Effects of Nasal Positive Expiratory Pressure on Dynamic Hyperinflation and 6-Minute Walk Test in Patients With COPD

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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: Twenty subjects (mean ± SD 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 6-min 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-exercise and post-exercise. RESULTS: Differences in mean pre- to post-exercise changes in total lung capacity (−0.63 ± 0.80 L, *P* = .002), functional residual capacity (−0.48 ± 0.86 L, *P* = .021), residual volume (−0.56 ± 0.75 L, *P* = .004), S_{pO_2} (−1.7 ± 3.4%, *P* = .041), and 6MWT distance (−30.8 ± 30.0 m, *P* = .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.* [Respir Care 2014;59(5):699–708. © 2014 Daedalus Enterprises]

Introduction

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 to as dynamic hyperinflation.[2] Studies addressing the lung volumes in COPD patients 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] The benefits of reducing hyperinflation in COPD patients could be demonstrated for a number of therapeutic methods, including lung volume reduction surgery, bronchoscopic lung volume reduction, pharmacotherapy, and rehabilitation pro-

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grams.[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 longstanding 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 air-trapping.[2,14] It is considered to have similarities to pursed lip breathing, a breathing maneuver that is spontaneously adopted by some patients with COPD and is routinely taught as a breathing technique in respiratory physiotherapy.[15,16]

Currently, PEP is often used in pulmonary rehabilitation as a breathing exercise, especially in terms of assistance in the removal of secretions, and can be applied by several techniques, including pursed lip breathing, blow bottle technique, oral high-frequency oscillators, and PEP devices.[16] PEP devices typically can be characterized as either flow-dependent or threshold-dependent, with 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 2 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 be more comfortable compared with an oral PEP device, because they may still be able to speak, drink, or eat while using PEP during daily activities.

QUICK LOOK

Current knowledge

Dynamic hyperinflation in COPD patients is a major cause of exertional dyspnea. Therapies aimed at reducing dynamic hyperinflation may improve exercise tolerance.

What this paper contributes to our knowledge

Positive expiratory pressure applied with a nasal mask and a flow resistance device during walking exercise, reduced dynamic hyperinflation, and was acceptable to patients with mild-to-severe COPD.

Methods

Subjects

Twenty men and women with stable mild-to-severe COPD, determined according to the Global Initiative for Chronic Obstructive Lung Disease criteria,[20] who were able to perform 6-min walk tests (6MWTs) and were free from orthopedic or neurological diseases limiting exercise tolerance, were consecutively recruited from a pulmonary out-patient clinic and included in the trial. Subjects were excluded from the study if they had an acute cardiac illness within the 4 weeks prior to study entry, had known severe bullous emphysema with large bullae, or had 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 a computer-generated randomization list to receive the experimental intervention (breathing with a nasal PEP device during physical exercise), followed by a wash-out period of 2–24 h, and then the control intervention (habitual breathing during physical exercise without PEP device), or vice versa (Fig. 1). Physical exercise was performed according to a standard 6MWT protocol. Before and immediately after exercise, an experienced, nonblinded investigator performed assessment of lung function and Borg dyspnea scale. Subjects received their regular medications in the morning and underwent testing 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 device (PARI PEP System I, 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 that 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 4-point head strap (Fig. 2). No training or practice test was performed with the device.

Spirometry and whole-body plethysmography measurements were performed according to the American Tho-

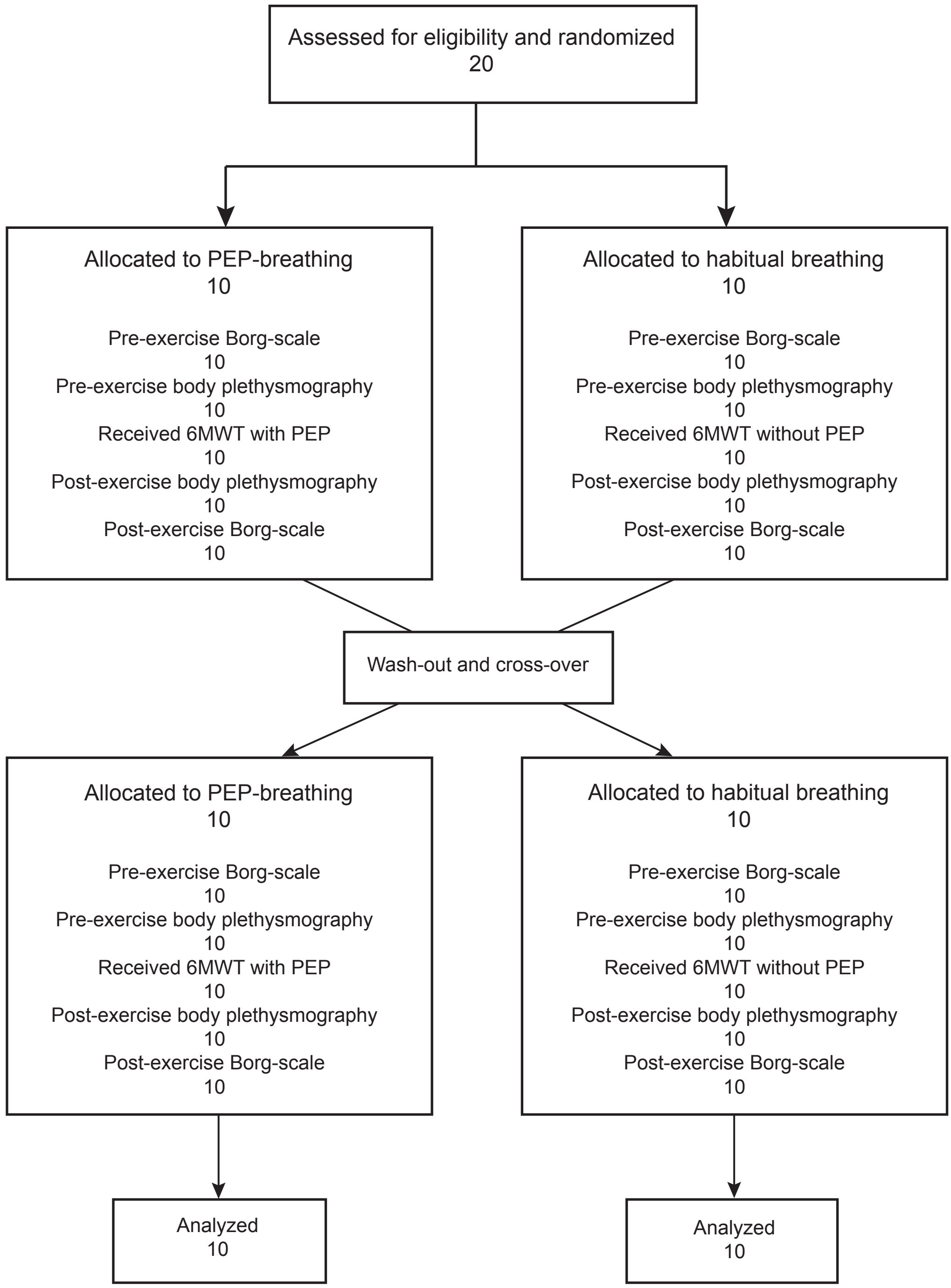

Fig. 1. Study protocol flow chart. PEP = positive expiratory pressure.

racic Society (ATS) and European Respiratory Society (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 functional residual capacity (FRC) measurement, followed by the slow inspiratory vital capacity (VC) maneuver, all performed as "linked" maneuvers.[22,23] Dynamic hyperinflation was measured as an increase in FRC and residual volume (RV) as measured before and after exercise.[24] Values for inspiratory capacity (IC) were calculated as total lung capacity (TLC) − FRC. The predicted normal values for spirometry and lung volumes were those of the European Community of Coal and Steel.[25,26] Pre-

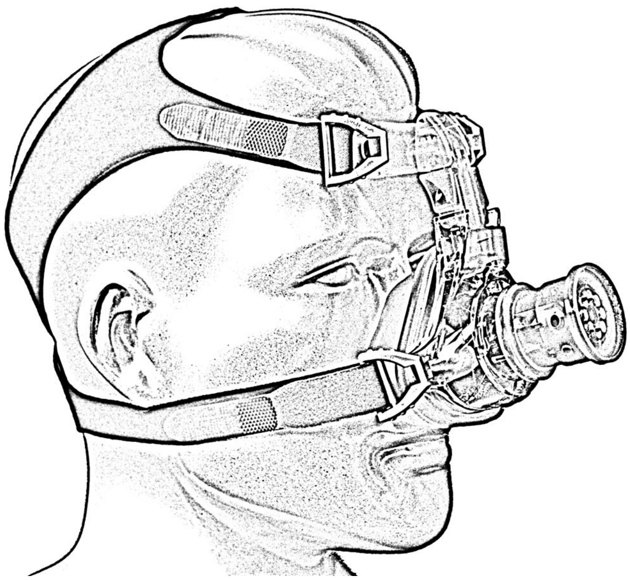

Fig. 2. Ventilatory Assistance Derived from Expiratory Resistance (VADER) concept. A silicone nasal mask is loaded with a flow-dependent expiratory pressure valve and held in place with a 4-point head strap.

dicted normal values for IC were calculated as predicted TLC − predicted FRC.

The 6MWT was administered by an experienced investigator according to the ATS and 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 with the test. Subjects were instructed to walk at a comfortable pace but with the aim of walking as far as possible in 6 min. 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 that 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 breathe habitually, and pursed lip breathing or any other particular breathing techniques were allowed according to how subjects were used to breathing 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 from a previous study[19] to detect an expected difference in FRC variation from pre-exercise to post-exercise of 0.5 L comparing tests with and without PEP. Twenty subjects were needed, assuming an SD of 0.75 L and using a 2-tailed *t* test for paired samples with 80% power and an α-level of 5%. This number of subjects seemed plausible and reasonable compared to sample sizes in 2 similar previously published studies that demonstrated effects of PEP on lung volume variations.[18,19] Lung volume measures pre-exercise 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 the mean ± SD unless otherwise stated. All tests were 2-sided, and a P value $< .05$ was considered statistically significant. All data were analyzed with statistical software (Prism version 5, GraphPad Software, San Diego, California).

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 performed 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. A total 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 min after exercise) without any significant delay due to shortness of breath or other cause and completed lung function measurements with good cooperation. Ten subjects (50%) performed nasal PEP in the first 6MWT followed by habitual breathing in the second 6MWT after the washout period, and 10 subjects (50%) vice versa. Subject characteristics are shown in Table 1. All subjects were treated according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards.[20]

Comparison of pre-exercise lung function values in the experimental and 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 (see Table 2). Accordingly, differences in pre-exercise to post-exercise changes in TLC (−0.63 ± 0.80 L, $P = .002$), FRC (−0.48 ± 0.86 L, $P = .021$), and RV (−0.56 ± 0.75 L, $P = .004$) were statistically significant between the experimental and the control interven-

Table 1. Baseline Data of Subjects

Characteristics	Total (n = 20)
Male sex, n (%)	13 (65)
Age (y)	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)

GOLD = Global Initiative for Chronic Obstructive Lung Disease

tions (see Table 2, Fig. 3). In addition, both interventions showed a significant post-exercise decrease in S_{pO_2} and an increase in the Borg dyspnea scale (see Table 2). A significant increase in post-exercise heart rate was observed in the experimental interventions (see Table 2). Comparison of the pre-exercise to post-exercise decrease in S_{pO_2} between the experimental and the control interventions revealed a small but statistically significant difference (−1.7 ± 3.4%, P = .041), whereas differences in heart rate and Borg scale were not significant (see Table 2). The 6MWT distance was significantly shorter in the experimental interventions (−30.8 ± 30.0 m, P = .001; see Table 2, see Fig. 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-exercise to post-exercise changes in TLC (−0.63 ± 0.80 L, P = .002), FRC (−0.48 ± 0.86 L, P = .021), and RV (−0.56 ± 0.75 L, P = .004) could be observed compared with walking exercise without nasal PEP.

A recent study[19] 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. In the cited study,[19] subjects were preselected on the basis of a pre-exercise to post-exercise decrease in IC of at least 15% and underwent, after a 24-h suspension of treatment with long-acting bronchodilators followed by the pre-exercise administration of short-acting bronchodilators, two 20-min treadmill exercise tests without and with PEP in a sequential study protocol without crossover. 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 the effects on IC and FEV_1 were not significant. Subjects in our study were not preselected, had different baseline characteristics including a more intense smoking exposure (41.4 vs 9.6 pack-years), continued their regular bronchodilator 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, crossover protocol.[18] In both of the cited 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 − FRC immediately before and after each intervention. We hypothesize that this difference in lung function procedures might be a possible reason why the 2 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 the 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) methods (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 with 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 2 methodologies remain uncertain.[23,28] However, the cited study[28] did not include post-exercise lung function measurements, and therefore the 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 2 methodologies may become even more pronounced when FRC is shifted closer to TLC due to dy-

Table 2. Assessed Parameters Before and After Exercise With and Without Nasal PEP

Parameters	Comparison Between Interventions				Difference Within Interventions*		Difference Between Interventions*	
	Pre-Exercise		Post-Exercise					
	Without PEP	With PEP	Without PEP	With PEP	Without PEP	With PEP	With PEP − Without PEP	*P*
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								
L	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
S_{pO_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 (b/min)	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 score	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)	NA	NA	352 ± 92	321 ± 93†	NA	NA	−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.
* Post-exercise − pre-exercise.
† $P < .05$.
‡ IC was calculated as TLC minus FRC using body plethysmography measurement and an inspiratory vital capacity maneuver.
§ $P < .001$.
PEP = positive expiratory pressure
TLC = total lung capacity
FRC = functional residual capacity
RV = residual volume
IC = inspiratory capacity
HR = heart rate
NA = not applicable

namic 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 study 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 IC maneuver is preferred for measuring 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 device during exercise when body plethysmography is not practicable.[29,30] In some studies, novel methods including optoelectronic plethysmography or inert gas dilution techniques are occasionally used.[31-33] How-

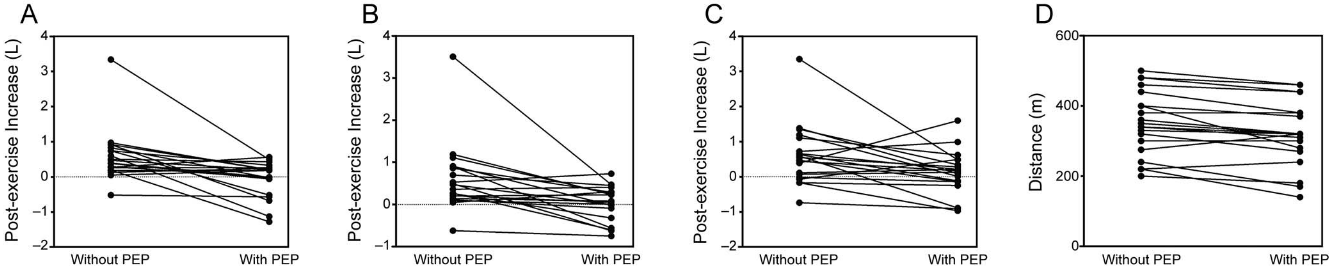

Fig. 3. Effect of nasal positive expiratory pressure (PEP) on 6-min walk test (6MWT) distance and pre- to post-exercise increase in lung volumes in each individual subject (n = 20). A: Total lung capacity (difference between means −0.63 ± 0.80 L, P = .002). B: Residual volume (difference between means −0.56 ± 0.75 L, P = .004). C: Functional residual capacity (difference between means −0.48 ± 0.86 L, P = .021). D: 6MWT distance (difference between means −30.8 ± 30.0 m, P = .001). PEP = positive expiratory pressure.

ever, body plethysmography remains the accepted 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 post-exercise TLC values did not remain constant, as previously assumed for TLC during submaximal exercise, but showed a marked increase, which is reminiscent of results from a previous study.[19] That assumption was based on a 1980 study[34] of 6 male subjects with evidence of air-flow obstruction, who underwent lung function measurements during exercise in a body plethysmograph containing pedals of a cycle ergometer. However, the number of subjects in that study[34] was smaller than in ours, and unlike the procedure used in our study, which involved an inspiratory VC maneuver at rest immediately after exercise, that study used an expiratory VC 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 the administration of salbutamol that were demonstrated in previous studies in patients with severe hyperinflation.[35,36] Questions arise of whether the reduction of dynamic hyperinflation observed with nasal PEP is similar to that observed with mechanisms provoking a reduction in hyperinflation after pharmacologic bronchodilation, and whether we can continue to accept the assumption that TLC does not change during physical exercise in patients with COPD when they are breathing without any imposed nasal or oral flow resistance, 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 indicates the need for further and detailed studies of the changes in TLC during and after exercise in patients with COPD and of the potential diagnostic benefit of post-exercise body plethysmography.

There are some other major issues in the current research regarding the use of PEP in COPD patients. 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 to some extent.[33]

The second point is that the methods of exposure to physical exercise as well as the methods used 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,[37,38] this test evoked effectively dynamic hyperinflation in our study. Although the 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 m. 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 S_{pO_2} 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 assessment of endurance performance. In fact, recent reports[39,40] 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. 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 an advantage from their improved ventilatory capacity.[40] Further studies are therefore needed to address 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 device might be superior to the more elaborate, constant-pressure, threshold-dependent type of PEP devices, which could cause an abrupt interruption of expiratory air flow 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 precise indication of extrinsic PEEP 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 in this concept, and with the objective of being able to more clearly distinguish the purpose and therapeutic method presented in this study from active, noninvasive ventilation (expiratory positive airway pressure, EPAP)[41] and airway clearance physiotherapy (ie, positive expiratory pressure, PEP),[42] we propose naming this concept of respiratory support based on expiratory flow resistance "ventilatory assistance derived from expiratory resistance" (VADER).

The underlying mechanism that is 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 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 equal pressure point 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 PEP. A study[44] of expiratory positive airway pressure in climbers with high-altitude pulmonary edema at rest and healthy climbers during exercise at 4,400 m demonstrated an improvement in gas exchange and suggested expiratory positive airway pressure as an effective temporizing measure for victims of high-altitude pulmonary edema.

Despite decades of research, the role of breathing techniques in patients with COPD remains a topic of debate.[45,46] A recent study[47] found a shift in breathing preferences toward mouth breathing during exercise in subjects with COPD compared with healthy subjects. 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[48] demonstrated that in subjects with COPD spontaneous pursed lip breathing resulted in increased endurance performance compared with obligate open mouth breathing. 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 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 methodological 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 volume, and breathing effort were not assessed systematically because 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 patients with a wide range of disease severity as well as patients with endobronchial coils or valves. Although this heterogeneous sample allowed demonstration of the idea 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 improvement could overcome the inconveniences of the device and vice versa. Future studies should therefore focus on more homogeneous target populations to avoid underestimation 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 physical activities of daily life. 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 to address improvements in endurance performance under daily, regular application of nasal PEP in patients with COPD.

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