-day variations, is acute in onset, and may warrant a change in regular medication.³¹

In every appointment, the settings and the hours of NIV use (as obtained from the machine's counter) were evaluated, in order to determine proper NIV use. During the follow-up period, patients underwent adjustments in NIV masks or ventilator settings as needed, in order to maintain patient-ventilator synchrony and optimize gas exchange and functional status. In order to be considered compliant with the device, each patient had to use the ventilator for at least 6 hours daily and with no more than 10 L/minute air leaks.

Statistical analysis

Normally distributed variables are expressed as mean (SD), while variables with skewed distribution are expressed as median (interquartile range). Qualitative variables are expressed as absolute and relative frequencies. Repeated measurements analysis of variance was used to evaluate the changes observed in all study parameters over the follow-up period in the total sample and among different groups. Log transformations were used in case of skewed distribution and effect sizes were also calculated. Bonferroni correction was used in case of multiple testing in order to control for type I error. Pearson's or Spearman's correlations coefficients were used to explore the association of two continuous variables. All reported *p*-values are two-tailed. Statistical significance was set at *p* < 0.05, and analyses were conducted using SPSS statistical software (version 19.0).

Results

Seventy-eight COPD patients from the outpatient clinic of a tertiary university hospital, while in stable conditions, were enrolled in the trial. Eight patients were excluded from the study when the PSG study gave a result of AHI >15/hour. Five patients were excluded because of their low BMI. Home NIV was offered to 65 patients. One month later, eight of our patients were excluded from our study because of their poor compliance with the ventilator (intermittent use, use <4 hours/day).

Eventually, our sample consisted of 57 participants (91.2% men and 8.8% women) with mean age 68.8 years (SD=8.0 years). Sample characteristics at baseline measures are shown in Table 1.

The mean inspiratory positive airway pressure setting was 17.04±2.81 cmH₂O with a range 16–20 cmH₂O, while the expiratory positive airway pressure setting was 5.7±1.62 cmH₂O with a range 5–8 cmH₂O. Patients made use of the device for 8.71±1.43/24 hours. All of our patients needed supplemental oxygen with the device with a range 2–4 L/min.

In Table 2, we can see the changes in study parameters through the follow-up period.

From baseline to 12 months, there was a significant improvement in COPD number of acute exacerbations (1.46±1.03 vs 0.7±1.07, *p*<0.001, *d*: 0.39) and CAT (18.7±6.9 vs 15.5±8.4, *p*<0.001, *d*: 0.22). BODE Index showed an improvement in the first 6 months (5.8±2.2 vs 4.8±2.4, *p*<0.001, *d*: 0.32), which was not maintained.

Table 1 Sample characteristics at baseline

	n (%)
Sex	
Men	52 (91.2)
Women	5 (8.8)
Age, years, mean (SD)	68.8 (8.0)
BMI, kg/m ² , mean (SD)	28.5 (5.4)
BMI	
Normal	14 (25.0)
Overweight	18 (31.6)
Obese	25 (43.9)
AHI, number of apnea-hypopnea/hour, mean (SD)	8.5 (4.6)
S1, minutes, mean (SD)	6.7 (4.3)
S2, minutes, mean (SD)	62.2 (17.1)
S3+S4, minutes, mean (SD)	14.4 (13.6)
REM, minutes, mean (SD)	12.3 (7.6)
SAT <90%, mean (SD)	71.7 (24)
SAT <80%, median (IQR)	4.1 (1.3–8.9)
Mean saturation, mean (SD)	86.2 (2.7)
Min saturation, mean (SD)	74.7 (6.1)
OD, number of oxygen desaturation/hour, median (IQR)	10 (4.8–17)

Abbreviations: AHI, Apnea-Hypopnea Index; BMI, body mass index; IQR, interquartile range; OD, oxygen desaturation; REM, rapid eye movement; SAT, saturation.

Table 2 Changes in study parameters through the follow-up period

	Baseline	6 months	12 months	Effect size	<i>p</i> -value** baseline vs 6 months	<i>p</i> -value** 6 vs 12 months	<i>p</i> -value** baseline vs 12 months
PO ₂ , median (IQR)	58.0 (54.0–59.0)	62 (58–68)	63 (58–67)	0.39	<0.001	0.919	<0.001
PCO ₂ , median (IQR)	52.9 (50.0–55.0)	46 (43–50)	45 (43–48)	0.67	<0.001	0.663	<0.001
pH, median (IQR)	7.41 (7.39–7.41)	7.42 (7.40–7.43)	7.41 (7.40–7.42)	0.25	<0.001	0.266	0.021
FEV ₁ , median (IQR)	30.0 (27.0–46.0)	38 (25–52)	33 (26–50)	0.15	0.013	0.439	0.652
FVC, mean (SD)	49.6 (15.1)	53.5 (17.7)	54.6 (16.5)	0.14	0.071	1.000	0.028
FEV ₁ /FVC, mean (SD)	56.0 (9.9)	55.1 (11.5)	53.6 (11.5)	0.15	1.000	0.180	0.115
MRC, mean (SD)	2.79 (0.92)	2.51 (0.98)	2.50 (1.07)	0.11	0.009	0.672	<0.001
BMI, mean (SD)	28.5 (5.4)	29.3 (5.6)	28.9 (5.6)	0.07	0.062	0.760	1.000
6MWT, mean (SD)	247.5 (106.8)	268.9 (114.6)	254.2 (134.9)	0.11	0.049	0.420	1.000
BODE, mean (SD)	5.8 (2.2)	4.8 (2.4)	5.2 (2.7)	0.32	<0.001	0.143	0.113
EXACERB, median (IQR)	1 (1–2)	0 (0–1)	0 (0–1)	0.39	<0.001	0.196	<0.001
CAT, mean (SD)	18.7 (6.9)	16.2 (6.8)	15.5 (8.4)	0.22	<0.001	0.499	0.001

Notes: Repeated measurements ANOVA. Effects reported include differences between the groups in the degree of change over the follow-up period. **Pairwise comparisons after Bonferroni correction. Log transformations were used in analysis. Bold values are statistically significant.

Abbreviations: 6MWT, 6 minute walk test; ANOVA, analysis of variance; CAT, COPD Assessment Test; EXACERB, exacerbations; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; MRC, Medical Research Council.

Figure 1 shows the mean BODE Index and CAT levels during the follow-up period.

BODE Index's parameters, FEV₁ (35.5±13.6 vs 39.2±15.5, *p*: 0.013, *d*: 0.15), 6MWT (247.5±106.8 vs 268.9±114.6, *p*: 0.049, *d*: 0.11), and MRC (2.79±0.92 vs 2.51±0.98, *p*: 0.009, *d*: 0.11) improved during the first 6 months and only MRC (2.79±0.92 vs 2.50±1.7, *p*<0.001, *d*: 0.11) continued its improvement in the entire follow-up period.

In our study, an improvement of PO₂ (56±2.9 vs 62.9±8.41, *p*<0.001, *d*: 0.39), PCO₂ (52.9±3.9 vs 45.8±4.6, *p*<0.001, *d*: 0.67), and FVC (49.6±15.1 vs 54.6±16.5, *p*: 0.028, *d*: 0.14) was found in the entire follow-up period. Indeed, patients with higher levels of PCO₂ at baseline were

found to have a greater improvement of CAT during 1 year of follow-up (*p*: 0.039). An interaction between age and BODE Index changes was also found. A significant improvement of BODE Index from baseline to 6 months (*p*=0.039) maintained to 12 months was found for patients aged >70 years, while for those aged <70, the improvement was not maintained after the sixth month (Figure 2).

Another finding was the improvement of PO₂ from baseline to the first 6 months for overweight and obese COPD patients (*p*: 0.002), which was maintained for the following 6 months (Figure 3).

Concerning PSG's baseline results, patients with higher rates of hypoxemia during sleep (minutes of SatO₂ <90%

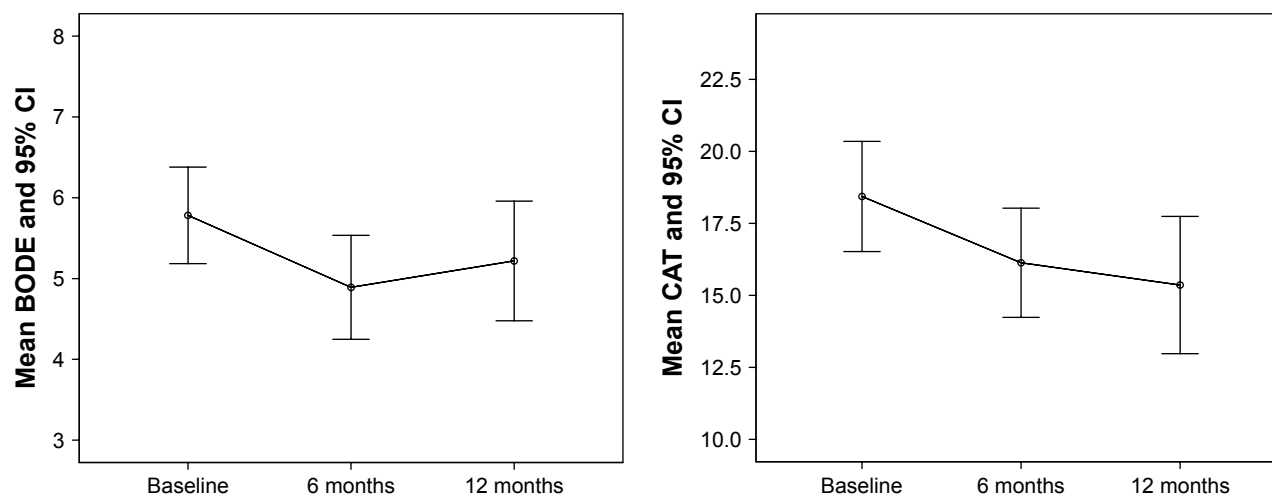


Figure 1 Mean BODE and CAT levels during follow-up.
Abbreviation: CAT, COPD Assessment Test.

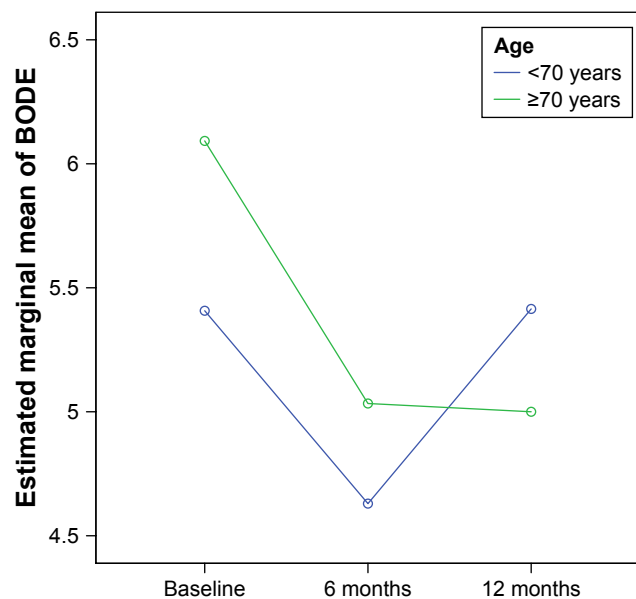


Figure 2 BODE Index changes during follow-up, according to age groups.

and $\text{SatO}_2 < 80\%$) were associated with a greater decrease in the number of acute exacerbations for the entire follow-up period ($p < 0.01$).

Discussion

In this study, we evaluated the effect of domiciliary NIV in stable COPD patients with CHRF on CAT, BODE Index, and acute exacerbations. We found an improvement in the number of acute exacerbations, CAT, and blood gases over time. BODE Index was improved in the first 6 months, but

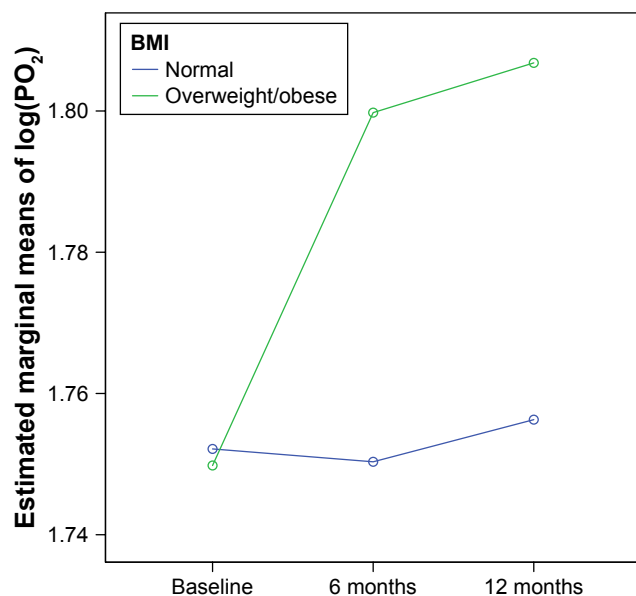


Figure 3 PO_2 changes during the follow-up, according to BMI status. Abbreviation: BMI, body mass index.

was not maintained for the entire monitoring time. On subsequent analysis of BODE Index parameters, we found that there was a statistically significant improvement in FEV_1 , MRC, and 6MWT measurements in the first 6 months. Of these three parameters, MRC was the one that maintained the improvement during the entire follow-up period. There was no change in BMI, which is the fourth parameter of BODE Index.

The role of NIV in the acute exacerbation of COPD is well established,^{11,32–34} but the role of domiciliary nocturnal NIV in stable COPD is still controversial. Despite the fact that meta-analysis and clinical guidelines do not recommend the routine use of domiciliary NIV for patients diagnosed with severe stable COPD and CHRF, it is a common practice followed in some countries. Recurrent exacerbations and failed weaning from in-hospital NIV were the main reasons for its prescription.³⁵ Although COPD is mainly characterized by the presence of airflow obstruction, several systemic manifestations that accompany this disease affect the progression of COPD and may contribute to the differences in the response of NIV.

To our knowledge, our study is the first study that used the BODE Index and CAT test in order to study NIV in stable hypercapnic COPD patients. Our findings are consistent with the literature. There are four short-term follow-up studies^{36–39} with a duration of 8 weeks to 3 months and three long-term studies^{3,12,18} with a duration of 6 months to 2 years, demonstrating no significant differences in FEV_1 between NIV and standard care groups, while in three long-term follow-up studies with a duration of 1–2 years, limited effects on FEV_1 have been demonstrated.^{21,40,41} In our study, other than FEV_1 , we found that FVC was also improved ($p: 0.028$) in the 1-year follow-up period. FVC improvement reflects an amelioration of lung hyperinflation. Theoretically, multiple mechanisms could attribute to a positive effect of domiciliary NIV. One of these mechanisms, the reduction of airway wall edema, could improve both FVC and FEV_1 , thus improving COPD patients' lung function. But it is well known that COPD is a progressive disease and stable COPD patients are not a homogeneous population. This could be the cause of the non-maintenance of FEV_1 improvement in the first 6 months.

As for the effect on exercise capacity, there are eight long-term follow-up studies^{3,5,18,20,21,40,42,43} with duration of 6 months to 2 years demonstrating moderate effect of treatment on 6MWT. Patients who participated in our study showed statistically significant improvement of 6MWT in the first 6 months of their follow-up, which was not maintained. NIV relieves fatiguing respiratory muscles by reducing the

degree of hyperinflation, providing patients a better exercise capacity. The insignificant improvement over time could be attributed to the fact that our patients did not follow a rehabilitation program in order to maintain their improvement.⁴⁴

The only parameter of BODE Index that presents a statistically significant improvement after 1 year of domiciliary NIV use is MRC. In fact, four studies^{3,12,21,40} demonstrated that significant improvements in dyspnea occurred in the NIV group. A plausible explanation of MRC amelioration could be attributed to the reduction of end-expiratory volume and, hence, the degree of hyperinflation.⁴⁵⁻⁴⁷

An important finding is that domiciliary NIV in stable COPD patients reduces the number of acute exacerbations in 1-year follow-up period. Our findings are in agreement with a recent study according to which long-term NIV seems effective in reducing recurrent acute exacerbations and readmissions in a highly selected group of severe COPD patients with frequent exacerbations.⁴⁸ A possible mechanism could be the mobilization of sputum. Positive end-expiratory pressure is known to help mobilize mucus,⁴⁹ reducing the risk of airway infections, which are the most important cause of COPD exacerbations. Symptom management and prevention of acute exacerbations are important in preventing COPD progression. A remarkable observation of PSG's baseline results was that patients with higher rates of hypoxemia during sleep (minutes of $\text{SatO}_2 < 90\%$ and $\text{SatO}_2 < 80\%$) were associated with a greater decrease in the number of acute exacerbations for the entire follow-up period. Probably, the second mechanism responsible for this is the improvement of sleep hypoventilation. Another possible mechanism ameliorating the number of exacerbations is the ventilation-perfusion (V/Q) matching. De Backer et al⁵ indicated that in NIV-treated patients who showed improvement in their blood gases, mass flow was redistributed toward areas with better perfusion. COPD patients who are treated with indicated standard treatment in combination with domiciliary NIV do not deteriorate quickly. Recurrent type II respiratory failure occurs in over 30% and readmission at 1 year in 60% of those who require NIV acutely in hospital.⁵⁰ A more recent study has shown that patients who require mechanical ventilation due to an acute exacerbation and remain hypercapnic thereafter may benefit from long-term NIV.⁴²

In our patients, there was a marked reduction of hypercapnia and a significant increase in diurnal hypoxemia. Patients with COPD are likely to develop nocturnal hypoventilation, especially during rapid eye movement sleep when the upper airway tone and accessory muscle activity is impaired.⁵¹ In two studies, 43% of COPD patients had a > 10 mmHg increase in PCO_2 during night, resulting in progressive resetting of

respiratory control to higher PCO_2 value.^{52,53} But worsening of V/Q matching is probably the leading mechanism for the occurrence of hypoxemia by the enlargement of physiological dead space and increase of wasted ventilation⁵⁴ leading to diurnal hypercapnic respiratory failure eventually. Kohnlein et al²⁰ suggest that when NIV is applied, it effectively reduces PCO_2 in stable COPD patients and on the other hand, improves PO_2 . In fact, in our study, it was noticed that overweight patients showed a significant improvement in PO_2 compared to those with normal weight. The answer is probably the removal of nocturnal hypoventilation and the redistribution of blood volume in the lung areas that are most ventilated.

Another important finding is the significant improvement of CAT for the entire monitoring time. To our knowledge, there are no studies using CAT in stable COPD patients using domiciliary NIV. However, evidence has shown CAT's good internal consistency and retest reliability,^{24,55} and that it is suitable for routine clinical use for stable COPD.^{33,56-59} In our study, patients perceived a significant improvement of their clinical symptoms, such as cough, sputum, and anxiety, and improvement in their sleep as reflected in the CAT's results. Also, an interaction between baseline PCO_2 and CAT was found. Specifically, patients with higher PCO_2 at baseline showed greater improvement in CAT. The most plausible explanation is the positive effect of NIV in nocturnal hypoventilation and the V/Q matching leading to better blood gas exchange. Furthermore, a reduction of hypercapnia leads to an improvement of the sensitivity of the respiratory center to carbon dioxide.⁶⁰⁻⁶² Patients are more alert, more mobilized, and more confident about themselves.

Additionally, in subgroup analysis, it was found that patients of age ≥ 70 years showed a steady improvement in BODE Index for the entire follow-up period. Our findings are in accordance with an earlier study,⁶³ which showed that COPD patients over 75 years of age using NIV at home improved their respiratory function and blood gases. This could be explained not only by the better compliance of the elderly patients, but also by the greater hypoventilation in the context of greater respiratory muscle hypotonia. So, the NIV benefits are more apparent in the elderly.

Conclusion

The present study demonstrates a positive effect of NIV on CAT, blood gases, dyspnea, and number of exacerbations in a year of domiciliary NIV use. No change in BODE Index does not necessarily mean failure of NIV, as COPD is a progressive disease. Use of NIV improves FEV_1 , MRC, and 6MWT, although it was not statistically significant in 1-year

follow-up, which could contribute to slowing the progress of COPD. The significant compliance of our patients in domiciliary NIV, the hours of NIV use, as well as the personalized ventilator settings are the reasons for the outcomes of the study. Perhaps it would be appropriate for COPD patients who are overweight with frequent exacerbations and without showing clinical symptoms of sleep apnea to undergo nocturnal oximetry to detect patients with nocturnal hypoventilation and predisposition to hypercapnia, in order to make timely use of domiciliary NIV, prevent COPD progression, and avoid serious socioeconomic consequences.

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Disclosure

The authors report no conflicts of interest in this work.

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