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Original Article

Adding Non-Invasive Positive Pressure Ventilation to Supplemental Oxygen During Exercise Training in Severe Chronic Obstructive Pulmonary Disease: A Randomized Controlled Study

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Abstract

OBJECTIVE: Chronic obstructive pulmonary disease is currently the fourth leading cause of death in the world. Pulmonary rehabilitation is recommended for chronic obstructive pulmonary disease.

MATERIAL AND METHODS: This study aimed to evaluate the effects of non-invasive ventilation, supplemental oxygen, and exercise training and supplemental oxygen during exercise training during pulmonary rehabilitation practice in comparison with only exercise training on lung functions, blood gases, lactate levels, respiratory muscle pressures, dyspnea, walking distances, quality of life, and depression in patients with severe chronic obstructive pulmonary disease. The main outcome measure is exercise capacity (6-minute walk test), and the secondary end-point included quality of life.

RESULTS: Thirty-five patients (mean ± SD age, 65.4 ± 6.5 years) with a mean bronchodilator forced expiratory volume in the first second of expiration of 39.4 ± 7%, undergoing an 8-week outpatient pulmonary rehabilitation, were randomized to either non-invasive ventilation, supplemental oxygen, and exercise training, supplemental oxygen during exercise training, or exercise training groups. The improvements in respiratory muscle strength were higher in non-invasive ventilation, supplemental oxygen, and exercise training patients than the moderate improvements in the exercise training group. Both non-invasive ventilation, supplemental oxygen, and exercise training and supplemental oxygen during exercise training groups showed significant increases in the 6-minute walk test and incremental shuttle walk test. However, the increase in walking distance was better in non-invasive ventilation, supplemental oxygen, and exercise training group (69.8 ± 53.2 m in 6-minute walk test and 66.6 ± 65.2 m in incremental shuttle walk test, $P = .001$ and $P = .005$, respectively) compared to supplemental oxygen during exercise training group (42.5 + 55.5 m in 6-minute walk test and 53.5 + 70.2 m in incremental shuttle walk test, $P = .01$ each, respectively). The total St. George's Respiratory Questionnaire score was similar in all study groups after the intervention. Symptoms of depression significantly improved only in non-invasive ventilation, supplemental oxygen, and exercise training group (−2.8 + 2.8, $P = .006$).

CONCLUSION: Non-invasive positive-pressure ventilation (NIPPV) added to supplemental oxygen during exercise training was associated with better physiological adaptations than other modalities.

KEYWORDS: COPD management, exercise training, non-invasive ventilation
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently 1 of the 3 causes of death in the world. Chronic airway obstruction, expiratory flow limitation, and increased respiratory frequency result in end-expiratory lung volume, known as dynamic hyperinflation (DH) in patients with COPD. Even though DH is a compensatory mechanism that increases expiratory flow during exercise, it has some disadvantages such as loading the inspiratory muscles and increasing the work of breathing.[1,2] Dynamic hyperinflation causes breathlessness and diminished exercise tolerance. Exercise training (ET) which is a part of pulmonary rehabilitation (PR) leads to improve functional capacity, exercise tolerance, and quality of life (QoL).[3,4] Recently, there has been an increasing use of non-invasive ventilation (NIV) during exercise aiming to train patients at intensity levels higher than those allowed by their pathophysiological conditions.[2,5] It seems reasonable that the combination of the 2 interventional approaches, NIV, and ET may improve muscle strength and QoL in patients with COPD.[6]

Different modalities exist which can increase the effectiveness of ET such as heliox supplementation, intermittent exercise, and NIV. The use of NIV seems more practical compared to the other methods.[7] Another study showed that COPD

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patients with severe hyperinflation and exercise-induced desaturation benefit from NIV plus oxygen supplementation (O_2) during ET.[8] On the other hand, NIV performed during high-intensity exercise can modulate endothelial function and improve exercise tolerance in especially COPD heart failure.[9] However, there is no conclusive information in regard to NIV use during ET. There has not been a controlled trial designed to compare the benefits of PR in severe COPD carried out ET, NIV, and O_2 (ET + NIV + O_2), ET with oxygen (ET + O_2), and ET alone.

It was aimed to investigate the effects of 3 exercise modalities in severe COPD patients during an outpatient PR program in this study. It was hypothesized that ET + NIV + O_2 during exercise could promote optimal physiologic adaptations to ET in severe COPD.

MATERIAL AND METHODS

Design

The interventional study, designed as a prospective randomized controlled trial, composed of 61 patients, 35 of whom were randomized through computer-generated randomization into 1 of 3 groups: ET + NIV + O_2, ET + O_2, and ET (Figure 1). Ethical approval was obtained from the Institutional Review Board of Ege University, Faculty of Medicine for Human Studies and Ethics Committee (Approval Acceptance Number: 2020-KAEK-139) and was carried out in accordance with the principles of the Helsinki Declaration. A written informed consent was obtained from all patients. Stable patients with COPD (corresponding to GOLD Group D) were included in this study.[1]

Participants

All patients were receiving COPD optimal treatment according to the GOLD guideline (Long-Acting β-Agonist [LABA] + Long-Acting Muscarinic Antagonist [LAMA] + Inhaled Corticosteroids [ICS]), but there were no patients taking oral steroids or antibiotics. The patients with orthopedic, neurologic conditions, or malignant disorders that could prevent participation in an exercise program, in addition to unstable cardiovascular conditions such as arrhythmias, uncontrolled hypertension, severe pulmonary hypertension, diabetes mellitus, or other pulmonary diseases were ruled out. Patients who were already on long-term oxygen therapy (LTOT) and/or NIV due to chronic respiratory failure and exacerbation over the last month and during the ET sessions were also excluded.

MAIN POINTS

- Pulmonary rehabilitation has been proved beneficial effects in chronic obstructive pulmonary disease (COPD).
- Although the use of NIPPV added to supplemental oxygen during pulmonary rehabilitation requires equipment and expertise in implementation, it can be used to promote additional physiologic effects.
- Pulmonary rehabilitation can be performed in COPD regardless of the severity of the disease, on the condition that necessary equipments are provided.

All patients were delivered an 8-week supervised outpatient PR program and randomized to either ET + NIV + O_2, ET + O_2 groups, or only ET as a control group by drawing lots (opaque, shuffled, and coded envelopes that were opened before implementation). The variables were measured at baseline and after the program. The outcomes of all assessments were compared with the results of the control group. Education was also given to the patients. All patients were given information about NIV on a routine control visit.

PROCEDURES

Lung Functions, Lung Volumes, and Respiratory Muscle Strength Measurement

Forced vital capacity (FVC) and vital capacity (VC) measurements were carried out with a Spirometer (Sensor Medics 2400, Yorba Linda, Calif, USA) by following American Thoracic Society Guidelines[10] by using reference values of the Guidelines of European Respiratory Society.[11] Inspiratory and expiratory muscle strengths [Pimax and Pemax were measured during inspiration and expiration against closed airway at residual volume (RV)] were measured using microRPM (respiratory pressure meter) according to the method of Neder et al.[12] The patients were encouraged to give maximum effort. Residual volume and total lung capacity (TLC) were performed with a body plethysmography (Master Screen Body, Jaeger GmbH, Hoechberg, Germany).

Blood Gas Analysis and Lactate Levels

Arterial blood gases (PaO_2, $PaCO_2$, and pH) were analyzed in 100 µL arterialized blood sampled from the radial artery while lactic acid (LA) concentrations were measured in venous blood samples (Nova Biomedical Critical Care Xpress, Waltham, Mass, USA). Samplings were performed at rest and before and after ET sessions.

Exercise Capacity and Dyspnea

Dyspnea was evaluated by a modified BORG scale.[13] The 6-minute walk test (6MWT) and incremental and endurance shuttle walk tests (ISWT, ESWT, respectively) were performed in accordance with the references.[14-16] The minimal important significant changes for the 6MWT, ISWT, and ESWT were approximately 30 m (18), 47.5 m (16), and 45-85 seconds[16] respectively.

Health Status, Anxiety, and Depression

Quality of life was evaluated by the Turkish validated version of St. George's Respiratory Questionnaire (SGRQ).[17] The SGRQ is composed of 4 sub-categories; symptoms, activities, impact and total score and ranged from 0 to 100; as the score is getting increase, QqL is poorer. Four score changes in all subgroups are accepted as significant.[17,18]

Hospital anxiety and depression scale (HADS), each consisting of 7 items, was used to assess anxiety and depression. All patients were self-administered. Anxiety (HADSa) and depression (HADSd) using hospital anxiety and depression scale are evaluated as 2 separate columns. If the score was ≥8, it is defined as anxiety and/or depression.[19]

Exercise Training Protocol

An 8-week outpatient supervised PR was performed with a fixed protocol which was applied to all patients in our PR unit.

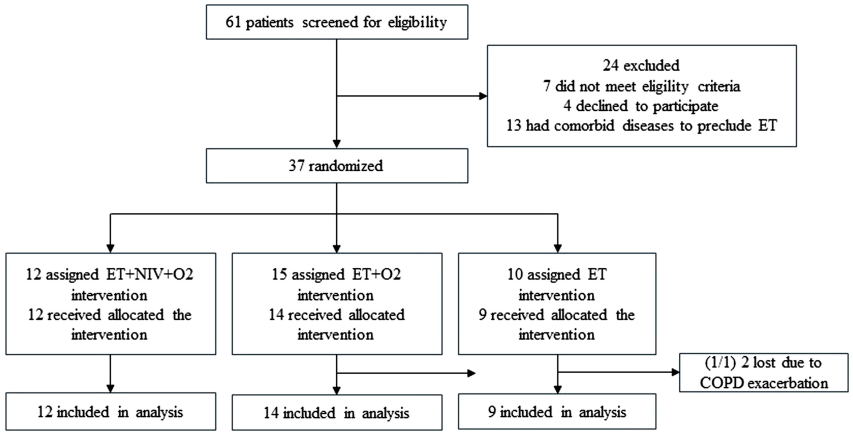

Figure 1. CONSORT diagram of the study.

The patients were delivered an ET program of cycle ergometer (15 minutes), treadmill (15 minutes), lower and upper extremity strength training (5-10 minutes), breathing and relaxation therapies (15-20 minutes, each), twice weekly for total 60-80 min/day, and home exercise program once a week. Breathing exercises were composed of glossopharyngeal, pursed lips, diaphragmatic, and segmental breathing. Relaxation exercises were administered in accordance with the Jacobson technique of progressive muscle relaxation. Exercise, first with a warm-up period, followed by workloads for walking and cycling speed for treadmill ergometer were calculated out of ISWT results. Patients were exercised at 50% of peak workload and 50%-80% of peak VO_2. Non-invasive ventilation was delivered with a bi-level ventilator (BIPAP-S, Respironics, Murrysville, Pa, USA) through a tight-fitting Silicon Gold Seal (Resipronics, Inc.) oro-nasal mask. The inspiratory pressure was started at 10 cmH_2O and increased 2 cmH_2O every minute according to the patient's tolerance.[20] The expiratory settings were started at 4 cmH_2O and increased 1 cmH_2O every minute. The expiratory and inspiratory pressures were slowly up-titrated to get the best ventilator support. Oxygen was inserted into the ventilator circuit at a flow rate (1-3 L/min) by dual-prong nasal cannulae for keeping the oxygen saturation during NIV at or above 90% during ET.

Statistical Analysis

Data were analyzed with Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA), and data were presented as mean ± SD unless otherwise stated. Comparing categorical variables was performed with chi-square with Fisher's exact test (when appropriate). Normality test for numeric data was performed with Shapiro Will test. Statistical comparisons between the groups were calculated using 1-way analysis of variance for normally distributed data, and post hoc test was performed when the analysis of variance determined a significant effect. Kruskal–Wallis test was used for the data that were not distributed normally. The comparisons before and after rehabilitation within the groups were calculated using paired Student's *t*-test and Wilcoxon signed-rank tests when appropriate. $P < .05$ was accepted significant.

RESULTS

Thirty-five patients who were included in this study completed 16 ET sessions with individual home exercise programs. Significant differences were not detected in each group in terms of demographic features, body composition, comorbidities, lung functions, respiratory muscle strengths, blood lactate levels, 6MWT distances, and endurance time except BORG scale and ISWT (m) (2.6, 4.8, 2.8, for BORG scale and 360, 252, 345 m for ISWT, ET + NIV + O_2, ET + O_2, ET, respectively). Patients' demographics and characteristics were presented in Table 1. Twenty-four patients were excluded due to severe pulmonary hypertension, lumbar disc herniation, and declining participation. After randomization, 2 of the patients prematurely terminated the study because of an exacerbation of COPD (Figure 1).

Residual volume and total lung capacity decreased after the program (−305 ± 489 and −325 ± 524, both $P = .05$, respectively) in only ET + NIV + O_2 group. However, there were no changes in lung volumes in the ET + O_2 group, while there was a slight increase in FVC in the ET group after PR. The decrease in lung volumes in ET + NIV + O_2 group was not statistically significant in comparison with the ET alone patients ($P > .05$). It was detected that there was a significant increase in both Pimax (13.5 ± 12.1 cmH_2O, $P = .003$) and Pemax (15.5 ± 24.1 cmH_2O, $P = .04$) in ET + NIV + O_2 group, while it was determined a slight increase in only Pimax (8.7 ± 9.8 cmH_2O, $P = .02$) in the ET group.

The improvements in respiratory muscle strength were higher in ET + NIV + O_2 patients than the moderate improvements in the ET group. In the ET + O_2 group, it was detected that a decrease in Pimax (−5.07 ± 25.8 cmH_2O, $P = .47$) and the change in Pemax were not statistically significant (12.1 ± 41.4 cmH_2O, $P = .29$). Changes in blood gases were not detected at any time period in any of the groups. Patients who received ET + NIV + O_2 demonstrated a decrease in blood lactate level; however, it was not statistically significant ($P = .06$) (Tables 2 and 3).

BORG score decreased only in ET + O_2 group (−2.4 ± 2.7, $P = .005$) after the intervention. Both ET + NIV + O_2 and ET + O_2 groups showed significant increases in 6MWT and ISWT tests. However, the improvement in walking tests was better in ET + NIV + O_2 group (69.8 ± 53.2 m in 6MWT and 66.6 ± 65.2 m in ISWT, $P = .001$ and $P = .005$, respectively) compared to ET + O_2 group (42.5 + 55.5 m in 6MWT and 53.5 + 70.2 m in ISWT, $P = .01$ each, respectively). In

Table 1. Baseline Demographics and Characteristics of the Patients

Variables	ET + NIV + O_2 (n = 12)	ET + O_2 (n = 14)	ET (Control) (n = 9)	*P*
Age (years)	64.2 ± 7.3	65.9 ± 6.6	66.1 ± 5.4	.76
Gender (male) (n)	11	14	9	.37
BMI (kg/m²)	24.4 ± 4.2	23.4 ± 5.1	25.3 ± 3.1	.57
Smoking history (pack/year)	56.9 ± 41.6	37.5 ± 17.7	44.3 ± 16.5	.22
Post. FEV_1 (mL)	1180 ± 215	1060 ± 307	1188 ± 225	.39
Post. FEV_1 (predicted %)	41.4 ± 6.4	35.5 ± 8.5	41.5 ± 6.1	.08
FEV_1/FVC (%)	51.5 ± 7.0	45.9 ± 7.0	48.4 ± 6.6	.13
Initial BORG score	0.6 ± 1.3	2.2 ± 2.4	0.7 ± 1.0	.2
Comorbidities (n)				
Coronary artery disease	1	0	0	NS
Hypertension	1	5	0	
Diabetes mellitus	1	0	0	
FVC (mL)	1945 ± 739	2247 ± 603	2196 ± 328	.42
FVC (%)	59.4 ± 9.1	58.8 ± 14.5	59.2 ± 10.8	.98
FEV_1 (mL)	1076 ± 162	996 ± 269	1084 ± 270	.60
FEV_1 (%)	37.7 ± 3.9	33.5 ± 7.7	37.6 ± 7.5	.20
RV (mL)	4375 ± 1176	4602 ± 1339	4835 ± 1163	.70
TLC (mL)	6670 ± 1451	6767 ± 1559	7870 ± 2291	.24
RV/TLC (%)	65.0 ± 6.7	67.3 ± 7.4	62.8 ± 11.8	.43
IC (mL)	1476 ± 518	1432 ± 549	1772 ± 396	.27
IC/TLC (%)	22.8 ± 7.7	21.4 ± 7.4	24.0 ± 7.2	.71
Blood lactate level (mmo/L)	1.2 ± 0.7	1.1 ± 0.5	1.0 ± 0.9	.53
mMRC	2.5 ± 0.7	3.0 ± 0.9	2.4 ± 0.5	.06
BORG scale (exercise)	2.6 ± 1.4	4.8 ± 2.1	2.8 ± 1.6	**.007**
CAT score (n)	18.8 ± 9.6	21.6 ± 8.4	20.0 ± 18.0	.87
6MWT (m)	400.8 ± 57.4	345.3 ± 95.0	350.4 ± 81.2	.18
ISWT (m)	360.8 ± 100.8	252.1 ± 101.1	345.5 ± 105.8	.02
ESWT speed (km/h)	3.9 ± 0.7	3.4 ± 0.7	4.2 ± 0.7	.05
ESWT time (minutes)	18.0 ± 3.9	11.6 ± 7.5	15.4 ± 6.1	.19
SGRQ				
Symptoms	47.0 ± 22.6	42.8 ± 30.3	35.9 ± 15.0	.85
Activity	50.0 ± 24.6	60.7 ± 21.3	51.3 ± 21.5	.51
Impact	29.3 ± 19.4	41.9 ± 28.2	28.1 ± 19.6	.25
Total score	39.2 ± 17.6	47.7 ± 23.7	36.7 ± 15.9	.49
CRQ				
Dyspnea	3.4 ± 1.0	3.3 ± 1.1	4.3 ± 1.0	.24
Fatigue	4.1 ± 1.4	3.7 ± 1.5	5.5 ± 0.7	.40
Emotional	4.5 ± 1.5	4.7 ± 1.5	5.6 ± 1.1	.64
Mastery	4.6 ± 1.4	5.2 ± 1.4	5.7 ± 1.4	.50
HADs				
Anxiety	6.0 ± 4.1	5.6 ± 4.9	2.7 ± 2.7	.45
Depression	5.3 ± 3.0	5.2 ± 4.0	10.0 ± 13.5	.27

Results were reported as mean ± SD after testing for normal distribution. $P < .05$ values were statistically significant.
BMI, body mass index; CAT, Chronic obstructive pulmonary disease assessment test; CRQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; IC, inspiratory capacity; ISWT, incremental shuttle walk test; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnea scale; 6MWT, 6-minute walk test; post-FEV1, post-bronchodilator forced expiratory volume in the first second of expiration; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

the ET group, increases in 6MWT and ISWT distance were 67.1 + 40.9 m and 51.1 + 33.7 m, $P = .01$ and $P = .02$, respectively. Symptom scores of SGRQ improved significantly only in the ET + NIV + O_2 group (−21.8 + 18.9, $P = .002$), whereas the total score improved in ET + O_2 patients (−12.2 + 20.1, $P = .04$). This finding may be associated with higher SGRQ baseline scores obtained in ET + O_2 group (47.7 ± 23.7). However, the total SGRQ score was similar in all study groups after the intervention. Symptoms of depression significantly improved only in ET + NIV + O_2 group (−2.8 + 2.8, $P = .006$) (Table 3).

DISCUSSION

The present study demonstrated that the addition of NIV as an adjunct to oxygen therapy during PR in severe COPD reduces DH and improves exercise capacity, respiratory muscle strength, symptom subgroup in SGRQ, and depression scores compared to ET + O_2 and ET groups. The intensity of ET during PR is important for achieving accurate physiologic effects. Exertional dyspnea and leg and respiratory muscle fatigue do not allow particularly severe COPD patients to maintain optimal intensity during training. Although the use of NIV has been proposed as another option to improve QoL, exercise tolerance, and respiratory performance, a similar effect between NIV and placebo was observed in the recent Cochrane review for the outcomes considered despite differences among studies. The authors concluded that due to a small number of available studies and sample sizes, the effects of adding NIV to conventional strategies are in need of further investigation.[21] A systemic review reported the results of the randomized controlled trials on oxygen during ET and found no beneficial effect on PR outcomes.[22] Another study concluded that patients with oxygen had longer exercise endurance but failed to improve maximal exercise capacity, walking distance, and QoL.[23] Borghi-Silva et al[24] made a comparison between the oxygen group and the NIV group in terms of similar physiologic outcomes and demonstrated that NIV was better than oxygen alone. Poor results in the oxygen group were related to the

Table 2. Changes in Lung Functions and Volumes, Respiratory Muscle Strength, Arterial Blood Gas Analysis, Quality of Life Scores, Walking Distances, Psychological Status Changes Before and After the Intervention in ET + NIV + O_2 Group, ET + O_2 Group, and ET Group

	ET + NIV + O_2 (n = 12)		ET + O_2 (n = 14)		ET (n = 9)	
Variables	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Post-FVC (mL)	1945 ± 739	2236 ± 495	2247 ± 603	2305 ± 572	2196 ± 328	2483 ± 383
Post-FVC (%)	59.4 ± 9.1	60.6 ± 8.09	58.8 ± 14.5	60.7 ± 13.7	59.2 ± 10.8	68.0 ± 10.6
Post-FEV_1 (mL)	1076 ± 162	1116 ± 212	996 ± 269	1072 ± 298	1084 ± 270	1284 ± 255
Post-FEV_1 (%)	37.7 ± 3.9	39.4 ± 5.6	33.5 ± 7.7	36.4 ± 9.7	37.6 ± 7.5	45.1 ± 7.7
RV (mL)	4375 ± 1176	4070 ± 1101	4602 ± 1339	4564 ± 1319	4835 ± 1163	4426 ± 1054
TLC (mL)	6670 ± 1451	6345 ± 1386	6767 ± 1559	6795 ± 1522	7870 ± 2291	7023 ± 1009
RV/TLC (%)	65.0 ± 6.7	63.6 ± 6.9	67.3 ± 7.4	66.8 ± 8.2	62.8 ± 11.8	62.3 ± 7.6
IC (mL)	1476 ± 518	1488 ± 518	1432 ± 549	1505 ± 355	1772 ± 396	1806 ± 242
IC/TLC (%)	22.8 ± 7.7	23.6 ± 6.8	21.4 ± 7.4	22.4 ± 4.9	24.0 ± 7.2	26.1 ± 4.7
$Pimax_{peak}$ (cmH_2O)	67.0 ± 27.7	80.6 ± 25.9	76.7 ± 42.1	71.6 ± 27.5	63.5 ± 21.7	72.3 ± 21.9
$Pemax_{peak}$ (cmH_2O)	87.4 ± 32.9	101 ± 30.8	99.5 ± 41.8	112.1 ± 36.5	105 ± 32.8	124.5 ± 45.1
PaO_2 (mmHg)	77.4 ± 8.7	76.2 ± 5.6	72.6 ± 16.5	71.9 ± 11.8	73.1 ± 4.4	75.7 ± 10.1
$PaCO_2$ (mmHg)	36.4 ± 3.6	34.3 ± 2.8	35.6 ± 6.2	35.9 ± 5.4	36.0 ± 5.7	35.7 ± 4.2
SpO_2	95.7 ± 1.0	95.3 ± 0.9	93.7 ± 3.6	94.1 ± 2.9	95.4 ± 1.1	95.4 ± 1.5
Lactate (mmol/L)	1.2 ± 0.7	0.9 ± 0.6	1.1 ± 0.5	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.9
BORG scale	2.6 ± 1.4	2.7 ± 1.5	4.8 ± 2.1	2.4 ± 1.6	2.8 ± 1.6	2.0 ± 1.3
CAT score	18.8 ± 9.6	7.4 ± 5.3	21.6 ± 8.4	12.1 ± 5.2	20.0 ± 18.0	10.7 ± 6.7
6MWT (m)	400 ± 57.4	470 ± 95.4	345 ± 95	387 ± 64	350 ± 81	417 ± 87
ISWT (m)	360 ± 100	427 ± 74	252 ± 101	305 ± 84	345 ± 105	396 ± 108
ESWT speed (km/h)	3.9 ± 0.7	4.7 ± 0.5	3.4 ± 0.7	3.9 ± 0.5	4.2 ± 0.7	4.5 ± 0.7*
ESWT time (min)	18.0 ± 3.9	19.4 ± 4.2	11.6 ± 7.5	16.0 ± 6.2*	15.4 ± 6.1	19.1 ± 4.9
SGRQ						
Symptom	47.0 ± 22.6	25.2 ± 18.2	42.8 ± 30.3	31.7 ± 23.7	48.7 ± 24.3	35.9 ± 15.0
Activity	50.0 ± 24.6	54.7 ± 22.8	60.7 ± 21.3	55.7 ± 20.3	55.7 ± 24.3	51.3 ± 21.5
Impact	29.3 ± 19.4	25.7 ± 19.8	41.9 ± 28.2	26.7 ± 20.7	26.3 ± 20.8	28.1 ± 19.6
Total score	39.2 ± 17.6	35.2 ± 17.9	47.7 ± 23.7	35.4 ± 18.4	38.9 ± 19.5	36.7 ± 15.9
CRQ						
Dyspnea	3.4 ± 1.0	3.8 ± 0.8	3.3 ± 1.1	3.3 ± 1.0	4.1 ± 1.2	4.3 ± 1.0
Fatigue	4.1 ± 1.4	4.6 ± 0.8	3.7 ± 1.5	4.7 ± 1.3	4.6 ± 1.4	5.5 ± 0.7
Emotional	4.5 ± 1.5	5.0 ± 0.9	4.7 ± 1.5	5.1 ± 1.0	5.2 ± 1.6	5.6 ± 1.1
Mastery	4.6 ± 1.4	5.2 ± 0.9	5.2 ± 1.4	5.6 ± 1.3	5.2 ± 1.6	5.7 ± 1.4
HADs						
Anxiety	6.0 ± 4.1	4.8 ± 3.0	5.6 ± 4.9	4.2 ± 4.4	3.7 ± 3.3	2.7 ± 2.7
Depression	5.3 ± 3.0	2.5 ± 1.9	5.2 ± 4.0	4.0 ± 4.0	10.0 ± 13.5	3.78 ± 2.58

Results were reported as mean ± SD after testing for normal distribution.
BMI, body mass index; CAT, COPD assessment test; CRQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; IC, inspiratory capacity; ISWT, incremental shuttle walk test; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnea scale; 6MWT, 6-minute walk test; post-FEV1, post-bronchodilator forced expiratory volume in the first second of expiration; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

Table 3. Comparison of Differences Among ET + NIV + O_2 Group, ET + O_2 Group, and ET Group

	ET + NIV + O_2 (n = 12)		ET + O_2 (n = 14)		ET (n = 9)	
Variables	**Δ (Post-pre)**	***P***	**Δ (Post-pre)**	***P***	**Δ (Post-pre)**	***P***
Post-FVC (mL)	291 ± 754	.20	57 ± 221	.34	286 ± 283	.16
Post-FVC (%)	1.1 ± 7.5	.59	1.8 ± 5.3	.22	8.3 ± 8.04	**.01**
Post-FEV_1 (mL)	40 ± 134	.32	75 ± 146	.75	200 ± 191	.14
Post-FEV_1 (%)	1.7 ± 4.7	.23	2.9 ± 4.8	.44	7.4 ± 7.4	.18
RV (mL)	−305.0 ± 489.1	**.05**	−38 ± 747	.85	408 ± 689	.11
TLC (mL)	−325 ± 524	**.05**	28 ± 759	.89	−846 ± 1715	.17
RV/TLC (%)	−1.3 ± 3.0	.16	−0.5 ± 5.7	.74	−0.5 ± 10.3	.87
IC (mL)	11 ± 387	.91	72 ± 464	.57	34 ± 306	.74
IC/TLC (%)	0.8 ± 5.6	.61	10.0 ± 5.8	.53	2.1 ± 5.9	.32
$Pimax_{peak}$ (cmH_2O)	13.5 ± 12.1	**.003**	−5.07 ± 25.8	.47	8.7 ± 9.8	.02
$Pemax_{peak}$ (cmH_2O)	13.6 ± 26.7	**.025**	12.4 ± 43.2	.02	19.1 ± 27.2	.62
PaO_2 (mmHg)	−1.2 ± 10.2	.69	−0.6 ± 14.1	.86	2.5 ± 8.8	.4
$PaCO_2$ (mmHg)	−2.5 ± 4.3	.11	0.2 ± 5.2	.85	−0.2 ± 4.7	.88
SpO_2	−0.3 ± 1.1	.29	0.3 ± 2.2	.56	0.0 ± 1.6	.93
Lactate (mmol/L)	−0.3 ± 0.6	.06	−0.1 ± 0.5	.36	0.0 ± 0.3	.69
BORG scale	0.0 ± 1.8	.88	−2.4 ± 2.7	**.005**	−0.8 ± 1.2	.06
CAT score	−11.4 ± 8.6	**.002**	−9.5 ± 7.0	**.02**	−10.6 ± 15.9	.36
6MWT (m)	69 ± 53	**.001**	42 ± 55	**.01**	67 ± 40	**.001**
ISWT (m)	66 ± 65	**.005**	53 ± 70	**.01**	51 ± 33	**.002**
ESWT speed (km/h)	0.7 ± 0.7	**.005**	0.4 ± 0.5	**.007**	0.3 ± 0.2	**.002**
ESWT time (min)	1.3 ± 6.3	.15	4.4 ± 6.6	**.01**	3.6 ± 8.9	.12
SGRQ						
Symptom	−21.8 ± 18.9	**.002**	−11.1 ± 22.8	.09	−12.7 ± 19.5	.08
Activity	4.6 ± 31.3	.61	−4.9 ± 16.3	.27	−4.3 ± 8.7	.17
Impact	−3.6 ± 20.2	.18	−15.1 ± 25.7	.06	1.8 ± 9.3	.86
Total	−3.9 ± 19.5	.49	−12.2 ± 20.1	**.04**	−2.2 ± 6.8	.35
CRQ						
Dyspnea	0.3 ± 1.3	.33	−0.0 ± 1.1	1	0.1 ± 0.5	.47
Fatigue	0.5 ± 1.1	.15	0.9 ± 1.2	**.01**	0.9 ± 1.4	.08
Emotional	0.5 ± 1.0	.13	0.4 ± 0.9	.1	0.4 ± 0.7	.14
Mastery	0.6 ± 0.8	**.01**	0.4 ± 0.9	.1	0.5 ± 1.0	.17
HADs						
Anxiety	−1.2 ± 2.4	.1	−1.4 ± 2.7	.07	−1.0 ± 3.2	.38
Depression	−2.8 ± 2.8	**.006**	−1.1 ± 1.9	.052	−6.2 ± 14.4	.23

Results were reported as mean ± SD after testing for normal distribution.
BMI, body mass index; CAT, COPD assessment test; CRQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; IC, inspiratory capacity; ISWT, incremental shuttle walk test; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnea scale; 6MWT, 6-minute walk test; post-FEV1, post-bronchodilator forced expiratory volume in the first second of expiration; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

dose delivered during ET. The mean flow of oxygen was 1.5 ± 0.8 L/min which corresponded to an FiO_2 of 0.24%-0.28%. In contrast to oxygen therapy, NIV was associated with better physiologic adaptations on submaximal performance, VO_2, dyspnea, and SpO_2. In the current study, an average of 2.0 ± 0.6 L/min oxygen with an FiO_2 of at least 28% was used. Despite delivering the optimal dose of oxygen, after exercise training, walking tests, dyspnea scores, and total score of SGRQ improved. However, adding NIV improved more parameters than ETO2. Therefore, the advantages of NIV in the physiologic adaptations may be superior to other adjuncts.

Costes et al[25] used BIPAP as an adjunct to a PR program. They assigned the patients to either NIV or spontaneous breathing. But they failed to report the inspiratory positive airway pressure (IPAP) settings used. The expiratory positive airway pressure (EPAP) is documented as 4-8 cmH_2O which may possibly lead to an increase in functional residual capacity as the EPAP is likely to exceed the intrinsic positive end-expiratory pressure (PEEP). In Menadue et al's[26] study, even though inspiratory pressure levels of ~10 cmH_2O were shown to be effective in reducing dyspnea, it was insufficient to adequately unload inspiratory muscles and thus increased exercise capacity. In the current study, inspiratory pressure levels of 12 ± 1.5 cmH_2O were effective as Pimax and Pemax were significantly increased when BIPAP was used. Only Pimax slightly increased in ET alone group. The mean EPAP was 5 ± 0.8 in this study, which is similar to previously reported levels. There was no significant effect of oxygen supplementation in terms of respiratory muscle strength in ET + O_2 group when compared with the ET group. This result may be due to several factors in the study. Baseline BORG was higher in the ET + O_2 group, which means that these patients were more dyspneic. This group included a higher number of very severe COPD patients; they had the worst bronchodilator forced expiratory volume in the first second of expiration and inspiratory capacity and also lower BMI than the other groups. With oxygen supplementation, the reduction in ventilation in submaximal workloads may be related to a slower increase in lactate level due to better oxygen delivery to peripheral muscles.

Another study found that NIV plus oxygen supplementation resulted in increased tidal volume (TV) and minute ventilation, decreased dyspnea intensity to compare with O_2 therapy at isotime (reduction of 1.0 ± 2.0 BORG units, $P < .05$), and a tendency but not significant changes in total dyspnea recovery time (326.2 ± 132.0s vs. 356.5 ± 156.9s, $P = .225$). Non-invasive ventilation has been effective in augmenting the effect of standard ET for exertional dyspnea in stable COPD with lower pulmonary function.[27] In the current study, pulmonary function tests of patients showed no change except for RV and TLC in ET + NIV + O_2 group. Dynamic hyperinflation improved in the participating patients in this study, but another study reported that this was not the case in patients with profound resting dynamic hyperinflation and ventilatory constraints during exercise.[7] Another study determined that COPD patients with severe static hyperinflation and exercise-induced desaturation significantly benefited from NIV adjunct to O_2 during exercise and recovery.[8]

Another study, which was similar to our study, investigated 88 elderly patients with severe COPD who were divided into 3 groups: control group (O_2 + regular treatment), interventional group A (plus NIV), and interventional group B (plus comprehensive PR). The improvement of mMRC, 6MWD, QoL scores, PaO_2, and $PaCO_2$ of intervention group B was better compared to intervention group A.[28] The patients in the current study showed improvement in exercise capacity (6MWT, ISWT, and ESWT) and QoL (BORG scale, CAT score, SGRQ, CRQ, and HADs). However, there was no change in the PaO_2 and $PaCO_2$ values of the participating patients.

In spite of promising results, the generalized use of NIV during exercise is unlikely to be adopted in routine PR settings. The use of NIV during exercise as a component of PR should be set aside in individual cases.[29] High-intensity NIV as an add-on tool during exercise is beneficial yet appropriate based on patient selection, and implementation is paramount in chronic hypercapnic respiratory failure.[30] A review proposed that NIV is an adjuvant intervention for ET in COPD as the intervention can improve exercise capacity and QoL.[31]

The sample size of the study is relatively small. Although 61 patients were screened, only 35 of them could be included. However, when considering patients' health status, especially the interventional group consisted of risky patients. Patients receiving NIV + PR + O_2 were taken to each session one by one. For that reason, this study took several years to complete.

CONCLUSION

It can be argued that although the use of NIPPV added to supplemental oxygen during PR requires equipment and expertise in implementation, it can be used to promote additional physiologic effects. Randomized clinical trials with larger sample sizes should aim to investigate the effect of training duration, intensity, ventilator modes, or settings in patients with severe COPD.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: The study was approved by the Institutional Review Board of Ege University Faculty of Medicine (Approval Acceptance Number: 2020-KAEK-139) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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