

## **Pulmonary Rehabilitation Efficacy in Patients COPD with Chronic Hypercapnia**

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### **Abstract**

**Background:** The aim of this study was to assess the effect of PR in hypercapnic patients with spirometric stage 3 - 4 COPD using NIMV, and to compare improvements of outcomes immediate and one year after PR in these patients with age, sex-matched normocapnic stage 3 - 4 COPD patients.

**Method:** It was retrospective cohort study. Dyspnea, exercise capacity, quality of life, body compositions of patients were recorded. Baseline, immediate and one year after PR values were compared between groups.

**Result:** The mean age of all patients was  $60.6 \pm 7.6$  years. 58 of 22 patients were hypercapnic. When age, sex-matched two groups were compared according to baseline parameters, the NIMV group had more BMI, decreased exercise capacity, worse quality of life. Immediately after PR program, in both groups MRC, SGRQ, anxiety-depression scores, ISWT, ESWT ( $p < 0.05$ ) were improved. When improved parameters were compared between groups,  $\Delta$ MRC,  $\Delta$ SGRQ,  $\Delta$ anxiety- $\Delta$ depression scores,  $\Delta$ ISWT,  $\Delta$ ESWT were similar. In the first year, MRC ( $p = 0.021$ ), SGRQ ( $p < 0.001$ ), anxiety ( $p = 0.034$ ) scores were under baseline scores, ISWT ( $p = 0.019$ ), ESWT ( $p = 0.039$ ) were over baseline values in NIMV group. When the changes in the first year were compared between groups,  $\Delta$ MRC,  $\Delta$ SGRQ,  $\Delta$ anxiety,  $\Delta$ depression scores,  $\Delta$  ISWT,  $\Delta$ ESWT were statistically similar.

**Conclusion:** Although chronic hypercapnic patients with COPD using NIMV might be more overweight, had lower exercise capacity, quality of life, these patients should be referred to PR due to similar improvements in dyspnea sensation, psychological status, exercise capacity, quality of life and preserving outcomes in the first year as much as normocapnics.

**Keywords:** NIMV; PR; COPD; Chronic Hypercapnic Respiratory Failure

### **Introduction**

Chronic obstructive pulmonary disease (COPD) is a systemic progressive disease that results in reduced exercise capacity and health related quality of life, progressive dyspnea, and mortality. It causes both health and economic burden unless pharmacologic treatment is optimized. Pulmonary rehabilitation (PR) is described as an evidence-based, multidisciplinary and comprehensive approach for patients with COPD with aim of increasing optimize functional status, decreasing symptoms and healthcare costs by stabilizing or reversing systemic manifestations of the disease [1]. PR as a part of COPD management, is proven effective intervention. Despite the proven and accurate utility, PR is often an under-utilized resource. There are many handicaps in referring to a PR center/unit or performing to the

more COPD patients who are candidates for PR. The one of most important reason for not being to be referred is the lack of knowledge as to who would be an ideal candidate and the value of PR. Even though it was shown that in stable patients with severe COPD with the home nocturnal noninvasive mechanical ventilation (NIMV), the exercise training was shown to an improvement in exercise capacity and health-related quality of life (HRQoL) [2], referral of this group of patients to outpatient PR center/units is limited.

**Aim of the Study**

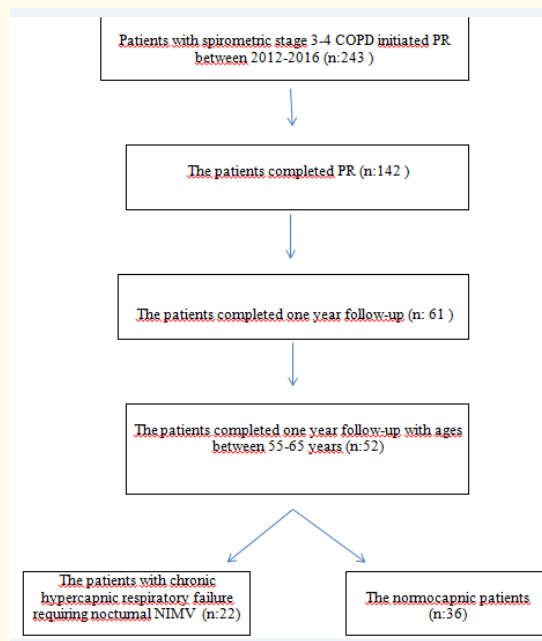
The aim of this study was to evaluate whether multidisciplinary, comprehensive outpatient PR program could improve the sensation of dyspnea, exercise capacity, psychological status, HRQoL and body composition in chronic hypercapnic patients with spirometric stage 3 - 4 COPD using home NIMV and to compare the improvement of outcomes immediate and one year after PR in these patients with age and sex-matched normocapnic spirometric stage 3 - 4 COPD patients.

**Methods**

**Study design**

The data of 58 patients with COPD were enrolled into retrospective cohort-study after patients’ approvals were taken with adherence to the guidelines of the Declaration of Helsinki. Approvals were obtained from Ataturk Chest Disease and Chest Surgery Education and Research Hospital review board before the parameters were recorded. The data of all patients who completed the multidisciplinary outpatient PR program and were followed up for one year from July 2012 to January 2016, were recorded. Patients receiving NIMV were selected according to inclusion criterias and then, age and sex-matched control group consisting of normocapnic patients were included.

Inclusion criterias were being in spirometric stage 3 - 4, completing PR program and attending the first year follow-up visit, receiving NIMV for about 6 hours per day during three months at least in NIMV group and not having decompensated respiratory acidosis in arterial blood gas analysis. The control group, consisting of normocapnic patients, was sex and aged- matched with NIMV group. Exclusion criterias were indication for using NIMV according to guideline recommendations [3] and having hypercapnic respiratory failure in control group (Figure 1).



**Figure 1:** Flow diagram.

### Pulmonary rehabilitation program

The PR consisted of comprehensive, multidisciplinary, hospital-based supervised outpatient program twice a week and an unsupervised home exercise program once a week. The program consisted of education, which included disease education; control of exacerbations; medication advice; bronchial hygiene techniques; breathing control techniques; energy conservation, relaxation, and dietary advice; exercise training; psychological support; and nutritional support. Educational courses were given by two pulmonologists, two physical therapists, a dietitian, a respiratory nurse, and a psychologist. The rehabilitation program was completely tailored to suit the needs of the individual.

According to guideline recommendations, the exercise program was also patient specific and the exercises were performed for each patient linked to exercise tolerance and disease severity. The exercise training and sessions included cycle ergometer and treadmill training (15 min each), strength training of both upper and lower extremities (5 - 10 min), and therapies for breathing and relaxation (15 - 20 minutes each) for a total of 70 - 90 min/day. Both cycling and treadmill training were applied. Workloads for both cycling and walking speed for the treadmill ergometer were calculated from the use of formula based on the incremental shuttle walking test (ISWT) and the exercise was also prescribed with the help of Borg dyspnea scores (4 - 6). Patients were trained at 50% of the peak workload on the cycle ergometer and 60 - 85% of  $VO_2$  peak on the treadmill. Intensity of exercise was increased according to the progress of the individual patient. Physiotherapists provided close supervision and heart rate, blood pressure, and oxygen saturation were monitored during the training sessions. Supplemental oxygen was administered to level oxygen saturation above 90%. Exercise training was not performed under NIMV. After the PR program finished, the individual home program was prescribed and patients were followed up at three-month intervals.

### Measures of outcome

The evaluated outcome measures were dyspnea, exercise capacity, psychological status, HRQoL, and body composition. Dyspnea was assessed using the Medical Research Council (MRC) scale [4] and exercise capacity was evaluated using the ISWT and endurance shuttle walking test (ESWT) [5]. Psychological status was revealed with the Hospital Anxiety and Depression Scale (HADS) [6]. HRQoL was assessed with the Turkish version of a standardized St. George's Respiratory Questionnaire (SGRQ) [7,8]. For body composition, bioelectrical impedance was used with a Tanita (BIA model TBF-300; Tanita Corporation, Tokyo, Japan). Body mass index (BMI) and fat-free mass index (FFMI) were calculated using a formula in which weight (body mass for BMI, fat-free mass for FFMI) in kilograms was divided by the square of the height in meters. All these measurements were assessed at baseline, at the end of PR, and one year after the completion of the PR program.

### Statistical analysis

SPSS version 18.0 (SPSS, Inc., Chicago, USA) for Microsoft Windows (Microsoft Corporation, Redmond, Washington) was used for analysis. Data are expressed as mean  $\pm$  SD. The variables were analyzed using the Shapiro-Wilks test for normal distribution. INTRA-group pre-post values within each group were matched and therefore used the Wilcoxon signed-rank test (for non-normal) vs. paired T test (for normal distributions). For the comparisons of improvements, Mann-Whitney U test was used. Statistical significance was set as  $p < 0.05$ .

### Results

Fifty-eight patients were enrolled into the study. Three of the 22 patients using NIMV were female. The patients who were normocapnic, comprised 36 patients with stable COPD, four of whom were female. The mean ages of the NIMV group and the non-hypercapnic group were  $60.2 \pm 5.3$  years and  $60.2 \pm 4.9$  years, respectively (Table 1). Both groups had similar FEV1 predicted % (patients with NIMV had  $26 \pm 10$ , the normocapnic group had  $27 \pm 6$ ). The mean values of the arterial blood gas analysis were pH  $7.38 \pm 0.02$ ,  $pO_2$   $61 \pm 10$  mm Hg,  $pCO_2$   $51 \pm 5$  mm Hg in the NIMV group, and pH  $7.39 \pm 0.03$ ,  $pO_2$   $62 \pm 7$  mm Hg,  $pCO_2$   $40 \pm 6$  mm Hg in the normocapnic group.

	Hypercapnic group (n = 22)	Normocapnic group (n = 36)	p
Male/Female (n)	18/4	33/3	0.264
Age (year) (mean ± SD)	60.2 ± 5.3	60.2 ± 4.9	0.779
Cigarette(packet.year)(mean ± SD)	39.4 ± 38	49.4 ± 30	0.162

Table 1: Demographic characteristics.

SD: Standard Deviation.

When age and sex-matched two groups were compared according to baseline parameters, FEV1 (p = 0.211), pack year of smoking history (p = 0.162), MRC (p = 0.123), anxiety (p = 0.764) and depression (p = 0.684) scores, FFMI (p = 0.229) were similar, but, BMI (p = 0.021), ISWT (p < 0.001), ESWT (p = 0.016), SGRQ (p = 0.024) were statistically different (Table 2). The NIMV group had more BMI, decreased exercise capacity and worse quality of life (Figure 2 and 3).

Before PR	Hypercapnic group	Normocapnic group	p
MRC	3.6 ± 0.1	3.3 ± 0.1	0.123
BMI	27.2 ± 1.0	23.0 ± 0.8	0.021
FFMI	19.3 ± 0.5	18.3 ± 0.4	0.229
Anxiety	9.8 ± 0.4	9.4 ± 0.3	0.764
Depression	9.7 ± 0.4	9.2 ± 0.3	0.684
ISWT	117 ± 20	223 ± 15	< 0.001
ESWT	3.4 ± 1.3	6.8 ± 1.0	0.016
SGRQ	73.7 ± 3.3	63.9 ± 2.5	0.024
FEV1	26 ± 10	27 ± 6	0.211
FVC	40 ± 13	43 ± 15	0.314

Table 2: Comparing groups according to baseline parameters.

MRC: Medical Research Council, BMI: Bodymass Index, FFMI: Fat-Free Mass Index, ISWT: Incremental Shuttle Walking Test, ESWT: Endurance Shuttle Walking Test, SGRQ: St.George’s Respiratory Questionnaire, FEV1: Forced Expiratory Volume in One Second, FVC: Forced Vital Capacity.

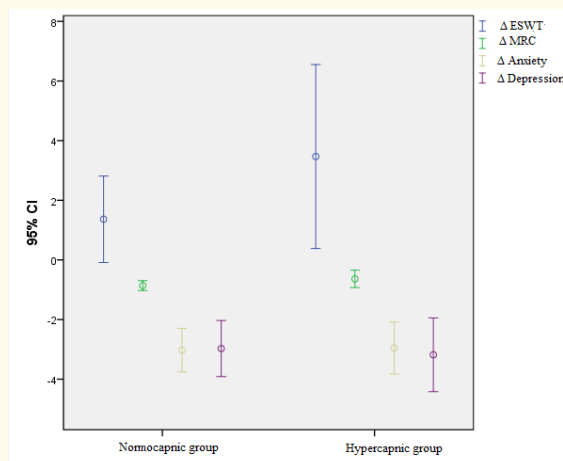
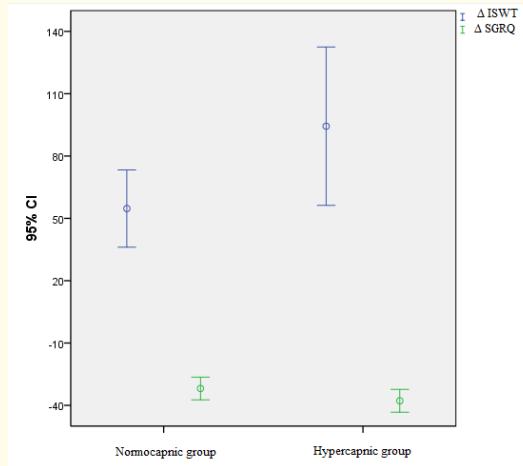


Figure 2: The improvements of ESWT, MRC, anxiety and depression scores after PR.



**Figure 3:** The improvements of ISWT, SGRQ scores after PR.

Immediately after PR program, in NIMV group MRC ( $p = 0.001$ ), SGRQ, anxiety, depression scores, ISWT ( $p < 0.001$ ) and ESWT ( $p = 0.012$ ) were improved but, BMI ( $p = 0.273$ ) FFMI ( $p = 0.676$ ) and FEV1 ( $p = 0.220$ ) did not statistically change. In normocapnic group, MRC, SGRQ, anxiety, depression scores, ISWT ( $p < 0.001$ ) and ESWT ( $p = 0.009$ ) were improved but BMI ( $p = 0.299$ ) FFMI ( $p = 0.879$ ) and FEV1 ( $p = 0.123$ ) did not statistically change, as well. When the improved parameters were compared between groups,  $\Delta$ MRC ( $p = 0.162$ ),  $\Delta$ SGRQ ( $p = 0.320$ ),  $\Delta$ anxiety ( $p = 0.776$ ),  $\Delta$ depression ( $p = 0.942$ ) scores,  $\Delta$ ISWT ( $p = 0.219$ ) and  $\Delta$ ESWT ( $p = 0.109$ ) were similar.

In the first year, MRC ( $p = 0.021$ ), SGRQ ( $p < 0.001$ ), anxiety ( $p = 0.034$ ) scores were under baseline scores, ISWT ( $p = 0.019$ ) and ESWT ( $p = 0.039$ ) were over baseline values in NIMV group. In normocapnic group, MRC ( $p = 0.001$ ), SGRQ ( $p < 0.001$ ) scores were under baseline scores, ISWT ( $p = 0.036$ ) was over baseline value. When the changes of improved parameters in the first year were compared between groups,  $\Delta$ MRC ( $p = 0.478$ ),  $\Delta$ SGRQ ( $p = 0.885$ ),  $\Delta$ anxiety ( $p = 0.955$ ),  $\Delta$ depression ( $p = 0.483$ ) scores,  $\Delta$ ISWT ( $p = 0.619$ ) and  $\Delta$ ESWT ( $p = 0.330$ ) were similar (Table 3 and figure 4).

Parameters	Hypercapnic group			Normocapnic group		
	Before PR	After PR	1 year	Before PR	After PR	1 year
MRC	3.6 ± 0.1	3.0 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	2.4 ± 0.1	2.8 ± 0.1
BMI	27.2 ± 1.0	27.4 ± 1.0	28.5 ± 1.1	23.0 ± 0.8	23.1 ± 0.8	23.4 ± 0.8
FFMI	19.3 ± 0.5	19.1 ± 0.4	19.8 ± 0.5	18.3 ± 0.4	18.3 ± 0.3	18.4 ± 0.4
Anxiety	9.8 ± 0.4	6.8 ± 0.5	8.8 ± 0.4	9.4 ± 0.3	6.3 ± 0.4	8.7 ± 0.3
Depression	9.7 ± 0.4	6.5 ± 0.5	9.7 ± 0.4	9.2 ± 0.3	6.3 ± 0.4	8.8 ± 0.3
ISWT	117 ± 20	212 ± 25	172 ± 23	223 ± 15	277 ± 19	253 ± 18
ESWT	3.4 ± 1.3	6.9 ± 1.5	5.4 ± 1.3	6.8 ± 1.0	8.7 ± 1.2	6.3 ± 1.0
SGRQ	73.7 ± 3.3	35.9 ± 2.4	55.3 ± 3.6	63.9 ± 2.5	32.0 ± 1.8	50.0 ± 2.8
FEV1	26 ± 10	27 ± 10	27 ± 12	27 ± 6	28 ± 8	28 ± 9

**Table 3:** Recorded parameters.

MRC: Medical Research Council, BMI: Bodymass Index, FFMI: Fat-Free Mass Index, ISWT: Incremental Shuttle Walking Test, ESWT: Endurance Shuttle Walking Test, SGRQ: St. George’s Respiratory Questionnaire, FEV1: Forced Expiratory Volume in One Second.

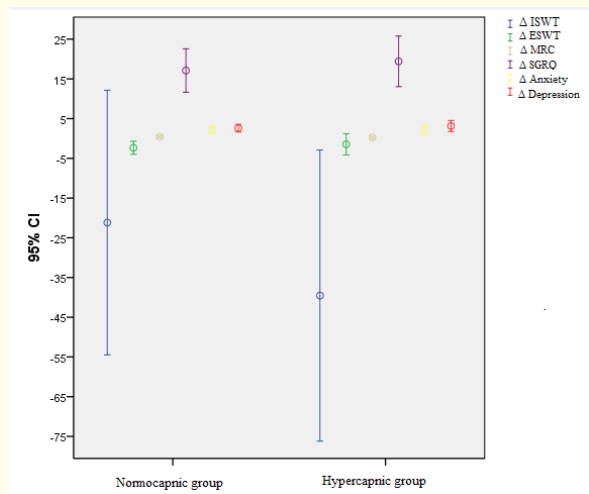


Figure 4: The improvements in the first year after PR.

## Discussion

This study showed that PR was as effective in chronic hypercapnic patients with severe COPD with indication for long-term use of NIMV as it was for normocapnic patients with severe COPD. It was also shown that although patients using NIMV were overweight, had lower exercise capacity and worse quality of life than normocapnic group, the improvements in dyspnea sensation, psychological status, exercise capacity and quality of life were similar, and furthermore, the improvements were preserved regardless of NIMV use after the first year of PR.

NIMV and PR are non-pharmacologic treatments in patients with COPD. NIMV relieves respiratory muscle by decreasing end expiratory volume and hyperinflation. Through the reduction of carbon dioxide levels, the chemosensitivity of the respiratory center improves and edema in the airways decreases. Moreover, mobilization of mucus is facilitated with the help of NIMV. As a result of these, the perception of dyspnea reduces and lung functions also improve [9-11]. A recent study showed that pulmonary functions did not improve in 20 patients with COPD using long-term NIMV after one year [12] and some randomized controlled trials failed to demonstrate the efficacy of home NIMV on gas exchange, nocturnal symptoms, and health-related results in the management of stable COPD besides pulmonary functions [13,14]. Another recent study showed that long-term NIMV had a better effect, NIMV could improve exercise capacity, quality of life, stabilize FEV1 and FVC (more than 2 years), and also decrease survival of patients with COPD [15]. Another proven effective approach is PR. PR has also been shown to have no definite effect on pulmonary functions but has benefits on exercise capacity, perceived density of dyspnea, HRQoL, and COPD-related anxiety and depression [16]. However, few studies on patients with severe COPD are available and the programs were heterogeneous. Exercise training was shown to enhance exercise tolerance and HRQoL in patients with very severe COPD in a systemic review- meta-analysis published in 2017 [17]. Besides the few studies, the referral of patients with severe COPD, especially with chronic hypercapnic failure, to PR centers/units is limited in clinical practice.

In a study that evaluated the short-term effects of PR, 72 chronic hypercapnic patients with COPD were randomly allocated to a combination of nocturnal NIMV and PR or PR alone. Although the daily step count improved significantly in the NIMV group compared with the

non-hypercapnic group, there was no difference significantly between the groups in exercise capacity evaluated in the 6-minute walk test, ESWT, and maximal oxygen uptake. It was concluded that no additional improvements were seen in pulmonary function, exercise capacity, dyspnea, anxiety, and depression when PR was combined with nocturnal NIMV because the gains in outcomes were similar after PR in both groups [18]. Similarly, in our study, improvements in dyspnea sensation, psychological status, exercise capacity, and health related quality of life were similar in both groups after PR program.

There are also few studies on the long-term effects of PR in patients with COPD using home NIMV. In a randomized-controlled study, patients with COPD who had chronic hypercapnic respiratory failure were followed up for two years with the purpose of comparing the efficiency of PR in patients using nocturnal NIMV. FEV1 was found preserved in the NIMV group after two years, whereas it deteriorated in the PR group [19]. In our study, FEV1 values remained stable in both groups.

In a two-year follow-up study, MRC, HAD scores, and six-minute walk test distance decreased significantly in the PR alone group, and no significant change was shown in the NIMV group. Exercise capacity deteriorated in PR alone group especially after the first year. HRQoL was enhanced in the NIMV group [19]. In our study, even though the NIMV group was more dyspneic and had lower exercise capacity, improvements in dyspnea sensation, exercise capacity, HRQoL, psychological status were preserved over a year in both groups. Adherence to the home program and attendance of regular outpatient PR center follow-ups were thought to be similar in both groups.

The benefits of PR have been shown likely to persist for 18 months [20], but there are inconsistent results as to whether the improvements in exercise capacity could be sustained for two years [21,22]. The British Thoracic Society guidelines state that the benefits from PR maintained for at least one year were at evidence level 2+ [23]. In another study, a significant impairment in exercise capacity and quality of life one year after PR was shown and the importance of post PR follow-up programs and number of exacerbations was emphasized [24]. In our study, all patients attended outpatient PR center follow-up programs at regular three-month intervals. Unsupervised home PR program prescribed individually at each follow-up. The success of sustaining improvements of outcomes was linked to the well-organized follow-up program, even if it was unsupervised.

The most important limitation is the retrospective and non-randomized design of the study. A group of patients who did not attend the PR program but used NIMV could be added to identify more effects of NIMV.

### Conclusion

A multidisciplinary comprehensive outpatient PR program may also be an effective intervention in patients with COPD using NIMV with chronic respiratory hypercapnic failure. Even though these patients were more overweight, had lower exercise capacity, worse quality of life, they should be referred to PR center or units due to similar improvements of outcomes such as dyspnea sensation, psychological status, exercise capacity, quality of life, and also preserving in dyspnea sensation, exercise capacity, and quality of life the first year as much as in normocapnic patients with COPD. It was suggested that chronic hypercapnic respiratory failure requiring NIMV in severe COPD patients was not a handicap or negative factor for utilizing PR benefits and preserving the improvements in a year period after PR.

### Quick Look

#### Current knowledge

Although pulmonary rehabilitation is an effective and proven approach even in patients with severe COPD, there are few studies about the effectiveness of PR in chronic hypercapnic patients with severe COPD requiring home NIMV in one year period after PR. Besides the few studies, the referral of patients with severe COPD, especially with chronic hypercapnic failure, to PR centers/units is limited in clinical practice.



### What this paper contributes to our knowledge

Even though chronic hypercapnic patients with severe COPD requiring home NIMV could be more overweight, have lower exercise capacity, worse quality of life, they should be referred to PR center or units due to similar improvements of outcomes such as dyspnea sensation, psychological status, exercise capacity, quality of life, and also preserving in dyspnea sensation, exercise capacity, and quality of life the first year as much as in normocapnic patients with COPD. Chronic hypercapnic respiratory failure requiring NIMV in severe COPD patients was not a handicap or negative factor for utilizing PR benefits and preserving the improvements in a year period after PR.

### Conflict of Interest

None.

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