Effects of Nasal Positive Expiratory Pressure on Dynamic Hyperinflation and Six Minute Walk Test in Patients with COPD

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Abstract

Introduction: Dynamic hyperinflation is an important target in the treatment of COPD. There is increasing evidence that positive expiratory pressure (PEP) could reduce dynamic hyperinflation during exercise. PEP application through a nasal mask and a flow resistance device might have the potential to be used during daily physical activities as an auxiliary strategy of ventilatory assistance. The aim of this study was to determine the effects of nasal PEP on lung volumes during physical exercise in patients with COPD.

Methods: 20 subjects (mean age 69.4 ± 6.4 years) with stable, mild-to-severe COPD were randomized to undergo physical exercise with nasal PEP breathing, followed by physical exercise with habitual breathing, or vice versa. Physical exercise was induced by a standard six-minute walk test (6MWT) protocol. PEP was applied by means of a silicone nasal mask loaded with a fixed-orifice flow resistor. Body plethysmography was performed immediately pre- and post-exercise.

Results: Differences in mean pre- to post-exercise changes in TLC (-0.63 ± 0.80 L; p = 0.002), FRC (-0.48 ± 0.86 L; p = 0.021), RV (-0.56 ± 0.75 L; p = 0.004), SpO_2 (-1.7 ± 3.4 %; p = 0.041) and 6MWT distance (-30.8 ± 30.0 m; p = 0.001) were statistically significant between the experimental and the control interventions.

Conclusions: The use of flow-dependent expiratory pressure, applied with a nasal mask and a PEP device, might promote significant reduction of dynamic hyperinflation during walking exercise. Further studies are warranted addressing improvements in endurance performance under regular application of nasal PEP during physical activities.

Key words: Airway Resistance, Chronic Obstructive Pulmonary Disease, Dyspnea, Lung Capacities, Positive-Pressure Respiration, Respiration

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent condition worldwide. It is predominantly characterized by chronic inflammation and dysfunction of the peripheral airways, as well as destruction of the lung parenchyma in highly variable appearance.[1] Reduced elastic recoil and increased airway resistance provoke expiratory flow limitation and hyperinflation, which are the pathophysiological hallmarks of COPD.[2,3] As a result of altered lung mechanics, increasing ventilatory demand can induce an increase in hyperinflation, which is traditionally referred as dynamic hyperinflation.[2] Studies addressing the lung volumes in COPD identified dynamic hyperinflation as a key determinant of dyspnea, exercise intolerance and reduced daily physical activity.[3–6]

Reversing dynamic hyperinflation is therefore an important aim for any therapeutic interventions.[3,7,8] Benefits of reducing hyperinflation in COPD could be demonstrated for a number of therapeutic methods, including lung volume reduction surgery, bronchoscopic lung volume reduction, pharmacotherapy and rehabilitation programs.[2,8–13] Combinations of different therapeutic approaches are considered to be even more effective in the reduction of hyperinflation and in the improvement of symptoms.[8]

There has also been long-standing interest in the effect of positive expiratory pressure (PEP) breathing in COPD patients, in whom it is thought to produce a reduction of breathing frequency, improved gas exchange as well as less airway collapse and airtrapping.[2,14] It is considered to have similarities to pursed lip breathing (PLB), a breathing maneuver which is spontaneously adopted by some patients with COPD and which is routinely taught as a breathing technique in respiratory physiotherapy.[15,16]

Currently, PEP is often used in pulmonary rehabilitation as breathing exercise,

especially in terms of assistance in the removal of secretions, and can be applied by several techniques, including PLB, blow bottle technique, oral high frequency oscillators and PEP devices.[16] PEP devices typically can be characterized as either flow dependent or threshold dependent, the latter providing constant expiratory pressure, but the optimal PEP technique and pressures are not yet established in the literature.[16] In particular, the effects of PEP during exercise in patients with COPD are poorly explored.

The recent recognition of dynamic hyperinflation as an important target in the treatment of COPD has renewed the interest in PEP breathing and its potential effects on respiratory effort and lung volumes.[17–19] Recently, the first two reports of PEP being successfully used to reduce dynamic hyperinflation during exercise in patients with COPD have been published,[18,19] demonstrating that the application of PEP is not limited to breathing exercises at rest, but has the potential to be used during daily physical activities.

Our study was conducted to assess the feasibility of a novel approach, the application of PEP through a nasal mask during physical exercise, and its effects on dynamic hyperinflation in patients with COPD. Our concept was created with the specific intent to allow patients to feel less constraint and more comfortable compared to an oral PEP device, since they may still be able to speak, drink or eat while using PEP during daily activities.

METHODS

Subjects

Twenty men and women with stable, mild-to-severe COPD, according to the Global Initiative for Chronic Obstructive Lung Disease Criteria,[20] who were able to perform six-minute walk tests and who were free from orthopedic or neurological diseases

limiting exercise tolerance, were consecutively recruited from a pulmonary outpatient clinic and included in the trial. Subjects were excluded if they had an acute cardiac illness within the 4 weeks prior to study entry, known severe bullous emphysema with large bullae or a history of spontaneous pneumothorax.

Study Design

This randomized crossover proof-of-concept study received approval from the local ethics committee. After obtaining informed consent, subjects were randomized by computer generated randomization list to receive the experimental intervention (breathing with nasal PEP device during physical exercise), followed by a 2 to 24 hours wash-out period, and then the control intervention (habitual breathing during physical exercise without PEP device) or vice versa (figure 1). Physical exercise was performed according to a standard six-minute walk test (6MWT) protocol. An experienced, non-blinded assessor performed before and immediately after exercise lung function tests and Borg dyspnea scale. Subjects took their regular medications in the morning and were investigated in the afternoon.

Procedures

PEP was applied with a silicone nasal mask (JOYCE, Weinmann Geräte für Medizin GmbH + Co. KG, Hamburg, Germany) loaded with the upper and lower part of a PARI PEP System I device (PARI GmbH, Starnberg, Germany). This device has an adjustable fixed-orifice resistor inducing a flow-dependent expiratory pressure in the range of 10-20 cm H_2O.[21] It also includes a one-way valve which opens upon inspiration. In all subjects, expiratory resistance of the PEP device was set to the largest available aperture (5.0 mm). The device was placed on the subject's nose

and held in place with a four-point head strap (figure 2). No training or practice test was performed with the device.

Spirometry and whole body plethysmography measurements were performed according to the American Thoracic Society and the European Respiratory Society (ATS/ERS) guidelines with a commercially available system (Masterscreen Body, Jaeger, Wuerzburg, Germany and JLAB LABManager, software version 5.3.0.4, Cardinal Health Germany 234 GmbH, Hoechberg, Germany), and lung subdivisons were determined by measuring expiratory reserve volume (ERV) immediately after the acquisition of the FRC measurement, followed by the slow inspiratory vital capacity maneuver, all performed as "linked" manoeuvres.[22,23] Dynamic hyperinflation was measured as an increase in FRC and RV, taken before and after exercise.[24] Values for IC were calculated as TLC minus FRC. The predicted normal values for spirometry and lung volumes were those of European Community of Coal and Steel.[25,26] Predicted normal values for IC were calculated as predicted TLC minus predicted FRC.

The 6MWT was administered by an experienced investigator according to the American Thoracic Society and the European Respiratory Society (ATS/ERS) in a flat, straight, indoor corridor (30 m long, marked by colored tape at each end to indicate turnaround points).[27] All subjects were familiar to the test. Subjects were instructed to walk at a comfortable pace but with the aim to walk as far as possible in 6 minutes. Participants were allowed to stop and rest during the test, but were encouraged to resume walking as soon as they were able. In those tests which were performed with nasal PEP-application, subjects were instructed to breath out only through their nose and to breath in either through their nose or mouth. When PEP

was not applied, subjects were instructed to breath habitually, and pursed lip breathing or any other particular breathing techniques were allowed as subjects were used to do in daily life.

Before the 6MWT started, after completion of the pre-exercise lung function test, the subjects were shown a Borg scale to rate their baseline dyspnea.[27] At the end of the 6MWT, immediately after completion of the post-exercise lung function test, the Borg scales were recorded again.

Statistical Analysis

The required sample size was estimated based on data of a previous study,[19] in order to detect an expected difference in FRC variation pre-to-post exercise of 0.5 L comparing tests with and without PEP. 20 subjects were needed, assuming a SD of 0,75 L and using a two-tailed t-test for paired samples with 80% power and an α level of 5%. This number of patients seemed plausible and reasonable considering sample sizes in two similar previously published studies that demonstrated effects of PEP on lung volume variations.[18,19] Lung volume measures pre- and post-exercise and variations with and without PEP were compared using the t-test for paired samples, after normal distribution was confirmed with the Shapiro–Wilk test. Data are reported as mean+/-SD unless otherwise stated. All tests were two-sided and a $p<0.05$ was considered statistically significant. All data were analyzed with GraphPad Prism (version 5, GraphPad Software, USA).

RESULTS

Breathing through the PEP-device caused a smooth whistle noise during expiration, which was generated by the small orifice in the device. That noise enabled both the

patient and the investigator to easily monitor whether breathing was done correctly through the PEP device. All subjects adopted the nasal PEP-breathing technique correctly according to the breathing instructions and stated that breathing through nasal-PEP during the 6MWT was acceptable but required additional breathing effort.

All of the 20 subjects completed the study protocol. An overall of 40 6MWTs and 80 body plethysmography and spirometry measurements were performed. All subjects entered the plethysmograph directly after the 6MWT, and, if used, the nasal PEP mask was removed simultaneously. In both groups, with and without nasal PEP, subjects started lung function measurement immediately (<1 minute after exercise) without any significant delay due to shortness of breath or other cause and completed lung function measurement with good cooperation. Ten subjects (50 %) had nasal PEP in the first 6MWT followed by habitual breathing in the second 6MWT after the wash-out period, and 10 subjects (50 %) vice versa. Patient characteristics are shown in table 1. All subjects were treated according to GOLD standards.[20]

Comparison of pre-exercise lung function values in the experimental and the control interventions did not show any significant differences (table 2). There was a significant increase in post-exercise values of TLC, FRC and RV in the control interventions, whereas in the experimental interventions no significant changes in lung volume values could be observed (table 2). Accordingly, differences in pre- to post-exercise changes in TLC (-0.63 ± 0.80 L; $p = 0.002$), FRC (-0.48 ± 0.86 L; $p = 0.021$) and RV (-0.56 ± 0.75 L; $p = 0.004$) were statistically significant between the experimental and the control interventions (table 2, figure 3). In addition, both interventions showed a significant post-exercise decrease in SpO_2 and increase in Borg-dyspnea scale (table 2). A significant increase in post-exercise heart rate was observed in the experimental interventions (table 2). Comparison of pre- to post-exercise decrease in SpO_2 between the experimental and the control interventions

revealed a small but statistically significant difference (-1.7 ± 3.4 %; p = 0.041), whereas differences in heart rate and Borg-Scale were not significant (table 2). 6MWT distance was significantly shorter in the experimental interventions (-30.8 ± 30.0 m; p = 0.001; table 2, figure 3).

DISCUSSION

The results of our study suggest that the application of nasal PEP through an expiratory resistance device during walking exercise reduces dynamic hyperinflation in subjects with COPD. When nasal PEP was used during walking exercise, a significant reduction in mean pre- to post-exercise changes in TLC (-0.63 ± 0.80 L; p = 0.002), FRC (-0.48 ± 0.86 L; p = 0.021) and RV (-0.56 ± 0.75 L; p = 0.004) could be observed compared to walking exercise without nasal PEP.

A recent study demonstrated similar beneficial effects of expiratory positive airway pressure on lung volumes during walking exercise in patients with COPD, using a silicone face mask loaded with a linear pressure resistor.[19] In the mentioned study, subjects were pre-selected on the basis of a pre- to post-exercise decrease of IC by at least 15%, and underwent, after a 24-hours suspension of long-acting bronchodilatators followed by the pre-exercise administration of short-acting bronchodilatators, two 20-minutes treadmill exercise tests without and with PEP in a sequential study protocol without cross-over. Reported improvements in lung volumes reached statistical significance for FRC, IC and FEV_1, whereas in our study significant changes were observed for TLC, FRC and RV, and effects on IC and FEV_1 were not significant. Subjects in our study were not pre-selected, had different baseline characteristics including a more intense smoking exposure (41.4 pack years vs 9.6 pack years), continued their regular bronchodilatator treatment and underwent a different study protocol which might explain the slightly different outcomes.

Another study showed an improvement in IC in patients with COPD who underwent knee extension exercise with and without an oral, flow dependent PEP device in a randomized, cross-over protocol.[18] In both of the mentioned studies,[18,19] IC was measured by spirometry using an IC maneuver followed by an expiratory VC maneuver, in contrast to our study, that used body plethysmography and an ERV maneuver followed by an inspiratory VC maneuver to calculate IC as TLC minus FRC immediately pre and post each intervention. We hypothesize, that this difference in lung function procedures might be a possible reason why those two studies mentioned demonstrated improvements in measured IC, whereas in our study improvements in TLC, FRC and RV could be observed, and calculated IC was not of great value for assessment of improvements in dynamic hyperinflation. Considering limited information from past literature, we can only speculate about the reasons for this effect. A recent study compared the preferred (ERV maneuver followed by inspiratory VC maneuver) and alternate (IC maneuver followed by expiratory VC maneuver) method (as suggested by the ATS/ERS standardization of lung volume measurement)[23] for the measurement of static lung volumes using body plethysmography at rest.[28] They found that a smaller TLC was achieved using the alternate method, compared to the preferred method and concluded that there might be a possibility that IC and TLC may be underestimated using the alternate method in some individuals.[28] Similarly, we could conclude from that study, that IC and TLC might be overestimated using the preferred method and consequently, that the values for TLC and IC measured in our study could be overestimated. Currently, the mechanisms for these differences in obtained lung volumes using the two methodologies remain uncertain.[23,28] However, the mentioned study did not include post-exercise lung function measurements and therefore effects of dynamic hyperinflation on the variation of measured IC and TLC values were not addressed.

But again, we speculate that the differences found at rest between the two methodologies may become even more pronounced when FRC is shifted closer to TLC due to dynamic hyperinflation during and after exercise. If those differences in measured lung volumes happen because the respiratory muscles are in a less advantageous starting position at FRC compared to RV for completing a maximal inhalation maneuver as hypothesized by the authors of the mentioned study,[28] these starting positions could become even more distinct when FRC is forced closer to TLC due to dynamic hyperinflation, potentially resulting in increased differences between measurement methods.

Although the results from our and previous studies demonstrate that a detection of exercise induced dynamic hyperinflation can be achieved with both methods, they also show that the marked discrepancy in the variations of static lung volumes need to be comprehensively investigated. The influence of different lung function maneuvers on post-exercise IC and other lung volumes should therefore be addressed in future studies.

However, in current studies, the inspiratory capacity (IC) maneuver is preferably used to measure dynamic hyperinflation during exercise. That method is based on the assumption that TLC remains almost constant during submaximal exercise in patients with COPD and can be easily performed with a mobile spirometry during exercise when the body plethysmography procedure is not practicable.[29,30] In some studies, novel methods including optoelectronic plethysmography or inert gas dilution techniques are occasionally used.[31–33] However, body plethysmography remains the gold standard for the measurement of hyperinflation and has therefore been used in our study for reliable measurement of lung volumes.[33] Surprisingly, in our study, reminiscent to results of a previous study,[19] post-exercise TLC values did not remain constant as previously assumed for TLC during submaximal exercise, but showed a

marked increase. That assumption based on a 1980 study on six male subjects with evidence of airflow obstruction, who underwent lung function measurements during exercise in a body plethysmograph containing pedals of a cycle ergometer.[34] However, the number of subjects in that study was smaller than in ours, and unlike the procedure used in our study, which involved an inspiratory vital capacity maneuver at rest immediately after exercise, they used an expiratory vital capacity maneuver during steady state exercise to calculate TLC. Interestingly, the pattern of effects of nasal PEP during exercise on lung volumes in our study turned out to be similar to the acute improvements in TLC, RV and FRC at rest after administration of salbutamol demonstrated in previous studies in patients with severe hyperinflation.[35,36] The question arises whether the reduction of dynamic hyperinflation observed with nasal PEP are similar to the mechanisms provoking a reduction in hyperinflation after pharmacological bronchodilatation and whether we can continue to accept the assumption that TLC does not change during physical exercise in patients with COPD when breathing without any imposed nasal or oral flow restistance including the possible flow resistance induced by certain spirometry mouthpieces and devices. The experience gained from body plethysmography in our and previous studies[19] therefore indicate the need for further and detailed studies on changes of TLC during and after exercise in patients with COPD and on the potential diagnostic benefit of post-exercise body plethysmography.

There are some other major issues in current research on positive expiratory pressure in COPD. The first aspect is that a definitive definition of dynamic hyperinflation is lacking in the literature,[2] and even the cut-offs for lung function values in hyperinflation at rest remain arbitrary in some extent.[33]

The second point is that the methods of exposure to physical exercise as well as the methods to assess exercise limitations vary across the studies published so far. In

our study, a 6MWT was used to generate physical exercise and was chosen because of its widespread availability, its easy combinability with body plethysmography and its relevance to activities of daily living.[27] As demonstrated in previous reports, this test evoked effectively dynamic hyperinflation in our study.[37,38] Although assessment of changes in exercise capacity was not an objective in this study, we observed that despite improvements in lung volumes, mean 6MWT distance in the experimental interventions was statistically significantly reduced by 30.8 meters. Given that the use of nasal PEP most probably results in an additional breathing effort as well as a reduced minute volume, in fact, it is not surprising that the submaximal level of peak performance may acutely decrease. This assumption is also supported by the finding of a small decrease in SpO2 when nasal PEP is used in our study. However, it is conceivable that the expiratory resistance generated by our device might have been higher than needed for an optimal outcome in exercise performance and that improvements in lung function parameters may have been outweighed by inconveniences and detrimental effects of a potentially excessive expiratory resistance. The determination of the optimal expiratory resistance might therefore be an important aim in future studies. Moreover, although 6MWT distance as a measure of submaximal level of exercise capacity could be quantified, our study design did not allow to assess endurance performance. In fact, recent reports suggest, that endurance tests such as the endurance shuttle walk are more sensitive than 6MWT for detecting exercise benefits following improvements in lung function in patients with COPD.[39,40] In addition, it is assumed that the reduction of dynamic hyperinflation may not result in an acute improvement in physical performance, because patients might require time or training to derive advantage from their improved ventilatory capacity.[40] Further studies are therefore needed addressing improvements in

endurance performance under daily, regular application of nasal PEP in patients with COPD.

The third aspect is that within the group of flow resistance PEP devices there are major differences in the underlying technical concepts. In our study, a flow dependent PEP device was used and we hypothesize that, in regard to a reduction of dynamic hyperinflation, this concept might be superior to the more elaborate, constant-pressure, threshold-dependent type of PEP devices, which could cause an abrupt interruption of the expiratory airflow each time the patient's expiratory pressure falls below the threshold pressure of the valve. Flow dependent PEP devices as used in our study do not allow to indicate a precise extrinsic positive endexpiratory pressure (PEEP) produced by this method in each individual, because the induced pressure is not constant. Induced pressures will be high at high-flow phases of expiration, while they may be marginal during low-flow phases. The flow resistance may therefore be regarded as the key mechanism of this concept, and with the objective of being able to more clearly distinguish the purpose and therapeutic method presented in this study from active, non-invasive ventilation (Expiratory Positive Airway Pressure)[41] and airway clearance physiotherapy (Positive Expiratory Pressure),[42] we propose to specify this concept of respiratory support based on expiratory flow resistance as descriptive as possible "Ventilatory Assistance Derived from Expiratory Resistance".

The underlying mechanisms considered to provoke the reduction in dynamic hyperinflation is the diminution of airway compression.[2,14,43] In patients with emphysema the equal pressure point (EPP) is moved more peripherally, resulting in earlier airway compression during expiration, particularly at high flow rates, which leads to hyperinflation.[1] Similar to the effect of pursed lip breathing, expiratory airway resistance increases intraluminal airway pressure resulting in a shift of the EPP back to central airways which counteracts early airway collapse.[43] It must be noted that in

certain diseases, other mechanisms might contribute to the beneficial effects of positive expiratory pressure: a study on EPAP in climbers with high altitude pulmonary edema (HAPE) at rest and healthy climbers during exercise at 4400m demonstrated an improvement in gas exchange and suggested EPAP as an effective temporizing measure for victims of HAPE.[44]

Despite decades of research, the role of breathing techniques in patients with COPD remains a topic of debate.[45,46] A recent study found a shift in breathing preferences towards mouth breathing during exercise in subjects with COPD compared to normal subjects.[47] It has been hypothesized that the switch to mouth breathing might be an adaptive response that reflects the need to reduce inspiratory resistance.[46] On the other hand, another study demonstrated that in subjects with COPD, spontaneous pursed lip breathing resulted in increased endurance performance compared to obligate open mouth breathing.[48] Such evidence suggests that a combination of techniques that increase expiratory resistance via pursed lip breathing or PEP and, if needed, reduce inspiratory resistance via open mouth breathing might be beneficial for some people with COPD, although additional effort is required during expiration. The novel approach of nasal PEP provides these features and future studies are warranted to address the effects of this concept on endurance performance using similar devices or more sophisticated solutions such as nasal valves which might be more comfortable to the patients. These studies should focus in particular on COPD patients with narrowing of larger airways during expiration, in whom techniques that increase expiratory resistance are assumed to be beneficial.[45]

Our study was limited in some respects. Diurnal variations in lung function and the effects of subjects' regular medications could have influenced our results, and the time intervals between the study procedures in the afternoon and previous bronchodilator intake in the morning were not systematically assessed in our study.

For methodical reasons the interventions were not blinded. In addition, both the patient and the investigator might have been influenced by the experimental intervention procedure because the subjects had to adopt a different breathing technique and because the device produced a reassuring, smooth noise during expiration, which could have affected walking pace and respiratory rate. Similarly, possible learning effects might have influenced walking pace and changes in 6MWT distance. It should also be noted that in the experimental intervention, the reduced 6MWT distance might have slightly contributed to the observed decrease in dynamic hyperinflation. In addition, the pressure curves generated by the flow dependent PEP-device were not recorded in our study, and respiratory rate, minute volumes and breathing effort were not assessed systematically, as these additional procedures could have influenced our results. Blood gas changes have not been determined and should be analyzed in future studies. Another aspect is that the small sample of COPD patients in our study included a wide range of disease severity as well as patients with endobronchial coils or valves. Although this heterogeneous sample allowed to demonstrate that nasal PEP is acceptable to a broad range of patients with COPD, it could be argued that the heterogeneity of the subjects might have influenced the response to the intervention and that there may be groups of patients in whom the potential improve could overcome the inconveniences of the device and vice versa. Future studies should therefore focus on more homogeneous target populations to avoid under- or overestimation of the true effect of nasal PEP.

In conclusion, this study demonstrated that the use of PEP, applied with a nasal mask and a flow resistance device during walking exercise, might promote significant reduction of dynamic hyperinflation and is acceptable to patients with mild-to-severe COPD. The novel concept of nasal application has the potential to be regularly used in daily live during physical activities. Therefore, the ultimate goal could be that this

method of ventilatory assistance might be used as an auxiliary strategy to improve physical performance. Although our results show that submaximal peak performance may acutely decrease, further studies are warranted addressing improvements in endurance performance under daily, regular application of nasal PEP in patients with COPD.

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Figure 1 Study protocol flow chart.

Figure 2   Ventilatory Assistance Derived from Expiratory Resistance (VADER) - concept: silicone nasal mask loaded with a flow-dependent expiratory pressure valve, held in place with a four-point head strap.

Figure 3 Effect of nasal PEP on 6MWT distance and pre-to-post exercise increase in lung volumes in each individual patient (n=20). (a) TLC (difference between means -0.63 ± 0.80 L; p = 0.002). (b) FRC (difference between means -0.48 ± 0.86 L; p = 0.021). (c) RV (difference bewtween means -0.56 ± 0.75 L; p = 0.004). (d) 6MWT-distance (difference between means -30.8 ± 30.0 m; p = 0.001).

Table 1. Baseline Data of Subjects.

	Total n = 20
Male, n (%)	13 (65)
Age, years	69.4 ± 6.4
Body height, cm	168 ± 8.4
Body weight, kg	75.8 ± 17.1
Body mass index, kg/m^2	26.5 ± 4.8
Smoking, pack years	41.4 ± 24.5
COPD GOLD Stage, n (%)	
I	1 (5)
II	8 (40)
III	8 (40)
IV	3 (15)
Current medication, n (%)	
Inhaled corticosteroids	16 (80)
Long acting β_2-agonists	19 (95)
Long acting anticholinergics	18 (90)
Long term oxygen therapy, n (%)	9 (45)
Endobronchial valves/coils, n (%)	3 (15)

Table 2. Assessed parameters pre and post exercise with and without nasal PEP.

	Comparison between interventions				Difference within interventions		Difference between interventions	
	Pre-exercise		Post-exercise		Post- minus pre- exercise		Post- minus pre- exercise	
	Without PEP	With PEP	Without PEP	With PEP	Without PEP	With PEP	With PEP minus without PEP	p-value
TLC, L	7.42 ± 1.25	7.59 ± 1.28	8.01 ± 1.45	7.53 ± 1.35*	0.58 ± 0.74*	-0.05 ± 0.52	-0.63 ± 0.80*	0.002
(% predicted)	(124 ± 20)	(127 ± 18)	(134 ± 26)	(126 ± 17)*	(10 ± 16)*	(-1 ± 10)	(-11 ± 16)*	0.006
FRC, L	5.22 ± 1.16	5.31 ± 1.27	5.82 ± 1.52	5.42 ± 1.37*	0.59 ± 0.85*	0.11 ± 0.61	-0.48 ± 0.86 *	0.021
(% predicted)	(162 ± 39)	(164 ± 41)	(180 ± 51)	(167 ± 39)	(18 ± 31)*	(2 ± 19)	(-16 ± 29)*	0.027
RV, L	4.76 ± 1.05	4.85 ± 1.14	5.34 ± 1.39	4.88 ± 1.21*	0.59 ± 0.81*	0.03 ± 0.41	-0.56 ± 0.75 *	0.004
(% predicted)	(203 ± 52)	(207 ± 54)	(228 ± 70)	(207 ± 53)*	(25 ± 41)*	(1 ± 18)	(-25 ± 37)*	0.007
RV%TLC, %	64.0 ± 8.73	64.0 ± 10.1	66.4 ± 9.53	64.9 ± 11.8	2.33 ± 3.43	0.93 ± 3.39	-1.40 ± 3.72	0.106
(% predicted)	(154 ± 24)	(154 ± 27)	(160 ± 25)	(157 ± 31)	(6 ± 8)*	(2 ± 8)	(-3 ± 9)	0.124
IC[‡], L	2.20 ± 0.76	2.28 ± 0.90	2.19 ± 0.84	2.12 ± 0.79	-0.01 ± 0.29	-0.16 ± 0.44	-0.15 ± 0.43	0.128
(% predicted)	(79 ± 21)	(82 ± 24)	(80 ± 26)	(77 ± 25)	(0 ± 10)	(-5 ± 14)	(-5 ± 14)	0.137
FVC	2.45 ± 0.79	2.50 ± 0.97	2.44 ± 0.85	2.47 ± 0.95	-0.01 ± 0.32	-0.02 ± 0.31	-0.01 ± 0.37	0.896
(% predicted)	(75 ± 16)	(77 ±25)	(75 ± 22)	(77 ± 28)	(0 ± 13)	(0 ± 9)	(0 ± 14)	0.921
FEV_1, L	1.27 ± 0.54	1.24 ± 0.54	1.33 ± 0.56	1.32 ± 0.54	0.06 ± 0.08	0.09 ± 0.09	0.03 ± 0.12	0.280
(% predicted)	(50 ± 18)	(49 ± 19)	(52 ± 19)	(53 ± 19)	(2 ± 3)	(3 ± 4)*	(1 ± 5)	0.216
SpO_2, %	93.2 ± 2.2	93.3 ± 2.3	86.1 ± 6.1	84.5 ± 7.6	-7.1 ± 4.9†	-8.8 ± 6.3†	-1.7 ± 3.4*	0.041
HR (bpm)	89.1 ± 19.2	83.4 ± 16.9	92.1 ± 27.3	101.5 ± 21.9	2.9 ± 34.1	18.1 ± 14.4†	15.2 ± 32.9	0.067
Borg-Scale	1.1 ± 2.1	1.0 ± 1.7	5.1 ± 1.9	5.7 ± 2.3	4.0 ± 1.9†	4.7 ± 1.8†	0.7 ± 2.1	0.165
Distance, m	n/a	n/a	352 ± 92	321 ± 93*	n/a	n/a	-30.8 ± 30.0*	0.001

Statistical analyses refer to comparisons between interventions, differences within interventions or differences between interventions as indicated in the first row.

* $p < 0.05$

† $p < 0.001$

‡ IC was calculated as TLC minus FRC using body plethsmography measurement and an inspiratory vital capacity maneuver
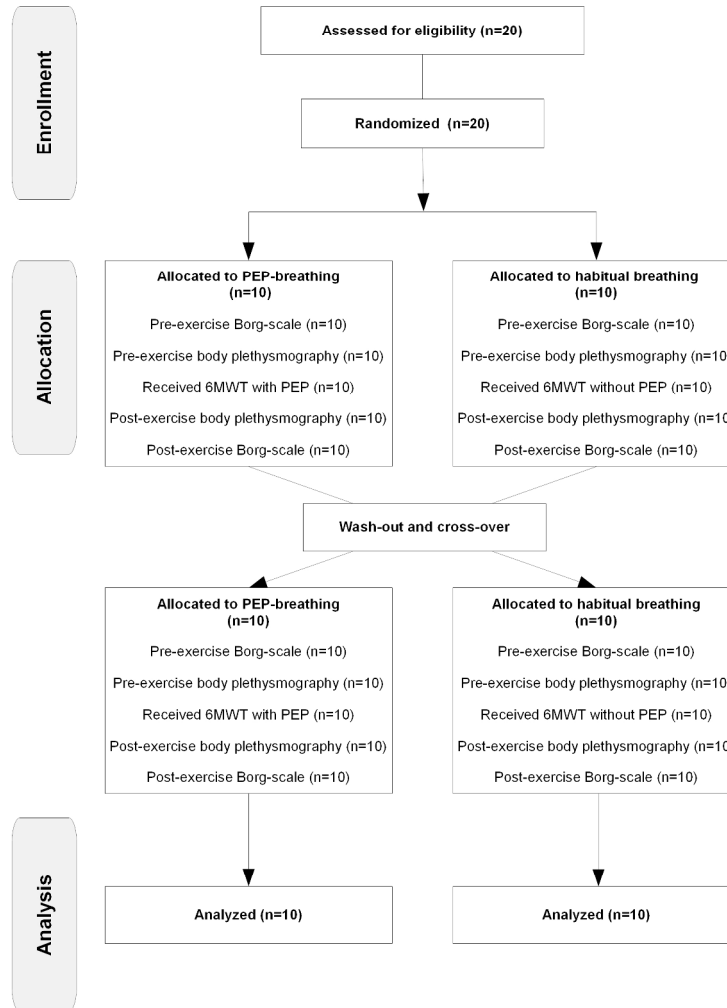
Figure 1 Study protocol flow chart.
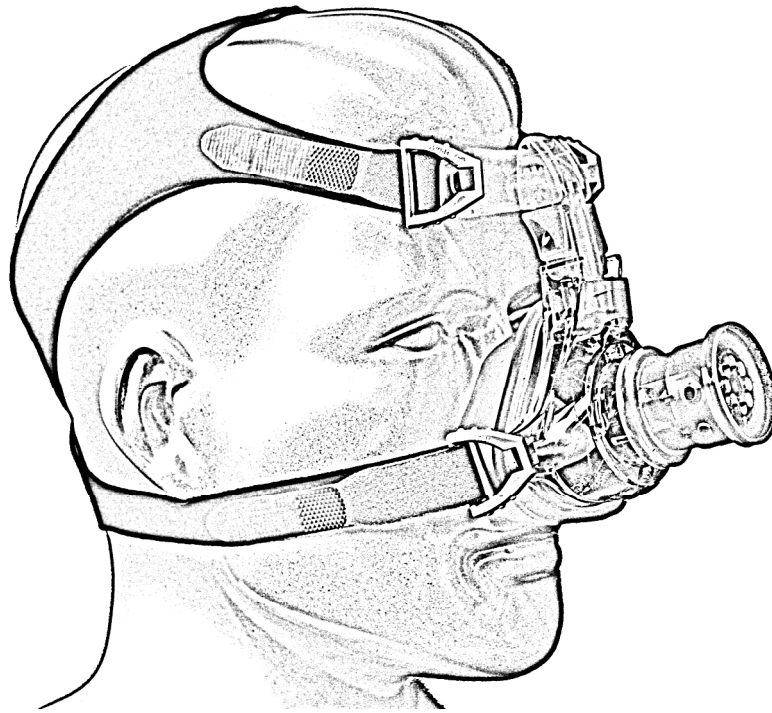884x1251mm (72 x 72 DPI)

Figure 2 Ventilatory Assistance Derived from Expiratory Resistance (VADER) - concept: silicone nasal mask
loaded with a flow-dependent expiratory pressure valve, held in place with a four-point head strap.
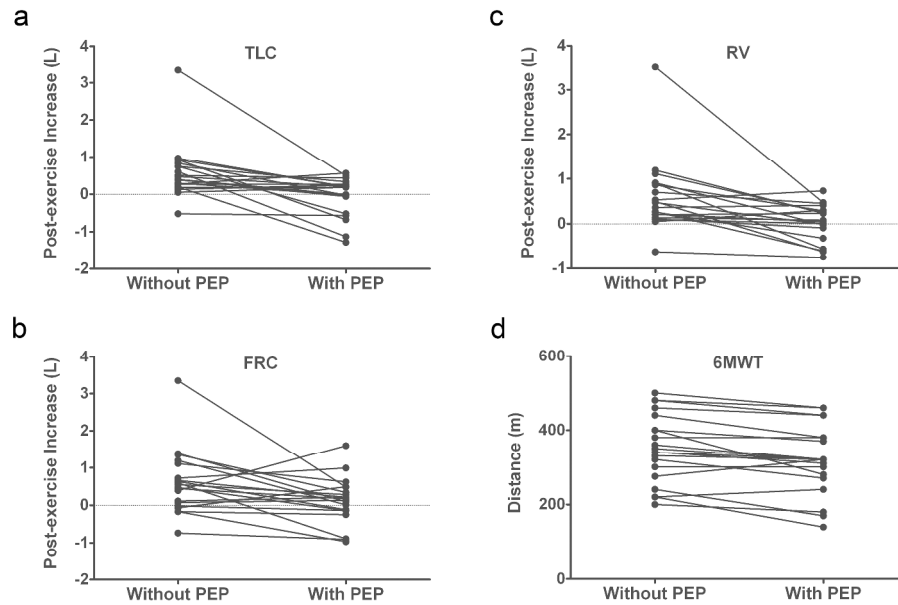1223x914mm (72 x 72 DPI)

Figure 3 Effect of nasal PEP on 6MWT distance and pre-to-post exercise increase in lung volumes in each individual patient (n=20). (a) TLC (difference between means -0.63 ± 0.80 L; p = 0.002). (b) FRC (difference between means -0.48 ± 0.86 L; p = 0.021). (c) RV (difference bewtween means -0.56 ± 0.75 L; p = 0.004). (d) 6MWT-distance (difference between means -30.8 ± 30.0 m; p = 0.001). 370x252mm (300 x 300 DPI)