RESEARCH ARTICLE

Effect of pulmonary rehabilitation programme including either O_2 inhalation or noninvasive ventilation in patients with chronic obstructive pulmonary disease

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Background: Pulmonary rehabilitation (PR) is crucial in managing chronic obstructive pulmonary disease (COPD) and enhancing functional capacity and health status. Oxygen therapy and noninvasive ventilation (NIV) may be needed to be incorporated into rehabilitation to augment the effectiveness of physical training.

Objectives: To compare and assess the impact of the PR programme alone and with augmentation with O_2 or NIV on COPD patients.

Methods: Seventy-five COPD patients were equally divided into three groups: group 1 patients performed 8 week-PR programme only. Group 2 performed the PR programme while receiving O_2. Group 3 completed the PR programme plus NIV. Modified Borg scale, VO_2 max, modified Medical Research Council Dyspnea Scale, 6-minute walk test, COPD assessment test score, spirometric measures and arterial blood gases were assessed before and after the programme.

Results: The outcome measurements showed meaningful improvement compared with the baseline in the three studied groups. However, VO_2 max in group 3 showed higher significant improvement than both groups 1 and 2. Regarding 6-minute walk test, groups 2 and 3 had a higher significant improvement than group 1. COPD assessment test score in group 3 showed higher significant improvement than groups 1 and 2. Arterial blood gases in groups 2 and 3 showed significant increase in partial pressure of arterial oxygen and arterial oxygen saturation, but group 3 only had a significant decrease in $PaCO_2$.

Conclusion: O_2 supplementation and NIV help severe to very severe COPD patients to perform higher exercise intensity, so they augment the benefits of PR.

Key Words: *6-minute walk test; chronic obstructive pulmonary disease; modified Borg scale; noninvasive ventilation; O_2 supplementation; pulmonary rehabilitation; Vo2 max*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is not only a pulmonary disease; it is a multisystemic disease. It causes weight loss, muscle myopathy, osteoporosis, cardiovascular complications, depression and cancer, which are the chief causes of morbidity and death in COPD patients [1]. COPD patients have decreased pulmonary function, shortness of breath and peripheral muscle dysfunction. These factors cause exercise incapability and worsen physical activity, even daily activities [2]. Pulmonary rehabilitation (PR) is an inclusive approach centred on a thorough patient evaluation followed by personalized therapies, which include exercise training, education and behaviour change, planned to improve the physical and psychological condition of people with chronic lung disease [3, 4]. Supplemental oxygen may increase the exercise performance of hypoxemic COPD patients by reducing the hypoxic stimulation of carotid bodies, causing pulmonary vasodilation and increasing arterial oxygen content [5]. Noninvasive positive pressure ventilation (NPPV) rests the muscles of respiration and decreases work of breathing during exercise in COPD, so it was added to exercise training in COPD patients to enable them to exercise at higher intensities, reduce dyspnea and increase exercise capacity [6, 7].

In our research, we study the outcome of the PR programme alone and with two different adjunctive methods, either O_2 inhalation or noninvasive ventilation (NIV), in patients with stable, severe and very severe COPD and comparison among them.

PATIENTS AND METHODS

This prospective randomly assign observational study was carried out on 75 severe to very severe stable COPD patients who underwent clinical and spirometric evaluation for diagnosis and grading of the disease severity according to the GOLD guidelines [8] having a post-bronchodilator forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) less than 0.7 and FEV1 less than 50% with no history of exacerbation in the last 4 weeks. It was held at the Chest and Physical Medicine and Rehabilitation Departments, Faculty of Medicine, Tanta University Hospitals, from January 2019 to January 2021. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Tanta

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University, with approval code (32847/01/19) and informed written consent was obtained from all patients after a detailed clarification of the benefits and risks of the study.

We excluded any patient having current participation in a rehabilitation programme, any orthopedic or neurological problem that might interfere with exercise, peripheral venous thrombosis, recent cardiac infarction, uncontrolled hypertension, cardiac arrhythmias, unstable angina, uncompensated heart failure, any chest condition other than COPD, oral steroid or antibiotics use, severe desaturation during exercise not corrected with oxygen therapy, severe cognitive disorders and lack of motivation.

All 75 patients were men and ex-smokers and were randomly divided into three equal groups: group 1 (PR only) involved 25 COPD patients who received the PR programme only. Group 2 (PR+ O_2 suppl) also involved 25 COPD patients who performed the PR programme while receiving O_2 inhalation via nasal cannula. Group 3 (PR+ bilevel positive airway pressure (BIPAP)) included 25 COPD patients who performed the PR programme while receiving NIV (BIPAP) via a fitted oronasal mask.

The patient participation and the study protocol was shown in Figure 1.

All 75 patients were submitted to meticulous and detailed history taking, a comprehensive examination (local and general) and radiological assessment, including chest x-ray for all patients and CT chest for some of them and were investigated for their routine laboratory work, including total and differential count of white blood cells, hemoglobin, fasting blood glucose level, liver and renal function tests, INR and prothrombin activity, ECG and ECHO if necessary.

All patients took their regular medical treatment ([in the form of long-acting muscarinic antagonists [LAMA] only or long-acting muscarinic antagonists+long-acting beta-agonists [LAMA+LABA] or inhaled corticosteroids+long-acting beta-agonists [ICS+LABA] according to ABCD assessment [8] of the studied patients) throughout the programme.

Pulmonary rehabilitation programme

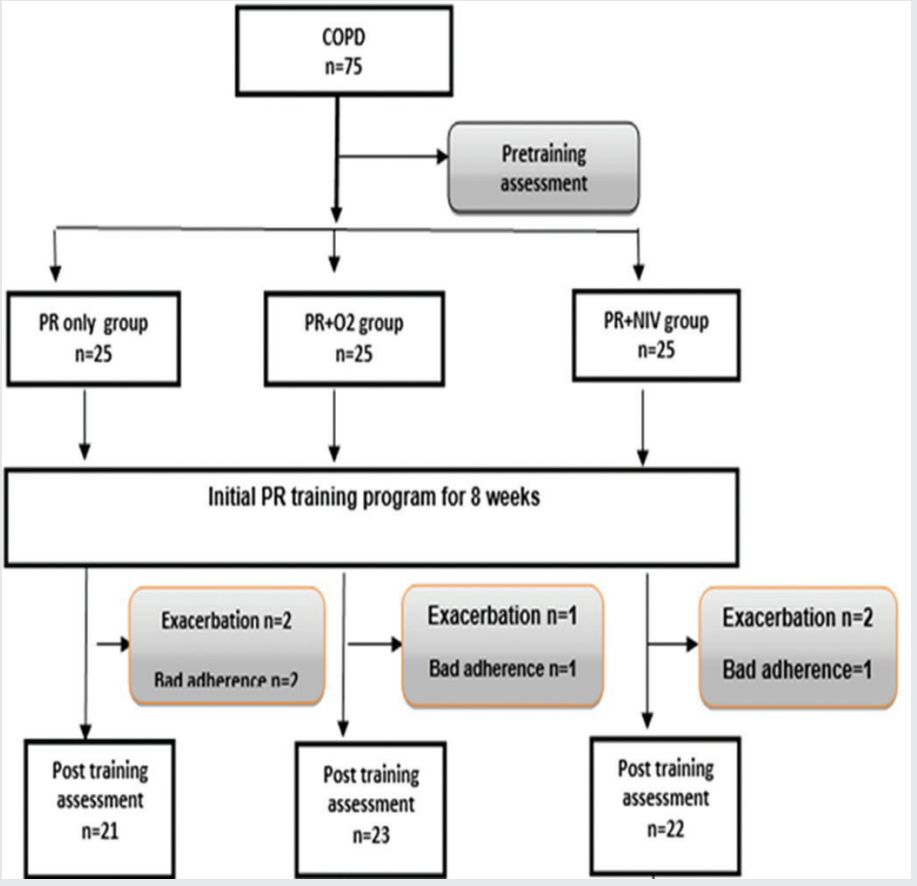
All patients were educated on early identification and dealing with the exacerbations and the correct inhalation techniques, good protection from COVID-19 infection and the importance of vaccination. All patients received a physical training programme for 8 weeks, with three sessions per week. In addition, each patient received an individualized exercise prescription based on the previous assessment.

Physical training protocol

Aerobic exercise training was performed using a treadmill (BIODEX RTM600, 950-421, USA): Starting at a speed of 1 km/h, then it was increased gradually until the patient complained of shortness of breath or muscle fatigue by using the modified Borg dyspnea scale. Each exercise session lasted 30 to 45 min (5 min to warm up, 20 to 35 min of exercise proper and the final 5 min to cool down) as the interval training method was applied. The total duration of exercise and its intensity gradually increased during sessions and was guided by the maximum heart rate, which equals (220-age). The patient had performed high-intensity

FIGURE 1

Flowchart of patient participation and study protocol. Statistical analysis. COPD chronic obstructive pulmonary disease; PR, pulmonary rehabilitation; NIV noninvasive ventilation



exercise (75% of maximal heart rate). Blood pressure, heart rate and O_2 saturation were measured during the exercise.

Some patients trained on a stationary bicycle (MONARK 970, Sweden) for 15 min three times per week. Upper limb exercise training was performed using Chest Press (EN-Dynamic, Enrafnonius 40119, The Netherlands) for 30 min, three times per week. In addition, neuromuscular electrical stimulation (NMES) of the quadriceps muscle and diaphragm was performed for severely impaired patients. During electrical muscle stimulation, electrical impulses are delivered through electrodes fixed to the skin, which induce intense contraction of the muscles below. The duration lasted 10 to 15 min using a Faradic muscle stimulator with intermittent frequency three times per week.

Respiratory training was performed by using a tri ball incentive spirometer twice daily for 5 days per week, in addition to pursed lip diaphragmatic breathing exercises for 5 to 10 min approximately 3 to 4 times per day with postural drainage for 5 min in different positions, mainly at the morning also were performed.

Group 2: This group was submitted to the PR programme while receiving oxygen via a double-prong nasal cannula at 1 to 3 L/min to maintain O_2 saturation greater than 90% during rehabilitation sessions.

Group 3: This group was submitted to the PR programme while receiving bi-level ventilator (BIPAP) via a tight-fitting oronasal mask. The inspiratory level was initially set at 6 cm H_2O, then gradually increased by 2 cm H_2O every minute up to the maximum tolerated pressure. Expiratory pressure was started at 3 cm H_2O, then gradually increased by 1 cm H_2O every minute up to the maximum tolerated pressure. The airway pressure was adjusted according to Diaz et al method [9]. The gradual increase in pressure was adopted to increase patient tolerance to the increasing exercise intensity and to keep arterial oxygen saturation (SaO_2) greater than 90% during exercise training.

Baseline and outcome assessment

A modified Borg dyspnea scale was used to evaluate the level of shortness of breathing between 0 and 10 during exercise [10].

VO_2 max measured the maximum amount of oxygen used during intense physical activity. It was calculated as follows: VO_2 max=15 × (HRmax/HRrest) (mL/kg/min) as maximum heart rate (HRmax=220-age) [11].

The grade of dyspnea was assessed by a mMRC scale, which is a scale rating dyspnea from 0 (no dyspnea) to 4 (too dyspneic to do any exercise) [12].

The exercise capacity of all patients was tested by 6-minute walk test (6-MWT), which was performed according to the protocol of the American Thoracic Society [13]. Patients were asked to walk as far as they can in 6 min in a 30-m straight corridor without interruption. The patients should be instructed not to do any heavy exercise for at least 2 h before the test and to immediately stop the 6-MWT if there is chest pain, intolerable dyspnea, leg cramps, sweating, or pale facial appearance. Oxygen saturation using pulse oximetry was monitored during the test.

Quality of life (QoL) was assessed using the COPD assessment test (CAT score) [14]. CAT score broadly evaluates the consequences of dyspnea and health status impairment in COPD. It is an 8-item questionnaire with a 6-item scale ranging from 0 to 5. A CAT score ≥10 is associated with a severely impaired health status.

Pulmonary functions were tested by using a pulmonary function spirometer (Master screen pet 672412, careVision, Germany) and measured as follows: Forced vital capacity (FVC), FEV1, FEV1/FVC.

Arterial blood gases were drawn and analyzed for: partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$) and SaO_2.

The present study's baseline and outcome data were analyzed statistically using the mean, standard deviation and χ^2 by SPSS V28 (IBM, Chicago, IL, USA). Also, analysis of variance (ANOVA) tests (f): was used for comparison among more than two means in quantitative data according to the computer program SPSS for Windows. P≤0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between the three groups regarding age, smoking history and body mass index, as shown in Table 1.

The patients of the three studied groups were classified according to GOLD classification of COPD based on FEV1% into severe and very severe as shown in Table 2.

Figure 2 shows that the intensity of training increased progressively across the training sessions in the three studied groups, with a significant difference between groups 2 and 3 compared with group 1 but no significant difference between groups 2 and 3.

Figure 3 illustrates the increased heart rate readings across the training sessions without significant differences between the studied groups.

Regarding the modified Borg scale, there was a significant improvement in each of the three studied groups after ending the PR programme compared with the baseline, with no significant difference between them.

VO_2 max showed significant improvement after programme completion in the three studied groups compared with baseline, with higher significant improvement in group 3 than in groups 1 (P2=0.001) and 2 (P3=0.001) with no significant difference between groups 1 and 2. In addition, mMRCS had significant improvement at the end of the programme in the three studied groups, with no significant difference between them at the end.

Six-minute walk tests showed significant improvement in the three groups at the end of the programme, with higher significant improvement in both group 2 and 3 (P1=0.001, P2=0.001), respectively, compared with group 1, with no significant difference between groups 2 and 3. Furthermore, regarding the CAT score, there was meaningful improvement at the end of programme in the three studied groups with higher significant improvement in group 3 compared with group 1 (P2=0.029) and group 2 (P3=0.048) with no significant difference between group 1 and group 2 (Table 3).

Spirometric measures in the studied groups significantly improved at the end of the programme, with no significant difference between them.

Regarding the arterial blood gases, in group 1, there was a slight increase in PaO_2 and O_2 saturation and a minimal decrease in $PaCO_2$ without significant changes after the PR programme compared with

TABLE 1

Demographic characteristics of patients of the three studied groups

		Range	Mean±SD	*F.* test	P
Age (years)	G 1	45–77	60.56±9.07	0.673	0.513
	G 2	45–80	63.44±10.90		
	G 3	42–75	60.88±8.74		
Smoking index (pack/years)	G 1	20–120	54.80±27.25	0.843	0.435
	G 2	20–120	47.40±23.50		
	G 3	30–90	55.00±19.36		
BMI (kg/m^2)	G 1	18–25	21.68±2.28	0.221	0.802
	G 2	18–26	21.92±2.17		
	G 3	18–25	21.50±2.28		

BMI body mass index.

TABLE 2

Represents the classification of the three studied groups according to GOLD classification based on forced expiratory volume in the first second%

GOLD classification	G 1		G 2		G 3			
	N	%	N	%	N	%	x^2	P
Severe	14	56	20	80	15	60	3.648	0.161
Very severe	11	44	5	20	10	40		
Total	25	100	25	100	25	100		

FIGURE 2

Intensity of training mean±SD across the training sessions in the three studied groups

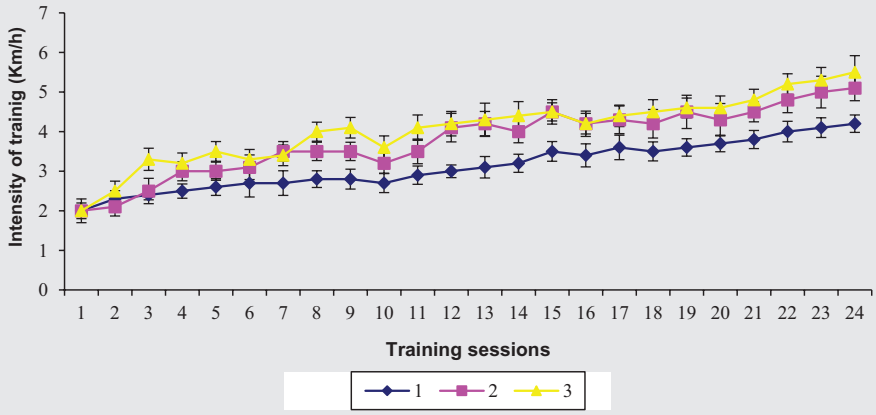
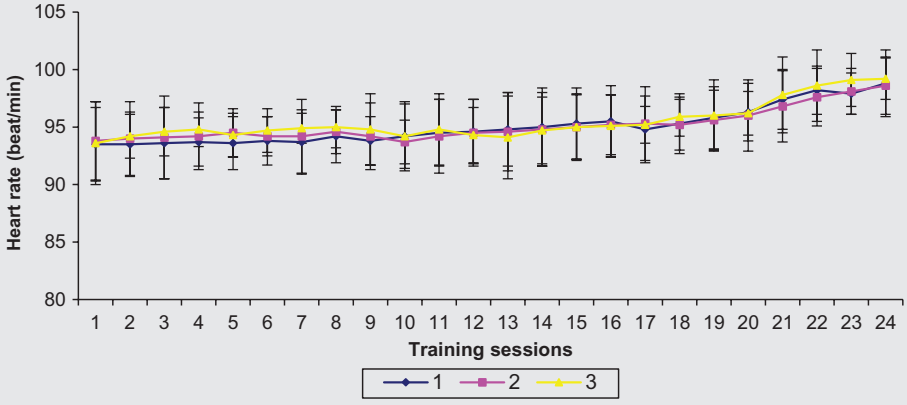


FIGURE 3

Heart rate readings mean±SD across the training sessions in the three studied groups



before the programme. In group 2, there was significant improvement in PaO_2 and SaO_2% at the end of the programme, with higher significant improvement than group 1 and no significant change in $PaCO_2$ after the PR programme as compared with baseline. In group 3, there was significant improvement in PaO_2 and SaO_2% after the training programme, with higher significant improvement than group 1 and no significant difference between it and group 2 at the end of the programme. Also, there was a significant decrease in $PaCO_2$ at the end of PR programme with higher significant improvement than groups 1 and 2 (Table 3).

DISCUSSION

COPD is characterized by chronic irreversible airflow limitation with many systemic manifestations such as cardiovascular diseases, skeletal muscle weakness and depressive symptoms (8). PR programmes, including physical training, have been prescribed for these patients to improve functional capacity and health-related QoL (4). In agreement with our results as regards the modified Borg scale, Ahmed et al (15) studied the effects of PR on exercise tolerance in 116 male stable, moderate COPD patients and observed significant improvement in the intensity of breathlessness and fatigue, 6-MWT and SaO2% in patients who completed the PR programme.

Also consistent with the findings of the present study, Voduc et al [16], in their study of the impact of oxygen on exercise duration in COPD patients, found a meaningful reduction in dyspnea and leg fatigue in the oxygen-receiving group than the PR-only group with statistically significant difference between them. In contrast with our results, Borghi-Silva et al [17], in their study to compare oxygen and NIV added to exercise training of patients with severe COPD. They reported higher significant improvement in dyspnea, measured by the Borg scale in the NIV group compared with the supplemental O_2 group.

Our study is supported by similar findings from Mehri et al [18], Sala et al [19] and Maltais et al [20] in their studies on the effects of physical training on COPD patients, they reported significant improvement in the VO_2 max post-training and attributed that to the effective oxidative metabolism and improved O_2 uptake kinetics. However, Emtner et al [21] reported a slight and insignificant increase in peak VO_2 in both oxygen trained and air trained groups with no significant difference.

Also, our current research is consistent with Toledo et al's findings [22] as they studied the effect of NIV during the exercise training in patients with moderate to severe COPD and found that the (exercise training+BI-PAP) group showed significant improvement in oxygen consumption, heart rate and blood pressure after training when compared with the (only exercise training) group. Furthermore, Borghi-Silva et al [17] agreed with our study as they reported higher significant improvement in VO_2 max in the NIV group compared with the supplemental O_2 group.

TABLE 3

Comparison between the three studied groups regarding the modified Borg scale, VO_2 max, mMRCS and CAT score, as well as PFTs and arterial blood gases

	Group 1			Group 2			Group 3					
Group	Baseline	End of programme	P#	Baseline	End of programme	P#	Baseline	End of programme	P#	P1	P2	P3
modified Borg scale	4.36±1.04	1.76±1.01	0.001*	4.64±1.19	1.72±0.94	0.001*	4.80±1.08	1.60±1.0	0.001*	0.886	0.567	0.667
VO_2 max(ml/kg/min)	21.82±1.38	22.76±1.30	0.017*	21.54±1.74	23.48±1.64	0.001*	21.70±1.43	27.39±1.83	0.001*	0.187	0.001*	0.001*
mMRCS	3.20±0.96	1.56±0.51	0.002*	3.28±0.84	1.48±0.51	0.003*	3.16±0.94	1.40±0.58	0.004*	0.579	0.291	0.597
6-MWT (m)	89.04±37.75	184.40±44.91	0.005*	104.80±2.55	246.48±48.30	0.002*	94.16±37.22	255.80±50.26	0.001*	0.001*	0.001*	0.494
CAT score	27.48±8.44	14.56±3.07	0.003*	27.84±7.34	14.20±3.01	0.002*	26.32±7.95	12.68±2.84	0.001*	0.670	0.029*	0.048*
FVC% predicted	50.12±15.00	61.32±12.88	0.009*	52.08±8.11	62.84±11.22	0.001*	52.60±12.80	63.88±15.16	0.004*	0.685	0.495	0.781
FEV1% predicted	34.72±11.36	40.2±9.03	0.038*	36.24±8.86	42.52±6.22	0.011*	32.44±8.41	42.96±6.30	0.001*	0.265	0.186	0.832
FEV1/FVC (actual value)	34.56±6.46	47.24±4.50	0.004*	34.44±6.23	48.76±2.50	0.002*	34.92±7.75	50.48±8.10	0.001*	0.336	0.062	0.276
$PaO_{2\ (mmHg)}$	66.06±2.35	67.05±3.24	0.217	65.41±2.42	71.78±3.96	0.002*	66.92±3.88	72.93±4.65	0.003*	0.002*	0.001*	0.311
SaO_2%	92.29±1.34	92.71±1.41	0.275	92.55±0.97	94.64±1.10	0.001*	92.98±1.55	94.95±1.41	0.002*	0.001*	0.001*	0.405
$PaCO_{2\ (mmHg)}$	41.84±3.40	40.72±2.98	0.223	42.20±3.00	41.40±2.57	0.331	41.96±3.31	36.36±2.78	0.001*	0.390	0.001*	0.001*

*Note: P# P value for comparing between the Baseline & End of the programme in each group, P1 P value for comparing between 1 & 2 at the end of the programme, P2: P value for comparing between 1 & 2 at the end of programme, P3: P value for comparing between 1 & 2 at the end of programme, *Statistically significant at P≤0.05, mMRCS modified Medical Research Council Dyspnea Scale, 6-MWT 6-minute walk test, CAT score COPD assessment test, FVC% forced vital capacity, FEV1% forced expiratory volume in the first second, PaO_2 partial pressure of arterial oxygen, SaO_2% arterial oxygen saturation, $PaCO_2$ partial pressure of arterial carbon dioxide.*

Our study is boosted by the same findings of De Torres et al [23] and Elkhateeb et al [24] in their studies of PR in COPD, as they observed improvement in mMRC dyspnea grade. Also, Garrod et al [25] and Dyer et al [26], in their study of the role of supplemental O_2 added to PR in COPD patients with exercise hypoxemia, suggested a small benefit of O_2 supplementation during PR regarding dyspnea. Furthermore, El Hoshy et al [27] in their study, compared patients performing exercise training only and those performing exercise training plus CPAP and found significant improvement in mMRCS dyspnea scale in the exercise group and (EX/CPAP group) after completion of the 4-week PR programme with no significant difference between both groups after rehabilitation.

As regards the 6-MWT, our current research is in line with the findings of Kerti et al [28], Cheng et al [29], Riario-Sforza et al [30] in their studies on the effects of PR in COPD, as they observed improvement in 6-minute walking distance 6-MWD after PR programme but Román et al [31] declared that patients with moderate COPD and low grade of impairment had significant changes in exercise tolerance. They attributed this result to their patients' selection with low basal symptoms. Also, Fujimoto et al [32] demonstrated a significant increase in 6-minute walking distance in the O_2-trained and air-trained groups with extra benefit for oxygen on exercise tolerance because oxygen promotes exercise capacity by decreasing ventilation and respiratory rate, making breathing pattern deeper and slower with more muscle strength and endurance, also slows down the onset of diaphragmatic muscle fatigue and improves oxygen delivery leading to decrease in metabolic acidosis during exercise [21] Others as Garrod et al [25] and Spielmanns et al [33], suggested no further benefits of supplemental oxygen over room air. Nicolini et al [34], Marrara et al [35] and Borghi-Silva et al [17] agreed with the present study as they speculated clinically significant improvement in 6-minute walk distance in the NIV group as it may be interpreted by improvement in respiratory muscle strength that led to decrease in leg fatigue as NIV during training may unburden the respiratory muscles; as a result, the effect of diminished respiratory muscle blood flow is lowered, enabling most potent physiologic modification in peripheral muscles.

Lending support to our findings regarding the QoL, which was assessed by CAT score, Smid et al [36] and Kon et al [37] reported statistical improvements in CAT score in patients with COPD following PR. Also, Greulich et al [38] and Hsiao et al [39] stated a considerable improvement in CAT score in the group receiving O_2 therapy, demonstrating the importance of oxygen supplementation during the exercise training in relieving the symptoms. Fekete et al [40] and Fakharian et al [41] found that the NIV group had significant CAT score improvement compared with the control group (PR group without NIV). Also, Borghi-Silva et al [17] concurred with our results as they stated that QoL had more significant improvement in the NIV group than O_2 supplementation group.

The spirometric findings of our current study are consistent with Cilekar et al's findings [42], as they reported an increase in spirometric parameters after a 6-week PR programme. These findings support the conception that COPD is associated with respiratory and generalized manifestations and that aerobic training programmes may produce great augmentation in skeletal muscle function (both respiratory giving improvement in pulmonary functions as well as peripheral muscles giving improvements in their functional performance) [43]. However, Yoshimi et al [44] did not find significant changes in COPD patients' pulmonary functions after PR. They explained their results by the fact that PR causes improvement in peripheral myopathy but not ventilatory impairment. Also, in accordance with our findings, Emtner et al [21] stated minor improvements in spirometric variables post-training in both O_2- and air-trained groups with no significant difference between them. Contrary to the present study's results, Spielmanns et al [33] noticed no improvement in lung functions in both groups (air-trained and oxygen-trained group) at the end of the PR programme, suggesting that airway obstruction was a permanent cause of exercise limitation. Fakharian et al [41] and Gad et al [45] demonstrated improvement in FEV1 and FVC values after the sessions in both groups (PR group and NIV+PR group). However, Duiverman et al [46] found a more significant improvement in FEV1 in (NIV+PR) than in the PR alone group. They attributed this improvement in FEV1 to either volume expansion and/or a decrease in airflow limitation.

Our results regarding arterial blood gases are supported by Arnardóttir et al [47], Casaburi et al [48] as they found no valuable change in arterial blood gases after training. However, Takigawa et al [49] observed improvement in arterial oxygen tension and arterial oxygen saturation after PR but with no statistical difference in the carbon dioxide tension after the PR programme. Also, Sahin et al [50], in their study of the benefits of PR in COPD patients having long-term oxygen therapy (LTOT), found that both non-LTOT group and LTOT

groups revealed a significant increase in the diffusion capacity, PaO_2 and SaO_2 after the PR. The $PaCO_2$ did not change in the (non-LTOT) group, while it decreased significantly in (LTOT) group. Contrary to these results, Rooyackers et al [51] and Wadell et al [52] claimed no statistically significant change in O_2 saturation and $PaCO_2$ between the O_2-trained group and control group, so they reported no additional benefit for super-added oxygen in PR concerning oxygen saturation. Moreover, Cui et al [53] and Gad et al [45], in their studies of the role the NIV in PR, showed improvement in spirometric measures, arterial blood gas, dyspnea and QoL in stable hypercapnic COPD patients with significant decrease of $PaCO_2$ in the NPPV group than (exercise only) group, so it matched with our results. Also, Garrod et al [54] reported a small improvement in arterial oxygenation in the (NPPV) group in comparison with the (exercise only) group, but with a significant difference between both groups, they explained the increase in PaO_2 in these patients by the improvement in alveolar ventilation and reduced hyperinflation but they stated no significant difference in $PaCO_2$ after ending their study in both groups.

STUDY LIMITATIONS

All patients in the study were men, reflecting the high prevalence in male patients, so we could not assess the benefits of the PR programme on female patients. Also, psychosocial and nutritional status was not evaluated adequately, so considering this point is recommended in further studies in the future.

CONCLUSION

The authors conclude that although the PR programme alone showed significant results in improving COPD regarding exercise tolerance and QoL, O_2 supplementation and NIV showed better results but without enough additional benefit to recommend NIV over O_2 inhalation or vice versa during exercise. Instead, the authors suggest using O_2 in severe COPD patients who desaturated during exercise and using NIV in patients with extreme disabling dyspnea because it reduces the dynamic hyperinflation and improves the work of breathing.

DISCLOSURES

Contributors

All authors participated in the study conception and design. Patient collection, data gathering and analysis were performed by Basma Elsaeed Saad Elmorshidy, Hoda Mokhtar Bahr and Mohamed Gamal Amer Elkholy. The preliminary form of the manuscript was written by Hanan Mohamed Elsaadany, Youssef Mohamed Mansour, Ragia Samir Sharshar and all authors contributed to the previous versions of the manuscript. The final manuscript has been read and approved by all authors.

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Competing interests

All authors have completed the ICMJE uniform disclosure form and declare no conflict of interest.

Ethical approval

Study protocol was approved by the Ethical Committee of Faculty of Medicine, Tanta University with approval code (32847/01/19) and informed written consent was obtained from all patients after a detailed clarification of the benefits and risks of the study.

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