Effect of Rehabilitation with or without Noninvasive Ventilation on Pulmonary Function in COPD Patients

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Introduction: Chronic obstructive pulmonary disease (COPD) is a serious and prevalent health condition, with many patients ultimately requiring a ventilation support. Noninvasive ventilation (NIV) has been suggested as a therapeutic option for improving pulmonary function in these patients. This study aimed to evaluate the effectiveness of NIV for improving the pulmonary function in patients with COPD. **Methods and Materials:** Fifty hemodynamically stable patients with stage 3 or 4 of COPD presenting to a referral pulmonary center were randomly assigned into two groups of rehabilitation with (n=25) or without NIV (n=25). NIV was administered using I=12 and E=4 with bilevel positive airway pressure (BiPAP) settings. Echocardiography, spirometry, six-minute walk test (6MWT), COPD assessment test (CAT), and venous blood gas (VBG) analysis were performed at baseline and after 4 weeks of rehabilitation and compared using the appropriate statistical tests. **Results:** The mean age of the participants was 60.8±10.6 years and 84% were males. The two groups were matched regarding their baseline variables, except for the higher number of stage 4 patients in the NIV group. The mean ejection fraction and pulmonary artery pressure were 53.6±4.3% and 37.2±9.6 mmHg, respectively, with no significant difference between the two groups (P>0.05). All pulmonary function indices by spirometry, 6MWT, and VBG values were significantly improved after rehabilitation in both groups (P<0.05), but NIV patients showed no advantage over the control group. However, NIV significantly increased the CAT scores after rehabilitation: 29.32 vs. 25.04, in the NIV and control groups, respectively (P<0.05). **Conclusion:** Despite having multiple health benefits in COPD patients including decreasing the mortality rate and the need for invasive ventilation, NIV showed superiority compared with rehabilitation alone only in improving the CAT score.

Keywords: Rehabilitation, Noninvasive Ventilation, Chronic Obstructive Pulmonary Disease, COPD Assessment Test

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent lung condition, leading to significant morbidity and mortality especially in the elderly. Many COPD patients ultimately require the ventilation during their disease course (1-4). It has been shown that a subset of patients who experience repeated pulmonary infections might benefit from short courses of noninvasive ventilation (NIV). Moreover, NIV can positively affect patients with the uncontrolled hypercapnia or patients with the symptomatic nocturnal hypoventilation. However, a continuous use can lead to dependence, or conversely, noncompliance to treatment in the long-term; a recent study reported that only 43% of the patients were still using NIV after a 5-year follow-up (1).

Recommendations for the best time to initiate NIV in COPD patients include a partial arterial pressure of carbon dioxide (PaCO2) equal to 50-55 mmHg and oxygen saturation (SpO2) <88% for more than 5 minutes on 2 liters/minute oxygen, or exacerbation of hypercapnia more than twice a year. Inspiratory pressure support during the exercise test as well as earlier initiation of NIV have been shown to be beneficial for improving dyspnea and increasing the walking distance in an 8-week trial of using NIV for 30 minutes, using the Chronic Respiratory Disease Questionnaire (1).

Table 1. Demographic characteristics of the NIV and control groups (n=25)

Variable		NIV	No-NIV	*P*-value
Sex, Male		21 (84%)	22 (88%)	0.64
Smoker		18 (72%)	23 (92%)	0.06
Education	Illiterate	7 (28%)	6 (24%)	0.18
	Elementary school	4 (16%)	6 (24%)	
	Elementary school	4 (16%)	1 (4%)	
	High school	5 (20%)	1 (4%)	
	High school diploma	4 (16%)	10 (40%)	
	University degree	1 (4%)	1 (4%)	
Employment	Employed	3 (12%)	4 (16%)	0.86
	Businessman	18 (68%)	18 (72%)	
	Housewife	4 (16%)	3 (12%)	
Marital status	Single	2 (8%)	1 (4%)	0.97
	Married	23 (92%)	24 (96%)	

Values are presented as n (%); NIV, noninvasive ventilation

Table2. Comparison of parameters after rehabilitation in the two study groups

Variable		NIV	Control	*P*-value*
Echocardiography	EF, %	53.64	52.4	>.05
	PAP, mmHg	37.2	38.4	>.05
Spirometry	FEV1	45.92	47.08	>.05
	FVC	55.72	58.04	>.05
	FEV1/FVC	66.88	65.6	>.05
6MWT	Walking distance, m	272.4	244.4	>.05
	First SpO2, %	93	92	>.05
	Last SpO2, %	89	89	>.05
VBG	pH	31.84	31.21	>.05
	pCO2, mmHg	53.6	52	>.05
	HCO3, mEq/L	31.84	31.32	>.05
CAT score		29.32	25.04	<.05

** Statistically significant difference; VBG, venous blood gas; CAT, COPD assessment test; 6MWT, 6-minute walk test; NIV, noninvasive ventilation; EF, ejection fraction; PAP, pulmonary artery pressure; FEV1, forced expiratory volume during the first second; FVC, forced vital capacity; SpO2, peripheral oxygen saturation; pH, potential of hydrogen; pCO2, partial pressure of carbon dioxide; HCO3, bicarbonate*

NIV is an established alternative to invasive ventilation in patients with acute exacerbations. Using the pressure-targeted ventilation and the end-expiratory pressure, NIV can alleviate the need for invasive ventilation to some extent and shorten the hospital stay. It can decrease the pH during the hospitalization as well (2). In another study, NIV led to fewer intubations in 23 intensive care unit (ICU) patients (5% vs. 16%), but it was not associated with a lower mortality rate. In addition, a number of studies have investigated on the non-ICU patients. The results showed that NIV resulted in favorable changes in pH and PaCO2, and lowered the mortality rates in two studies while demonstrating similar efficacy in preventing invasive ventilation (2, 5). A study by Diaz-Lobato et al. on 18 COPD patients receiving oxygen therapy at home, found a lower PaCO2 and higher partial arterial pressure of oxygen (PaO2) levels in these patients (6).

Given the scarcity of data in this field and a low number of participants in available studies, we aimed to undertake a study to compare the effect of rehabilitation with or without NIV on pulmonary function test and patients' daily lives using COPD assessment test (CAT).

Materials and Methods

Study design and participants

We conducted a Randomized Controlled Trial on 50 patients with COPD presenting to the referral pulmonary center, Masih Daneshvari Hospital, Tehran, Iran from September 2016 to March 2017. Patients with hemodynamically stable COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) in stage 3 or 4 needing rehabilitation with a PaCO2 >55 mmHg (VBG), and able to complete the tests and fill out the CAT questionnaire, were included. The exclusion

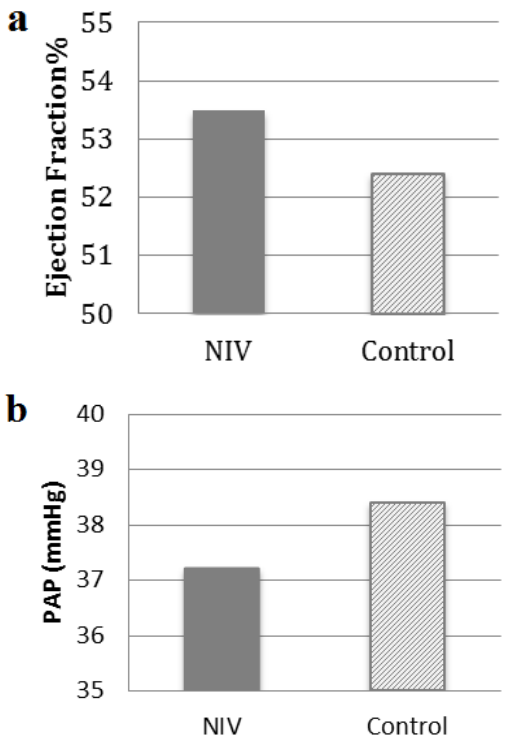

Figure 1. Ejection fraction (a) and pulmonary artery pressure (PAP) (b) in NIV and control groups

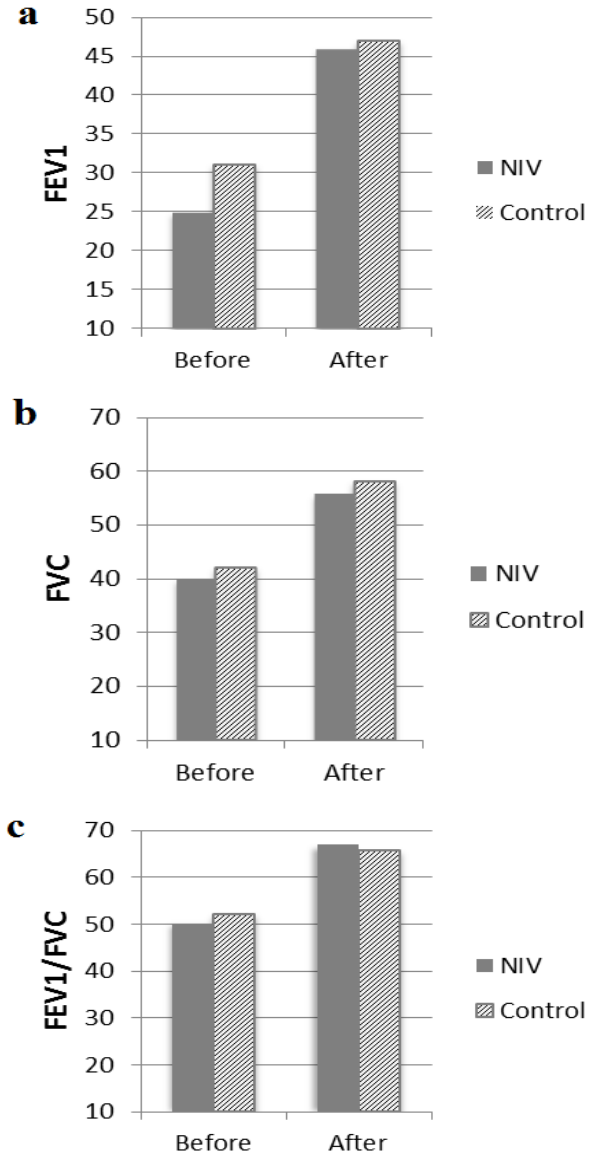

Figure 2. Spirometry results including FEV1 (a), FVC (b), and FEV1/FVC ratios (c) before and after rehabilitation in each group

criteria were the inability to complete the assessments or rehabilitation, or acute exacerbations of COPD requiring intensive treatment. Patients were randomized after providing the written informed consent into two groups of rehabilitation with NIV (study group: 25) and rehabilitation without NIV (control group: 25).

Rehabilitation

Patients participated in the rehabilitation program at 4 weeks, in three sessions per week. Each session lasted for 45 minutes. In the first 20 minutes, Pursed-lip and diaphragmatic exercises, and the second time, aerobic exercises (bicycle exercises) were performed. For the NIV group, during the training which was similar to the control group, patients were connected to bilevel positive airway pressure (BIPAP).

In both groups, venous blood gas (VBG) test (to determine pH, partial pressure of carbon dioxide (pCO2), and bicarbonate (HCO3) levels), spirometry (including forced expiratory volume during the first second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio), and six-minute walk test (6MWT) were performed. Also, the CAT questionnaire was completed before and after the sessions. The CAT questionnaire had translated and validated in the Persian language before (25). All patients, moreover, underwent an echocardiography to determine the pulmonary artery pressure (PAP) and the ejection fraction (EF). Patients in the NIV group received similar settings of I=12 and E=4 with the BiPAP during their rehabilitation. This study was approved for ethical issues in Shahid Beheshti University of Medical Science (Tehran-Iran).

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) and categorical variables as frequency and percentage. The normality of the data was assessed using the Kolmogorov–Smirnov test, and parametric or non-

parametric tests were used accordingly. The Student t-test or Chi-Square was used for comparing the means and proportions between the two groups. A two-tailed $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 50 patients with a mean age of 60.8 ±10.6 years and 84% of males were randomized into two groups. The demographic characteristics of each group are summarized in Table 1. Eighty-two percent of patients were smokers. Patients were matched in the two groups regarding their baseline variables.

Echocardiography

Table 2 summarizes all findings of the imaging, spirometry, CAT, 6MWT, and VBG. The mean patients' EF was 53.6 ±4.3% and the mean PAP was 37.2±9.6 mmHg. There was no significant difference in the mean EF between the two groups: 53.6% in the NIV and 52.4% in the control groups. Moreover, the mean PAP differences were not statistically significant, 37.2 and 38.4 mmHg in the NIV and control groups, respectively (Figure 1).

Spirometry

FEV1 and FVC values were significantly different before and after the sessions in both groups ($P<0.05$), but not between the two groups. Moreover, FEV1/FVC ratios were calculated and showed significant improvement after the study, but the difference between the groups was not significant ($P>0.05$) (Figure 2).

CAT questionnaire

Questionnaire was completed before and after the study in each group and showed a significant score improvement in the NIV group compared to the control group (29.32 vs. 25.04, $P<0.05$).

6MWT

There were no significant differences regarding between two groups in walking distance and first and last SpO2%, although these parameters improved in all subjects after the rehabilitation (Table 2).

VBG

HCO3 and pCO2 levels were significantly decreased in both groups without a difference between two groups. There was also no significant change in pH values (Table 2).

Discussion

Respiratory diseases are among the leading causes of death worldwide (7, 8). Among them, COPD is a common health problem in the elderly worldwide and is a growing cause of mortality in the recent reports. It is estimated to become the third leading cause of death and the fourth leading cause of disease related to economic status by 2020. Pulmonary rehabilitation is a patient-tailored treatment modality incorporating exercise, education, and behavioral techniques to maximize patient wellbeing (9). It remains an effective option in COPD patients, superior to drug therapy alone. However, rehabilitation programs are not as effective during the acute phase of COPD and are recommended to be complemented by NIV. Nevertheless, although NIV can strengthen respiratory muscles and improve ventilation (10), data regarding the effectiveness of NIV are inconclusive. A report stated that using NIV less than five hours per day had no effect on blood gas values, 6MWT, or respiratory muscles (11). In addition, patients with higher levels of hypercapnia during a day did not benefit from NIV as much as do patients who had nocturnal hypercapnia. Other factors such as systemic inflammatory states, excess oxidative stress, and nutritional state may also play an important role in the patients' improvement by rehabilitative programs (12).

The effect of NIV on pulmonary function tests needs to be further studied. Although there is evidence which shows that complementing rehabilitation with NIV can effectively lower airway edema and mucus accumulation (13), and that improving edema positively affects FEV1 values causing lower PaCO2 (14). Our results did not show any superiority for patients receiving NIV compared with no NIV. Our results, in fact, followed those of previous studies showing that rehabilitation generally improves spirometric parameters in COPD patients (15). Gad et al., while reporting improved FEV1 in patients receiving NIV compared to rehabilitation alone, did not find any significant difference in FVC or FEV1/FVC values (16).

In addition, NIV had no clear advantage in improving patient activity measured by 6MWT in our study. Although we found a 28-meter advantage for patients receiving NIV, this difference was not statistically significant. A meta-analysis (2013) (11) and another review (2009) (17) found no clinically or statistically significant effect for NIV in COPD patients even after 12 months of continuous nocturnal use on many variables including gas exchange, sleep efficiency, and lung function; however, a subset of patients may benefit from

NIV, reflected by their improved walking distance in their 6MWTs (18). Similar to this finding, Garrod et al. reported a significant improvement in 6MWT results, as well as Chronic Respiratory Disease Questionnaire scores and PaO2 levels, in patients receiving NIV and exercise training at home (19).

Regarding blood gas values, our study did not find any significant differences between two groups, which may be the result of the relatively short four-week duration of our study. In contrary to the results of studies with short duration (20), longer periods of rehabilitation with NIV (more than three months) might show a significant advantage for NIV (21). Moreover, the results of a study indicated that NIV resulted in rapid improvement of pH and PaCO2 in hospitalized patients (22). This controversy might be explained by the pCO2 pattern in various studies. Based on the result of the present study, patients in negative reports generally had lower pCO2 levels (<45 mmHg), compared to the subjects of studies with positive findings who had higher pCO2 levels. However, our findings failed to demonstrate any VBG improvement advantage by using NIV in our patients, despite having a high pCO2 level of 70 mmHg.

Our results confirmed the positive effect of NIV on COPD patients' quality of life and daily activities using the CAT questionnaire, in line with previous reports. Developed by Dodd et al in 2012 (23), the CAT score was found to closely correlate with other questionnaires such as St. George's and COPD Clinical Questionnaire and has been validated in a number of studies. CAT scores can be used as a predictive tool to determine the duration and extent of rehabilitation for individual patients (24).

As limitations of our study, we should mention the low number of participants, which was due to limited time and funding for this study. In addition, smoking, as a known factor affecting the pulmonary function test, could be a confounder in our study since a high percentage of our patients were smokers. Other factors including but not limited to age, sex, and nutritional status should also be investigated more comprehensively, which was beyond the scope of this study.

Conclusion

In conclusion, despite the proposed advantages of using NIV such as shortening hospital stay and lowering invasive ventilation, our findings showed a significant benefit for NIV only in CAT score, but not in pulmonary function tests, 6MWT, and VBG tests during a four-week period of rehabilitation. However, more comprehensive studies with larger populations are needed in order to come to a definite conclusion regarding the usefulness of NIV in COPD patients.

Abbreviations

COPD: Chronic obstructive pulmonary disease; NIV: Noninvasive ventilation; 6MWT: six-minute walk test; CAT: COPD Assessment Test; VBG: venous blood gas; PaCO2: arterial pressure of carbon dioxide; SpO2: oxygen saturation; ICU: intensive care unit; PaO2: partial arterial pressure of oxygen; GOLD: Chronic Obstructive Lung Disease; FEV1: forced expiratory volume during the first second; FVC: forced vital capacity; PAP: pulmonary artery pressure; EF: ejection fraction

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Conflict of interest:

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Authors' contributions:

All authors made substantial contributions to conception, design, acquisition, analysis and interpretation of data.

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