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ORIGINAL ARTICLE

Non-invasive positive pressure ventilation and exercise training in patients with stable hypercapnic chronic obstructive pulmonary disease

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Abstract *Background:* Chronic obstructive pulmonary disease (COPD) is a disease with progressive course of dyspnea which leads to reduced health related quality of life (HRQoL). Exercise training has useful effects toward their exercise tolerance and health related quality of life (HRQoL). However extreme breathlessness limits these patients in maintaining exercise training. Non-invasive positive pressure ventilation (NIPPV) is considered a beneficial treatment option for chronic stable hypercapnic respiratory failure. So, the aim of this study is to assess the effect of adding NIPPV to Exercise training program compared to Exercise training program alone in stable hypercapnic COPD patients.

Patients and methods: Thirty patients with stable hypercapnic COPD were selected, subdivided into two groups; 15 patients underwent Exercise training alone (Ex. group) and another 15 patients performed Exercises training in association with receiving NIPPV (Ex. + NIPPV group). Baseline and after 3 months assessment of arterial blood gases analysis (ABGs), pulmonary function tests (PFTs), dyspnea scale by modified Medical Research Council (mMRC) and assessment of HRQoL guided by COPD Assessment Test (CAT) were done for both groups.

Results: In the Exercise training group, they showed statistical significant improvement in dyspnea scale (mMRC) and CAT score after 3 month performance ($p < 0.05$), but insignificant changes occurred in their ABGs or PFTs ($p > 0.05$). While in the Ex. + NIPPV group, a highly statistical significant improvement regarding PCO_2, FEV_1 and dyspnea scale (mMRC) ($p \leqslant 0.001$) and a significant difference as regards HRQoL assessment score ($p < 0.05$) were found after 3 month follow up.

Conclusion: Addition of NIPPV to exercise training in patients with stable hypercapnic COPD patients improved PCO_2, FEV_1, dyspnea scale and HRQoL.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide [1]. Patients with severe COPD often develop chronic hypercapnic respiratory failure with a worse prognosis and more frequent exacerbations [2]. Even during stable states and with optimal medications, these patients are always suffering from dyspnea which is a very common complaint especially during physical activities [3].

This leads to chronic physical inactivity, exercise intolerance and sedentary life style, with more ventilation demands feeding the dyspnea-inactivity-dyspnea cycle [4]. Among the wide range of non-pharmacological therapeutic approaches for stable COPD, starting from smoking cessation, long term oxygen therapy (LTOT) [5], pulmonary rehabilitation [6] and ending with Bronchoscopic lung volume reduction [7], there are still a few interventions which diminish the number of exacerbations and improve survival [8].

Exercise training as a part of multidisciplinary pulmonary rehabilitation (PR) has useful effects toward exercise tolerance and health related quality of life in stable COPD patients [9]. These effects underwent via reduction of lactic acidosis, minute ventilation, heart rate and enhance the activity of mitochondrial enzymes with increased capillary density in the trained muscles [10], However extreme breathlessness limits these patients in maintaining exercise training [10]. Therefore, there is a need for additive therapies enhancing the effectiveness of PR [11].

Non-invasive positive pressure ventilation (NIPPV) is considered a beneficial treatment option for chronic stable hypercapnic respiratory failure [12].

A number of positive effects have been documented during NIPPV; it improved gas exchange, unloaded respiratory muscles and reset the central respiratory drive [13]. Clinical manifestations of these physiologic changes are reflected as reduced dyspnea, improved health related quality of live (HRQoL) [14], and potentiated the benefits of rehabilitation program [15].

The effect of NIPPV in association with multidisciplinary pulmonary rehabilitation program in chronic stable COPD had been investigated by different studies, but with different contradictory results. Garrod et al. [16], Kohnlein et al. [17] and Duiverman et al. [18], had assessed the effect of combination of NIPPV and PR but in short term interval. Other studies used low ventilator pressure settings which resulted in unbeneficial effect [19].

So, the aim of this study is to assess the effect of adding NIPPV to Exercise training program compared to Exercise training program alone in stable hypercapnic COPD patients for a period of 3 months.

Patients and methods

This study was conducted at (Chest, Rheumatology and Rehabilitation) Departments and outpatient clinics Faculty of Medicine, Zagazig University hospitals in the period from October 2012 till April 2014. Written informed consents were obtained from all patients. The study was approved by the local ethics committee of the institute.

Patients

Thirty patients were selected with severe and very severe COPD (GOLD 3 and GOLD 4) with Forced expiratory volume in 1st second/Forced vital capacity (FEV_1/FVC) $<70\%$ and FEV_1 $<50\%$ predicted [20], associated with day time hypercapnia ($PaCO_2 \geqslant 50$ mmHg) and stable clinical condition (no exacerbation for the prior four weeks with (pH $\geqslant 7.35$) [21], receiving proper medications according to GOLD 2011 [20]. They were 20 males and 10 females with age range 66.05 ± 9.4 years.

They were subdivided into two groups:

Exercise Training group (Ex): 15 patients performed Exercise training.

Exercises training + NIPPV (Ex. + NIPPV): 15 patients performed exercise training in association with NIPPV in the form of BiPAP home mechanical ventilation.

Exclusion criteria were: After invasive mechanical ventilation, obstructive sleep apnea [8], cardiac diseases limiting exercise tolerance [11], neuromuscular diseases [18] or orthopedic impairment of shoulder girdle [4].

Method

All patients were subjected to:

(1) Thorough medical history taking.
(2) General and local chest examination.
(3) Chest X-ray (posteroanterior and lateral views).
(4) Arterial blood gases analysis (ABGs).
(5) Routine laboratory investigations:
   - Complete blood count
   - Liver function tests
   - Kidney function tests

(6) ECG.
(7) Pulmonary function tests (PFTs):
All patients underwent spirometric PFT with reversibility testing after inhalation of short acting B_2-agonist (200 μg salbutamol) of metered-dose inhaler. PFT was done using ZAN-100 (flow HANDY II) pulmonary function apparatus. The following parameters were assessed as absolute values and percentage of predicted post bronchodilator: Forced expiratory volume in 1st second (FEV_1), Forced vital capacity (FVC) and (FEV_1/FVC) ratio.
(8) Assessment of health related quality of life (HRQoL) by using COPD Assessment Test (CAT) [22,23]:
This score included eight items assessing: cough, phlegm, chest tightness, breathlessness going up a hill/stairs, activity limitations at home, confidence leaving home, sleep and energy. Each item was scored from 0 to 5 giving a total score from 0 to 40, corresponding to the best and worst health status in patients with COPD. Scores of 0–10, 11–20, 21–30 and 31–40 represented mild, moderate, severe or very severe clinical impact, respectively.
(9) Assessment of dyspnea level by modified Medical Research Council (mMRC) dyspnea scale [20]:
It is a 5-point scale from 0 to 4 based on levels of dyspnea according to patient's response, describing dyspnea from none (Grade 0) to almost complete incapacity (Grade 4).

(10) NIPPV set up:
Before starting Exercise training to (Ex. + NIPPV) group, 15 patients were admitted to Chest Department for at least 2–3 days and instituted on NIPPV (Bilevel positive airway pressure (BiPAP), Spontaneous/time mode (S/T), using nasal or full face mask) [11] (Sunrise Medical, Somerset, PA 15501-2125, USA). Inspiratory positive airway pressure (IPAP) is gradually increased till reaching 15–20 cmH_2O [21] and Expiratory positive airway pressure (EPAP) 3–6 cmH_2O [24], this titration is stopped prior to the point where the patient cannot tolerate. When patient accommodates BiPAP >5 h during the day [8], nocturnal BiPAP ventilation started for 9 ± 2 h/night [2]. This occurs under careful supervision of SPO_2, respiratory rate, heart rate. Patient was discharged to continue at home mechanical ventilation BiPAP device. In case of fulfilling criteria of requiring long term oxygen therapy (LTOT) according to GOLD (2011), NIPPV was administrated with additional oxygen delivered by using a cannula attached to a port in the nasal masks till reaching $SPO_2 \geqslant 90\%$ [25].

(11) Exercise training:
All patients involved in the study underwent Exercise training program in the form of 12 weeks of physical training, 2 times a week at Rehabilitation Unit in the Rheumatology and Rehabilitation Department, Zagazig University Hospitals. Each training session lasted approximately 30–35 min, divided as:

- 8 min breathing exercises in the form of forced expiration, slow and deep breathing, pursed lips breathing and diaphragmatic breathing [26], each is repeated 10 times.
- 8 min shoulder wheel exercise, aiming to increase the mobility of the chest and thus increasing the respiratory capacity [27].
- 8 min of electrical stimulation of both quadriceps muscles, to improve muscle strength and exercise performance [28]
- 8 min walks or riding a stationary bicycle or a treadmill [29] as preferred by each patient.

End point of the study:

(1) Intolerance
(2) Death

Statistical analysis

Data were checked, entered and analyzed by using SPSS version 19. Data represented as number and percentage for categorical variables, Chi-squared (χ^2) or Fisher's exact test were used when appropriate, $p < 0.05$ was considered statistically significant.

Results

This study included 30 patients with stable hypercapnic COPD with mean age 66.15 ± 9.3. They were 20 males and 10 females. They were divided into; Exercise training group (15 patients) and Exercise training in association with NIPPV group (15 patients). Patients were followed up after 3 months with recorded changes regarding ABGs, PFTs, mMRC and CAT score.

The socio-demographic data of both groups are shown in Table 1. The two groups were matched for age, sex, BMI, and number of patients receiving LTOT ($P > 0.05$). There were non-significant differences between the two groups regarding baseline recorded ABGs, PFTs, mMRC and CAT score at the start of the study with $p > 0.05$ (Table 2).

In the Ex-group, there were non-significant differences of ABGs, PFTs at baseline and after 3 months ($P > 0.05$), while a statistically significant improvement in mMRC and CAT score was found after 3 months ($p = 0.02$ and 0.03, respectively) (Table 3). As shown in Table 4, a highly statistically significant decrease in PCO_2 and a highly statistically significant increase in FEV_1 after 3 months in the Ex. + NIPPV group ($p = 0.00$ and 0.001, respectively) were observed. However, there was an improvement in PH, PO2, FVC and FEV_1/FVC but this improvement did not reach statistically significant levels. Besides, there was a statistically significant

Table 1 Demographic data of the studied groups.

Parameter	(Ex.) group no. = 15	(Ex. + NIPPV) group no. = 15	P-value
Age (years)	66.41 ± 9	65.70 ± 10	0.84
Sex: M/F	11/4	9/6	0.43
BMI (kg/m^2)	25 ± 7	26 ± 4	0.49
LTOT (no., %)	4 (26.6%)	5 (33.4%)	0.62

Table 2 Baseline ABGs, PFTs, mMRC and CAT of the studied groups.

Parameter	(Ex.) group no. = 15	(Ex. + NIPPV) group no. = 15	P-value
ABGs			
pH	7.38 ± 0.02	7.38 ± 0.03	0.71
$PaCO_2$ (mmHg)	57.7 ± 6.8	58.3 ± 5.6	0.79
PaO_2 (mmHg)	59.1 ± 4.2	58.5 ± 5.8	0.74
PFTs			
FEV_1 (% pred.)	35.7 ± 7.3	34.4 ± 5.8	0.54
FVC (% pred.)	52.3 ± 7.5	52.4 ± 2.0	0.82
FEV_1/FVC (%)	45.8 ± 9.3	46.6 ± 1.8	0.57
Dyspnea scale (mMRC)	2.8 ± 0.6	2.9 ± 0.9	0.26
CAT	29 ± 4.2	27 ± 4.4	0.22

Table 3 Baseline ABG analysis, PFTs, mMRC, CAT and after 3 months in the exercise training group.

Parameter	At baseline	After 3 months	P-value
ABGs			
pH	7.38 ± 0.02	7.38 ± 0.04	0.81
PCO_2 (mmHg)	57.7 ± 6.8	56.6 ± 5.3	0.96
PO_2 (mmHg)	59.1 ± 4.2	59.7 ± 3.4	0.63
PFTs			
FEV_1 (% pred.)	35.7 ± 7.3	35.7 ± 8.6	0.84
FVC (% pred.)	52.3 ± 7.5	53.4 ± 9.1	0.72
FEV_1/FVC (%)	45.8 ± 9.3	47.3 ± 2.4	0.45
Dyspnea scale (mMRC)	2.8 ± 0.6	2.3 ± 0.7	0.002
CAT	29 ± 4.2	23 ± 2.2	0.03

Table 4 Basline ABGs, PFTs, mMRC, CAT and after 3 months of performing exercise training and receiving NIPPV.

Parameter	At baseline	After 3 months	*P*-value
ABGs			
pH	7.38 ± 0.03	7.40 ± 0.03	0.56
PCO_2 (mmHg)	58.3 ± 5.6	47.3 ± 4.7	0.00
PO_2 (mmHg)	(58.5 ± 5.8)	61.3 ± 7.1	0.27
PFTs			
FEV_1 (% pred.)	34.4 ± 5.8	42.3 ± 6.5	0.001
FVC (% pred.)	52.4 ± 2.0	54.2 ± 3.1	0.06
FEV_1/FVC (%)	46.6 ± 1.8	48.7 ± 3.8	0.15
Dyspnea scale (mMRC)	2.9 ± 0.9	2.1 ± 0.72	0.00
CAT	27 ± 4.4	20.2 ± 1.4	0.02

Table 5 Changes in ABGs, PFTs, mMRC, CAT after 3 months in both groups.

Parameter	(Ex.) group no. = 15	(Ex. + NIPPV) group no. = 15	*P*-value
ABGs			
PH	7.38 ± 0.04	7.40 ± 0.03	0.39
PCO_2 (mmHg)	56.6 ± 5.3	47.3 ± 4.7	0.001
PO_2 (mmHg)	60.5 ± 1.3	61.3 ± 7.1	0.32
PFTs			
FEV_1 (% pred.)	35.7 ± 8.6	42.3 ± 6.5	0.02
FVC (% pred.)	53.4 ± 9.1	54.2 ± 3.1	0.57
FEV_1/FVC (%)	47.3 ± 2.4	48.5 ± 3.8	0.21
Dyspnea scale (mMRC)	2.3 ± 0.7	2.1 ± 0.72	0.01
CAT	23 ± 2.2	20.2 ± 1.4	0.01

improvement regarding assessment of dyspnea by mMRC which was high and HRQoL guided by CAT score ($P = 0.00$ and 0.002, respectively).

Comparison between the two groups regarding changes in ABGs, PFTs, mMRC and CAT after 3 months revealed a highly statistically significant decrease in PCO_2 ($p = 0.01$) with a non-significant difference regarding both PH and PO2 ($p > 0.05$) in the Ex. + NIPPV group. Also, a significant increase in FEV_1 ($p = 0.02$), with non-significant changes in FVC and FEV_1/FVC were observed in the same group. Besides, a significant improvement in mMRC and CAT score was detected in patients of the Ex. + NIPPV group ($P = 0.01$) (Table 5).

Discussion

COPD is a disease with progressive course of dyspnea which leads to reduced health related quality of life and high mortality rate [18].

Exercise training remains the cornerstone of rehabilitation programmes and offers benefits to exercise tolerance that are complementary to the effects of pharmacotherapy in COPD management [30]. However in severe COPD rehabilitation program may be difficult to be maintained, therefore there is a need for additive therapies like NIPPV. NIPPV has effect in resting the respiratory muscles [31], improving lung mechanics [32] and improving ventilation during the day [33].

So, this study was designed to assess the role of NIPPV in addition to exercise training compared to exercise training alone and their impact on HRQoL, gas exchange and pulmonary functions in stable hypercapnic COPD patients.

In the current study assessment of HRQoL was done using COPD Assessment Test (CAT). Dodd et al. [34] had introduced CAT instrument to assess COPD HRQoL after rehabilitation program. They emphasized from their results of study that CAT is a robust and practical alternative to Chronic Respiratory Questionnaire-Self Report (CRQ-SR).

Another study performed by Ringbaek et al. [23] had reported a good correlation between CAT, St George's Respiratory questionnaire (SGRQ), and COPD Clinical Questionnaire (CCQ) in assessment of COPD after PR, furthermore CAT and CCQ showed more advantage of being easier and faster to complete than SGRQ especially in those patients with low education level.

In the current study, exercise training group, has a significant improvement in dyspnea scale assessed by mMRC and HRQoL guided by CAT with $P < 0.05$, while pulmonary function tests (PFTs) and blood gases had no significant changes after completing 3 month exercise training ($P > 0.05$) (Table 3). This result is in accordance with that of Hui et al. [35], Hildegrade et al. [36] and Spencer et al. [37] who found no changes in PFTs while dyspnea and HRQoL had a significant improvement. Suh et al. [14] had explained this result as ; during exercise training there is improvement in skeletal muscle performance and reduced lactate production which enhances the relationship between respiratory muscle load and capacity. This is achieved through modifications in breathing pattern with optimization of pulmonary mechanics, and reduction in exertion related dyspnea with further improvement in skeletal muscle performance.

Also, in the present study, addition of NIPPV to exercise training compared to exercise training alone for 3 months had improved PFTs, blood gases, dyspnea and HRQoL in patients with stable hypercapnic COPD. Significant decline of PCO_2 in the Ex. + NIPPV group than those of the exercise training group was observed (56.6 ± 5.3 versus 47.3 ± 4.7) ($P = 0.01$) (Table 5). On the other hand pH values were improved in the previous group but this improvement did not reach a statistically significant level (7.38 ± 0.04 versus 7.40 ± 0.03) ($P = 0.39$) (Table 5).

Similar results were demonstrated by Nava et al. [31], Wijkstra [1], Duiverman et al. [11], Backer et al. [8] and Duiverman et al. [18], results of study. On the other hand Garrod et al. [16] disagreed with our results, they concluded no changes regarding ABGs. This difference may be attributed to their usage of short duration of NIPPV (2.08 h/day) and the inclusion of mild chronic respiratory failure (mean $PaCO_2$ 6.0 kPa or 45 mmHg), while our study involved COPD patient with grade III or IV severity spending 9 ± 2 hrs/day on NIPPV with $PaCO_2 \geqslant 50$ mmHg. In the same way Mezzanotte et al. [38] demonstrated no benefits on gas exchange as they had a short follow up time 2 weeks. Other contradictory results were introduced by Casanova et al. [25]. This difference is attributed to their usage of low pressures of NIPPV (IPAP: 12 cmH_2O, EPAP: 4 cmH_2O).

Struik et al. [39] recommended from their results of study that higher IPAP levels, more ventilated hours with higher $PaCO_2$ baseline, all improve $PaCO_2$ after 3 months on NIPPV.

As regards PFTs, the Ex. + NIPPV group showed improvement in FEV_1 than the exercise training group alone with $P = 0.02$ while FVC, FEV_1/FVC were improved but without significant changes ($P > 0.05$) (Table 5). Our results were in accordance with Duiverman et al. [18] who reported a significant change in FEV_1 in NIPPV + PR more than PR alone. They explained this improvement in FEV_1 either by volume expansion and/or a decrease in airflow obstruction. Burns and Gibson [40] postulated that reduction in hypercapnia aided by NIPPV leads to a decrease in airway edema via reducing salt and water retention. Windisch et al. [41], Dreher et al. [42] and Schonhofer [19] speculated from their studies that using high inflation pressure causing significant reduction in hypercapnia is essential for improvement in pulmonary functions.

Furthermore, Windisch et al. [24] explained a relation between hypercapnia and dilatation of precapillary sphincters which is believed to be a permanent factor of airway edema, So improvement in FEV_1 is related to lowering $PaCO_2$ level.

As for dyspnea assessment: mMRC scale was significantly improved in the Ex. + NIPPV group than that of the exercise training group alone (2.3 ± 0.7 versus2.1 ± 0.72) ($P = 0.01$) (Table 5). This result agreed with that of Duiverman et al. [18]. It was in contrast with Pessoa et al. [4] who reported that dyspnea score was increased after performing upper limb exercises with NIPPV. This result indicates indirectly an overload of the respiratory muscles which is attributed to; 1) applications of low pressures (IPAP = 10) and (EPAP = 4), low EPAP pressure was insufficient to counter balance intrinsic positive end expiratory pressure (iPEEP) with more load on the inspiratory muscles. 2) the application of upper limb exercises as reported by many results of studies [43–45] that COPD patients always complaining from more dyspnea after performing prolonged tasks with unsupported elevated upper limbs compared to lower limb exercises. This fact demonstrates the possibility of upper limb exercises to generate greater dynamic hyperinflation than lower limb exercises.

In the current study HRQoL assessed by CAT in the Ex. + NIPPV group improved than those of exercise group alone with significant changes (23 ± 2.2 versus 20.2 ± 1.4) ($P = 0.01$) (Table 5). Duiverman et al. [18] disagreed with our results of study and explained the disimprovement in HRQoL to the debate of using chronic respiratory questionnaire (CRQ) as an optimum instrument for dyspnea assessment in chronic respiratory failure.

On the other hand, Windisch et al. [46], Duiverman et al. [11] and McEvoy et al. [12] documented from their studies an improvement of HRQoL using Maugeri Respiratory Failure-28 (MRF 28) and Severe Respiratory Insufficiency questionnaires while others using St. George's Respiratory questionnaire reported no changes or more worsened HRQoL after NIPPV. So using of disease specific tool, is more appropriate and useful one [15].

In patients with stable hypercapnic respiratory failure, the combination of night time non-invasive ventilation and day time pulmonary rehabilitation had many beneficial effects [30]. The former intervention has a mechanical effect of blowing air into the lungs over a longer period which leads to better perfused area resulting in more efficient gas exchange [8].

Exercise training reverses the systemic consequences of COPD mainly skeletal muscle dysfunction, via enhancing the mechanical efficacy of physical activities, improves oxidative capacity, enhances the anabolic process in skeletal muscles and reduces the perception of dyspnea [30].

Conclusion

Addition of NIPPV to exercise training in patients with stable hypercapnic COPD improved PCO_2, FEV_1, dyspnea scale and HRQoL.

Conflict of interest

There is no conflict of interest.

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