Effect of a noninvasive ventilatory support during exercise of a program in pulmonary rehabilitation in patients with COPD

Shahin Barakat[1]
Germain Michele[2]
Pascale Nesme[3]
Viallet Nicole[2]
Annat Guy[4]

[1]PhD student, EDISS, Lyon, France; [2]Service of EFR, Hospital of the Croix-Rousse at Lyon, France; [3]Hospital of Croix-Rousse at Lyon, France; [4]UFR Médecine Lyon Grange-Blanche Université Claude Bernard Lyon I INSERM ESPRI ERI 22

Background: Breathlessness is the most common symptom limiting exercise in patients with chronic obstructive pulmonary disease (COPD). Exercise training can improve both exercise tolerance and health status in these patients, intensity of exercise being of key importance. Nevertheless, in these patients extreme breathlessness and/or peripheral muscle fatigue may prevent patients from reaching higher levels of intensity.

Study objective: This study was to determine whether inspiratory pressure support (IPS) applied during sub maximal exercise could enable individuals with severe but stable COPD to increase their exercise tolerance.

Participants: Twelve subjects with severe stable COPD (mean (SD): age = 63(8.2) years; FEV_1 = 0.89(0.42) L (34)% predicted; FEV_1/FVC = 0.31(0.07) only nine subjects completed the study.

Intervention: Each subject completed ten sessions of cycling at 25%–50% of their maximum power without NIVS and another ten sessions using NIVS.

Measurements and results: Dyspnea was measured using Borg scale. Subjects reached high levels of dyspnea 4.7 (1.81) during the sessions without NIVS vs low levels of dyspnea during the sessions using NIVS 1.3 (0.6). Exercise time during the sessions without NIVS and with NIVS was 19.37 (3.4) and 33.75 (9.5) min, respectively. Maximal workload during the sessions without NIVS and with NIVS was 27 (3.7) and 50 (10.5) watt, respectively.

Conclusion: We conclude that IPS delivered by nasal mask can improve exercise tolerance and dyspnea in stable severe COPD patients and hence this mode of ventilatory support may be useful in respiratory rehabilitation programs.

Keywords: noninvasive ventilation pressure support, COPD, exercise, pulmonary rehabilitation, dyspnea

Introduction

In patients with chronic obstructive pulmonary disease (COPD), exercise limitation is a major symptom (Killian et al 1992). Reduced ventilatory capacity combined with an increased ventilatory load leads to intolerable dyspnea at low level of exercise (Belman 1992). Avoidance of dyspnea and, hence, exercise produces progressive deconditioning in lower limb muscles indicated by reduced capillary density, mitochondria, and oxidative enzymes (Maltais et al 1999).

Exercise training as a part of multidisciplinary pulmonary rehabilitation can improve both exercise tolerance and health-related quality of life in patients with chronic obstructive pulmonary disease (COPD) (Toosters et al 2005). The following physiological changes contributing to these improvements were: reduction of lactic acidosis; minute ventilation and heart rate for a given work rate; and enhanced activity of mitochondrial enzymes and capillary density in the trained muscles. Intensity of exercise training is of key importance. High-intensity training has improved both maximal and sub-maximal exercise tests and

Correspondence: Shahin Barakat
6. Chemin du grand bois
69120 Vaulx en velin France
Tel +33 6279 23058/+33 4788 00177
Fax +33 4721 68675
Email barakat.shahin@free.fr/
shahinbarakat@yahoo.fr

has induced both cardio-respiratory and peripheral muscle adaptations (Casaburi et al 1991). However, patients with severe COPD are unable to exercise sufficiently to produce a true physiological training effect because of ventilatory limitation (Casaburi et al 1997).

Noninvasive mechanical ventilation, administered in the form of continuous positive pressure ventilation or pressure support ventilation (bi-level positive airway pressure or proportional assisted ventilation), unload the respiratory muscles (Mehta and Hill 2001). However, noninvasive mechanical ventilation has therefore found use during severe exacerbations of COPD (Lightowler et al 2003) and hypoxic respiratory failure (Ferrer et al 2003). It also has been shown to improve dyspnea and exercise endurance in patients with COPD (Maltais et al 1995; Van't Hul et al 2004). Using inspiratory support, the load in the inspiratory muscles is reduced, with a consequent reduction in the work of breathing (Maltais et al 1995). Blood gases improve (Babcock et al 2002) and patients are able to sustain lactic acid accumulation for longer periods of time (Keilty et al 1994). Hence, the application of inspiratory support, through proportional assisted ventilation, or continuous positive airway pressure ventilation may potentially lead to enhanced training intensity.

Proportional assisted ventilation (PAV), a mode of ventilation that matches ventilator output to patient effort (Younes 1992), is more tolerable for patients with COPD (Stell et al 2000) and is as effective at prolonging exercise.

We hypothesized that in patients with COPD, training using inspiratory support through proportional assisted ventilation would lead to an improvement in exercise tolerance, dyspnea, and would prolong the period of training, through its decrease of the ventilatory requirement.

Methods

Patients gave their informed consent to participate into the study which was approved by our local institutional review board.

Patients

A total of twelve patients (10 males, 2 females) with severe COPD (based on history, clinical, chest radiology, and physiologic evidence) who were clinically stable were included in the study. COPD was defined according to American Thoracic Society (ATS) criteria (American Thoracic Society 1987). Patients with overt cardiovascular or musculoskeletal disease, other organ failure, cancer and inability to co-operate were excluded from the study. Only nine patients completed the study. Reasons for not completing the study included exacerbation of underlying disease (one patient with a problem of a trial fibrillation), noncompliance with the ventilator (one patient) and long pulmonary hospitalization (one patient). At the time of the study, the patients had been free from exacerbations for at least 2 months. All of the patients were on long-term oxygen therapy; two patients were on long-term home mechanical ventilation (MV). Demographic and functional characteristics of patients are shown in Table 1.

Exercise regimen

Patients participated in a program of exercise on a calibrated cycle ergo meter. Twenty exercise sessions were held two to three times per week for about 8 weeks or 20 sessions, the first ten sessions were without NIV (unsupported sessions) and the last ones were with NIV (supported sessions). Exercise duration was 25 minutes for the first ten sessions, although initially many patients were unable to cycle continuously for this length of time, and the exercise duration was 30 minutes for the last ten sessions, and we encouraged the patients to increase this duration as much as they could. Each session was observed by one of the authors who vigorously encouraged the patients to reach the intensity and the duration targets. Initial intensity targets were set at 10 watts for all patients, this work was increased progressively during the first 5 sessions in order to reach the rate of 70% of the peak work rate observed in the incremental maximal exercise test.

This was achieved by increasing the work rate by 5 watts once the subject was able to maintain the existing work rate for 25 minutes. In patients who were unable to cycle continuously at the initial work rate, short rest periods were allowed. Breathlessness and leg fatigue were assessed during training sessions using Borg score (Borg 1982). Patients were

Table 1 Baseline characteristics of patients

Subject characteristics	
Patients n	12
Age years	63.3(8.2)
Sex female/male	2/10
Smokers/nonsmokers	8/4
Body-mass index (kg/m²)	22.3(2.6)
Lung function	
FEV_1 L	0.89(0.42)
FVC L	2.86(0.56)
FEV_1/FVC	0.31(0.07)
RV L	3.28(1.18)

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; RV, residual volume.
Data are presented as mean ± SD.

strongly encouraged not to stop until a symptom rating of 5 (severe) or more was achieved.

During the exercise sessions, heart rate and arterial oxygen saturation, measured by pulse oximetry, were recorded continuously. For patients requiring supplemental oxygen, oxygen was delivered by nasal cannulae during the sessions without NIV and by the ventilator during the sessions with NIV, the oxygen was delivered at a sufficient rate to keep the fingertip oxygen saturation at 92% or above.

Ventilatory assistance was delivered using a AI or AIVT visions in PAV mode (VS Ultra) applied via a tightly fitting nasal mask (type Fisher and Paykel "ACLAIM"). The ventilator settings were individually chosen prior to the program to maximize patient comfort; typically the trigger was as sensitive as possible. At the beginning of the session, patients were instructed to breathe quietly on the bicycle without pedaling for ~5 min to become accustomed to the breathing circuit. In the last 2 min of this adaptation, quiet breathing data were recorded, therefore the parameters of the ventilation were: the inspiratory support ranged from 14 to 17, the expiratory pressure from 3 to 4 cm H_2O, the minimal respiratory frequency from 5 to 12 per minute, the trigger pressure from 4 to 6 cm H_2O, the inspiratory time was 25% of the ventilatory cycle, the minimal inspiratory time was 1.4, the maximal inspiratory time was 2.7 and the slope ranged from 2 to 3.

Measurements

Patients visited the laboratory on two occasions before and two occasions within one week of finishing the program. Testing sessions were performed at the same time of day for each individual patient.

Spirometric tests

Spirometric tests were performed using a pneumocheck(R) Spirometer (ms medi-soft module 5500, USA), and all procedures were carried out according to ATS guidelines. The parameters evaluated were: forced vital capacity (FVC), forced expiratory volume (FEV_1), Tiffenau index (FEV_1/FVC) ratio, and a plethysmography (medi-soft) for residual volume (RV) measurements.

Quality of life

Health status was assessed using the St. George's Respiratory Questionnaire (SGRQ), which is a self-report questionnaire and scores health status in three areas: symptoms (dyspnea, wheezing, and coughing), activity (the severity to which activities of daily living are impaired by dyspnea), and impacts (the influence of respiratory symptoms on social participation) (Jones et al 1992).

Walking test

Each patient was submitted to a 6-minute walking test (6MWT), conducted in a closed corridor of 30 meters. Each test was given twice, with a 10–15 minute interval between the two. During the test the patient was instructed to walk as fast as possible for six minutes and to decrease speed or interrupt the test if experiencing severe dyspnea or any other limiting discomfort. The examiner gave patients verbal encouragement once per minute using standard motivational phrases intended to ensure that patients walked as fast as possible throughout the test. Heart rate, dyspnea, and partial oxygen saturation were measured before and after each test. A trained investigator who did not have access to previous evaluations applied the test or information on the group the patient belonged to.

Statistical analysis

All values are presented as mean ± SD. Comparisons between responses before and after the training program were made using paired Student's *t*-tests. Comparisons between the two groups (with and without NIV) were made using unpaired *t*-tests. Mean values are reported with 95% confidence intervals (95%CI).

The strength of association between variables was tested using the Mann-Whitney/Wilcoxon Two-Sample Test. Significance was accepted at the $p < 0.05$ level.

Results

Subjects

Twelve subjects were screened for the study. Three were excluded, as they were unable to complete the program of rehabilitation with noninvasive ventilation. Nine subjects (two female), with a mean age of 63.3 ± 8.2 yrs, completed the protocol. The demographic details are given in Table 1. The mean FEV_1 was 0.89 ± 0.42 L (34% pred). The mean FEV_1/FVC ratio was 0.31 ± 0.07% of the predicted value. The mean residual volume was 3.28 ± 1.18 L (153% pred). Two subjects were already using nocturnal home ventilation and one subject was using nocturnal continuous positive airway pressure (CPAP) via nasal mask for obstructive sleep apnea.

Quality-of-life measures

Baseline and after rehabilitation SGRQ scores are given in Table 2.

Table 2 Change in St. George's respiratory questionnaire score among patients with chronic obstructive pulmonary disease who received pulmonary rehabilitation(unsupported and supported) by NIV

	St. George's respiratory questionnaire			
	Unsupported sessions		Supported sessions	
	Baseline	After 10 sessions	Baseline	After 10 sessions
Symptoms*	51.57(19)	54.57(20)	54.57(20)	48.44(21)
Activities*	76.54(16)	79.74(15)	79.74(15)	74.83(12)
Impact	62.97(13)	64.5(16)	64.50(16)	66.05(22)
Total*	60.69(10)	63.71(12)	63.71(12)	58.39(17)

Data are presented as mean+/-SD.
*significant changes for the supported sessions with a decrease of each score of more than 4.

SGRQ scores

Table 2 shows the results of the SGRQ. For the supported sessions, there were significant improvements (with a decrease of more than 4 for the score) in symptom, activity and total scores but worsening of the impact score. For the unsupported sessions, there was worsening for all scores.

Walking distance

All patients had a shorter 6-min mean distance at study entry compared with that at the end of the study, and this improvement of the distance walked was statistically significant. There was a mean increase of the distance walked of 37.5 m at the end of the study for the supported sessions and only an improvement of 14 m for the unsupported ones, which was also lower than the significant clinical difference (more than 54 m (Redelmeier et al 1997)) as noted in Table 3.

Exercise physiology

Session duration, dyspnea and maximal workload for the supported sessions and for the unsupported sessions are noted in Table 3.

All subjects exercised longer while using the ventilation; mean session duration increased from 19.37 ± 3.4minutes at the end of the unsupported sessions to 33.75 ± 9.5 minutes at the end of the supported ones. The comparison between the supported with the unsupported session duration was statistically significant ($p < 0.05$); session duration was limited with dyspnea for the unsupported sessions whereas it was limited by the subjects voluntary for the supported sessions; the increase in exercise duration was not associated with any adverse symptoms or morbid changes in the ECG.

We noticed also a significant improvement ($p < 0.05$) in the level of post-effort dyspnea (measured at the end of each session) for the supported sessions from 4.7 ± 1.81 to 1.3 ± 0.6 using Borg score, whereas this improvement was lower for the unsupported sessions (from 6 ± 2.6 to 4.7 ± 1.81).

By the end of the twenty training sessions, the patients (of the supported sessions) showed an improved W_{max} ($p < 0.05$) of 90 % (from 27 to 50), whereas the same patients (but after the unsupported sessions) were not able to improve their W_{max} more than 25% (from 20 to 27), as noted in Table 3.

Discussion

In severe COPD patients, the respiratory muscle strength and endurance are often reduced which can lead to the development of a respiratory muscle fatigue and contribute to the poor exercise tolerance. Although some studies have demonstrated an individual benefit of respiratory muscle training on overall exercise tolerance (Lisboa et al 1997), the actual efficacy of such a training program has been contested (Smith et al 1992). The increase in minute ventilation performed during lower limb exercise could achieve a similar level of respiratory muscle training (Sergysels 1996). However, in patients exhibiting dyspnea and CO_2 retention at lower intensities of exercise, the training load is often much reduced (limited to unloaded cycling). In our study, we demonstrated the feasibility and the benefit on the ventilatory adaptation with training of the application of a ventilatory support during every exercise session.

The results of this study show that, in stable patients with severe COPD, short term, noninvasive application of IPS during exercise sessions of an outpatient program of rehabilitation: (1) improves the quality of life, (2) improves the exercise tolerance, (3) augments the period of exercise and (4) decreases the sensation of breathlessness during the exercise.

The cornerstone of respiratory rehabilitation is exercise training. Other modalities such as education and psychosocial support may be useful as an adjuncts to exercise training but by themselves are unlikely to influence exercise tolerance or health-related quality of life (Ries et al 1995; Sassi-Dombron et al 1995). The magnitude of the physiologic training effect is strongly influenced by the intensity of the exercise

Table 3 Changes in the walked distance within 6MWT, post-effort dyspnea, session duration and the maximal workload during the incremental maximal exercise test

6MWT, Session duration, post-effort dyspnea, maximal workload					
	Unsupported sessions		Supported sessions		
	Baseline	After 10 sessions	Baseline	After 10 sessions	p
Walking distance of 6 MWT (m)	231(97)	245(87)	245(87)	282(111)	<0.01§
Session duration (minute)	9(4.2)	19.37(3.4)	19.37(3.4)	33.75(9.5)	0.039§
Dyspnea (Borg scale)	6(2.6)	4.7(1.81)	4.7(1.81)	1.3(0.6)	<0.01§
W_{max} (watts)	20(5)	27(3.7)	27(3.7)	50(10.5)	0.043§

Data are presented as mean ± SD.
§: $p < 0.05$, unpaired t-test between the changes in both groups of sessions.

(Casaburi et al 1991). However, many subjects with COPD are unable to tolerate high workloads because they are limited by severe dyspnea.

Several studies have examined the acute effects of different modalities of ventilatory assistance on dyspnea and exercise tolerance in advanced COPD. The message of these physiological studies could be summarized as follows: assisted ventilation delivered as noninvasive positive pressure ventilation (NPPV), either as continuous positive airway pressure (CPAP), or inspiratory pressure support (IPS) or proportional assisted ventilation (PAV), during exercise reduces dyspnea and work of breathing and enhances exercise tolerance in COPD patients (Ambrosino and Strambi 2004).

To date, five randomized, controlled studies have compared the effects of training with NIVS to unsupported training in patients with COPD. Johnson et al (2002) and Van ′t Hul et al (2006) found a significant between-group difference in the gain in walking endurance in favor of the group training with NIVS. In contrast, two studies (Hawkins et al 2002; Costes et al 2003) reported a between-group difference in the maximal incremental cycle exercise test in favor of patients training with NIVS, but not for the constant work rate cycle endurance test. Bianchi et al (2002) observed no differential effect of training with NIVS on exercised performance or health status. Finally, Van't Hul et al (2006) have evaluated the effects of training with mask IPS in COPD patients. They compared 10 cm H_2O IPS with 5 cm H_2O IPS delivered during high-intensity training. IPS10 resulted in significantly larger improvements in exercise performance than training with IPS5; the authors of this article have done their best to demonstrate the effectiveness of NPPV as an aid to exercise training in COPD patients. The first four studies, apart from having different outcomes, suffer from considerable methodological limitations. First, observers were not blinded to treatment allocation in any of these studies. Secondly, none incorporated a "sham" type of NIVS, contrasting the effects of training. Consequently, a placebo effect of NIVS could not be ruled out to explain the differences in effect. Nevertheless, the last study (Van't Hul et al 2006) raises some concerns and does not solve the problems regarding the practical use in a routine setting.

As we know, IPS is a form of mechanical ventilation when applied noninvasively to patients in acute and chronic respiratory failure. It is a pressure-targeted mode in which each breath is patient-triggered and supported (Brochard 1994). It provides breath-by-breath ventilatory support by means of a positive-pressure wave that is synchronized with the inspiratory effort of the patient. During inspiration, the airway pressure is raised to a pre-set level: the pressure support level. This level is maintained until the machine determines the end of a patient's respiratory effort or detects a patient's demand for expiration. The diaphragmatic work, as assessed by the transdiaphragmatic pressure, was reduced during exercise with IPS which confirms its physiological effect on exercise tolerance (Maltais et al 1995).

In addition, it was clear from numerous studies, that application of NPPV unloads the inspiratory muscles during exercise. Younes et al (1992) showed that in normal subjects undergoing heavy exercise, PAV reduced the esophageal pressure (Poes) swings giving a sensation of easier breathing. Although experimental data are lacking, it seems reasonable to hypothesize a similar mechanism to explain the improvement in exercise tolerance in severe COPD.

On the other hand, it has been shown that PSV reduces the diaphragmatic pressure-time product (*Ptp, di*), dyspnea (Kyroussis et al 1996), and slows down the maximum relaxation rate of inspiratory muscles.

In our study, 3 patients were not able to comply with the rehabilitation program, which was sometimes because of the difficulty of the patient's adaptation to the requests of the ventilation, and on the other hand, the low number of our group was also because of the difficulty to persuade most of the COPD patients to participate in such a program.

Our group of patients was well matched with respect to lung function and age, but there were only two women (14%) in the group which was due to the decreased females diagnosed with COPD compared with this diagnosis among males.

As for the effects of training on health status, there were significantly lower scores in the activity, symptom and total components of the SGRQ and lower scores but not significantly for the impact component. An improvement of more than 4% in total score (expressed as a percentage of maximum score) is considered to be clinically relevant (Schunemann et al 2003). Thus the improvement of total score for supported patients of 4.68 was clinically relevant.

An improvement in the parameters of the exercise tolerance was noted at the end of the supported sessions, which was clear by the increase of the distance walked during the 6 MWT of 37 m, this increase was lower than the significant clinical increase (54 m, Redelmeier et al 1997). This lack of significance was probably due to the small number of subjects in the actual study.

Finally, a notable decrease in the post-effort dyspnea was noted during the supported sessions and also an increase in the duration of the supported sessions which were statistically significant.

The mean findings of our present study are that patients with severe COPD who received ventilatory assistance during an exercise program achieved greater training intensities, longer exercise duration and with less dyspnea after this exercise.

The mean effect of the ventilatory assistance was to increase the training intensity tolerated during the period of application of NIVS, which was apparent from the third session of the ten supported sessions, and maintained to the end of the program, as we could not increase the work load for our patients within the first unsupported ten sessions more than 25–30 watts.

A limitation of our study is the lack of blindness of the researchers to the treatment allocation which is also true for most other "positive" studies, and therefore the subjects were not blinded to the intervention that they received and the use of mask ventilation can produce a significant placebo effect. However, there is no convincing way of blinding subjects to this intervention.

Although the results of this study could, in part, possibly be explained by a placebo effect of the application of IPS, allowing the patient to achieve greater training intensities, as well as all the fact that all subjects received the same encouragement and support, we doubt that this is an important factor, given that the improvements noted within the parameters of the exercise tolerance during the supported sessions were very large especially for the session duration and the post-effort dyspnea during these sessions.

The small number of subjects that were recruited in our study is another limitation, as for most other studies which deal with NIVS as an aid to exercise training in COPD patients, and therefore had a limited power to confirm our findings.

The application of NIVS by a nasal mask gave also some difficulties to our patients, in that nasal breathing is common at rest but oronasal breathing appears to be universal during exercise. This made some difficulties for our patients especially at the first period of our protocol, because they had to use only nasal breathing during our protocol of NIVS.

Conclusion

The mode of ventilation (Inspiratory pressure support (IPS)) delivered by a nasal mask was able to improve exercise tolerance and reduce dyspnea in severe stable chronic obstructive pulmonary disease patients. Further investigations are needed to elucidate the appropriate application of NIVS in respiratory rehabilitation programs.

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