Original Article

Airway Clearance with Expiratory Flow Accelerator Technology: Effectiveness of the "Free Aspire" Device in Patients with Severe COPD

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Abstract

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is associated with a higher risk of pulmonary infections. This risk not only negatively affects patients' quality of life but also increases social and health costs. Hence, there is a need for an effective rehabilitative treatment including airway clearance. The aim of this pilot study was to evaluate the efficacy of a new tool for bronchial clearance based on expiratory flow accelerator (EFA) technology compared with positive expiratory pressure (PEP) treatment.

MATERIALS AND METHODS: Twenty stable patients with COPD, Global Initiative for Chronic Obstructive Lung Disease 3–4 stage, were enrolled and allocated to treatment with EFA or Bubble-PEP (BP) for 20 days during a pulmonary rehabilitation program. At baseline and the end of treatment, the following parameters were measured: arterial blood gases (ABG); respiratory function, including peak cough expiratory flow (PCEF), maximal inspiratory pressure (MIP), and maximal expiratory pressure exercise capacity using the 6-minute walk test (6MWT), dyspnea using the Medical Research Council scale, and quality of life using the St. George's Respiratory Questionnaire.

RESULTS: Expiratory flow accelerator showed a significant pre- and post-improvement in ABG and a significantly greater improvement than BP in PCEF, MIP, and 6MWT post-treatment.

CONCLUSION: Expiratory flow accelerator is a valid device compared with BP as an adjunctive therapy for the treatment of patients with severe COPD.

KEYWORDS: Chest physiotherapy, chronic obstructive pulmonary disease, expiratory flow accelerator technology, positive expiratory pressure

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive lung disease characterized by chronic airflow limitation caused by a mixture of diseases of the small airways and parenchymal destruction [1]. Chronic inflammation induces structural changes, narrows the small airways, and leads to the destruction of lung parenchyma [2]. Narrowing and leakage of small airways may also contribute to airflow limitation and mucociliary malfunction [1-3]. Several studies have highlighted the fact that hypersecretive patients with impaired bronchial clearance are more exposed to pulmonary infections [3-6]. This risk negatively impacts not only patients' quality of life but also social and healthcare costs [1-6]. The need for an efficient rehabilitative treatment aimed at bronchial secretion clearance has been established [7, 8]. Airway clearance techniques (ACTs) are techniques involving the external application of forces to clear pulmonary secretions from the lung. There are many types of ACTs used in clinical practice including conventional chest physiotherapy (postural drainage and percussion), breathing exercises, positive expiratory pressure (PEP) devices, and mechanical devices that are applied externally (e.g., high-frequency chest wall oscillation). ACTs may affect sputum transport by relative changes of lung volume, gas flow, pulmonary pressure, and compressive forces [9]. PEP increases sputum and facilitates expectoration [10, 11]. There is evidence supporting the effects of these techniques on mucus clearance in patients with COPD [9, 12].

A new type of ACT expiratory flow accelerator (EFA) is utilized by the device introduced in 2009, named Free Aspire® (MPR-Legnano, Italy), and is based on years of research on the respiratory and clearance system. Removal of respiratory secretions via the creation of a "vacuum" effect by expiratory flow acceleration has been found to be effective and safe in patients with COPD and neuromuscular diseases, as well as in pediatric patients [13, 14]. Free Aspire (Figure 1) is an Italian patented device using EFA technology, designed for the non-invasive removal of mucus secretions in adult and pediatric patients with impaired capacity to cough or expectorate [13, 14]. Several studies [15-19] showed that EFA is one of the fundamental mechanism for improving clearance [17-19].

This technology favors the passive expiratory flow acceleration during a tidal volume breath, without generating negative pressures in the site interfacing the airways. The individual, while spontaneously breathing, can be connected to the machine through a mask or a mouthpiece. The subject is asked to breathe through the mouthpiece (with a nose clip on the nose) and, if on oxygen therapy, to use the mask with a connection to the oxygen source. The airflow generated by a compressor is directed to a valve, through which the subject breathes at tidal volume. By adjusting the valve, the expired air is accelerated due to the Venturi effect [13, 14]. The aim of the present study was to evaluate the effectiveness of EFA in improving the bronchial clearance in patients with severe COPD, in comparison with a PEP system, in the therapist made bubble-PEP (BP).

MATERIAL AND METHODS

Study Design
This was a pilot randomized parallel clinical trial. The study was conducted at the outpatient clinic of the Pulmonology and Rehabilitation Unit at Cuasso al Monte Hospital, Italy from August 1, 2016 to November 30, 2016. The study was approved by the local ethics committee and registered at the Chinese Clinical Trial as ChiCTR-INR-16009518 in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the patients to participate in the trial. This clinical trial included stable patients with severe COPD, with daily chronic sputum of ≥10 mL over the previous year, who were not practicing any regular ACT or pulmonary rehabilitation program.

Patients
Thirty-eight patients with severe stable COPD were screened. Eighteen patients who did not fulfill the inclusion criteria were excluded from the study (FEV_1 >50% of predict). A total of 20 patients were enrolled into the study (Figure 2). COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and patients were assessed as having severe to very severe COPD stage 3–4 (C–D on the COPD patient staging assessment tool) [2, 7, 8]. All patients were under treatment with a combination of long-

acting beta-agonists and long-acting muscarinic antagonists. No changes in therapy were made in the month prior to the study. Inclusion criteria were COPD GOLD stage 3–4 (C and D), bronchial encumbrance as defined by the patient medical history, clinical examination, and chest auscultation. Exclusion criteria were presence of tracheostomy, previously diagnosed bronchial asthma, bronchiectasis, exacerbations in the previous 2 months, cardiac arrhythmias, respiratory failure, mechanical ventilation, recent spontaneous pneumothorax, costal fractures or orthopedic impairments, inability to fill out the questionnaire, and absence of written informed consent. Participants who met the inclusion criteria were allocated to one of two groups following a randomization schedule generated by an independent statistician using an online random sequence generator from http://www.randomization.com. To prevent selection bias, the allocation sequence was hidden from the investigators and patients in numbered, opaque sealed envelopes. The patients and physiotherapists were not blinded to patients' allocation group. Each group of patients was treated by a different chest physiotherapist. The statistician, not involved in the study, as well as the chest physicians were blinded to treatment assignments.

Protocol

Baseline Assessment
At baseline, patients' demographic, anthropometric, respiratory, and cardiac parameters were recorded (respiratory rate, heart rate, and oxygen saturation). In addition, patients were performed respiratory function tests: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC%, total lung capacity (TLC), residual volume (RV), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), peak cough expiratory flow (PCEF), arterial blood gases (ABG) (PaO_2, $PaCO_2$, and pH), exercise capacity using the 6-minute walk test (6MWT), and dyspnea using the Medical Research Council (MRC) scale. Pulmonary function tests were performed using a computed body plethysmography (VMax 20 PFT Sensor Medics, Yorba Linda, CA, USA) according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [18]. Inspiratory muscle strength was assessed by measuring the

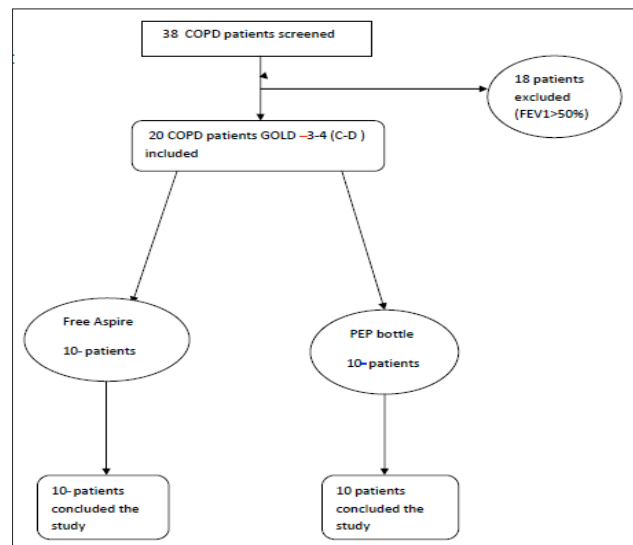**Figure 1.** Efa device (it was used with the permission of MPR company)

Figure 2. Study flow chart
COPD: chronic obstructive pulmonary disease; PEP: positive expiratory pressure

MIP at RV. Expiratory muscle strength was also measured at MEP at TLC. PCEF was used to evaluate cough effectiveness. The best value obtained from at least three efforts was used. All measurements were obtained with the patient in the upright position [19]. Functional exercise capacity was measured by the 6MWT according to the ATS Guidelines [20]. The patients were guided to walk back and forth in a 30 m corridor. Modified Borg Dyspnea Scale, respiratory rate, and heart rate were recorded along with the total walking distance at the end of 6 min. At least two tests were performed, and the best values were recorded [21]. The MRC scale [22] was used to evaluate the variations in dyspnea, and the St. George's Respiratory Questionnaire (SGRQ) [23] was used to evaluate the quality of life.

Rehabilitation Program
The whole sample (experimental and control groups) followed a supervised pulmonary rehabilitation protocol (PRP) consisting of daily exercise sessions lasting 30 min, 5 days/week, for a total of 20 days. The PRP included endurance training consisting of walking on a treadmill or along a corridor twice a day. Exercise programs and workload intensity were targeted at 60%–85% of the maximal workload information gathered from 6MWT. The PRP sessions included upper and lower limb strengthening and breathing exercises (0.5–1 kg dumbbell/Cosfer dumbbell sets) and cycle ergometer and training for 30 min. Workload intensity was increased in accordance with each patient's improvement [24]. In addition, the EFA group received three supervised physiotherapy sessions with the EFA device, and the PEP group received three supervised physiotherapy sessions with the PEP bottle. Each group was followed by a different chest physiotherapist who provided supervised physiotherapy intervention.

EFA Group
Expiratory flow accelerator (Free Aspire®) utilization lasted 30 min twice a day and followed a protocol previously published [12, 13]. The session was performed with the patient in the right and left lateral recumbent positions for 15 min for each side.

BP Group
Bubble-PEP utilization was performed using 5 cm of water [25-27]. The patient was asked to breathe slowly and continuously, with a tele-inspiratory apnea of 3–5 s duration, followed by a continuous and non-forced expiration, strong enough to produce bubbles in the water (visual and auditory feedbacks). Each session lasted 30 min and was performed with the patient in the right and left lateral recumbent positions twice a day [25-27]. Both of the two devices are checked and suitable in patients with emphysema with or without bullae [28, 29].

Outcomes and Measurements
The primary outcomes were changes in:

- ABG (PaO_2, $PaCO_2$, and pH),

- PCEF.

The secondary outcomes were changes in:

- Respiratory muscle strength: MIP and MEP,

- Exercise capacity: 6MWT,

- Dyspnea evaluation: MRC scale.

Quality of life was evaluated at the end of treatment with the SGRQ.

Statistical Analysis
The statistical analysis was performed using MedCalc Statistical Software, version 17.5 (©1993–2017, MedCalc Software Bvba, Ostend, Belgium; https://www.medcalc.org; 2017). Shapiro–Wilk test was used to analyze data with normal distribution. Mann–Whitney U test was used for non-parametric data, and Student's t-test was used for parametric data. Student's t-test was used to determine the level of significance of the difference between the pre- and post-treatment measurements. Between-group differences were expressed as mean differences with 95% confidence interval. A p-value <0.05

Table 1. Baseline characteristics of the two study groups[a]

	PEP bottle group (n=10)	FREE aspire group (n=10)	p
Age years	70.3±8.03	74.7±6.09	0.18
FVC, L (%)	48.06±12.88	48.05±13.06	0.09
FEV_1, L (%)	190±39.16	166±54.81	0.21
FEV_1/FVC (%)	48.06±12.88	47.05±13.06	0.28
TLC, L (%)	316.23±124.22	287.47±192.48	0.27
RV, L (%)	48.06±12.88	48.05±13.06	0.08
PCEF L/min	190±39.16	166±54.81	0.27
MRC scale (0-4)	3.3±1.16	2.3±1.34	0.07
6MWT, m	316.23±124.22	287.47±192.48	0.32
Respiratory rate	15±2	13±3	0.11
Heart rate	79±6	83±6	0.09
Oxygen saturation %	94±2	93±1	0.18

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; TLC: total lung capacity; RV: residual volume; PCEF: peak cough expiratory flow; MRC: medical research council scale; 6MWT: 6-minute walk test; L: liters; m: meters
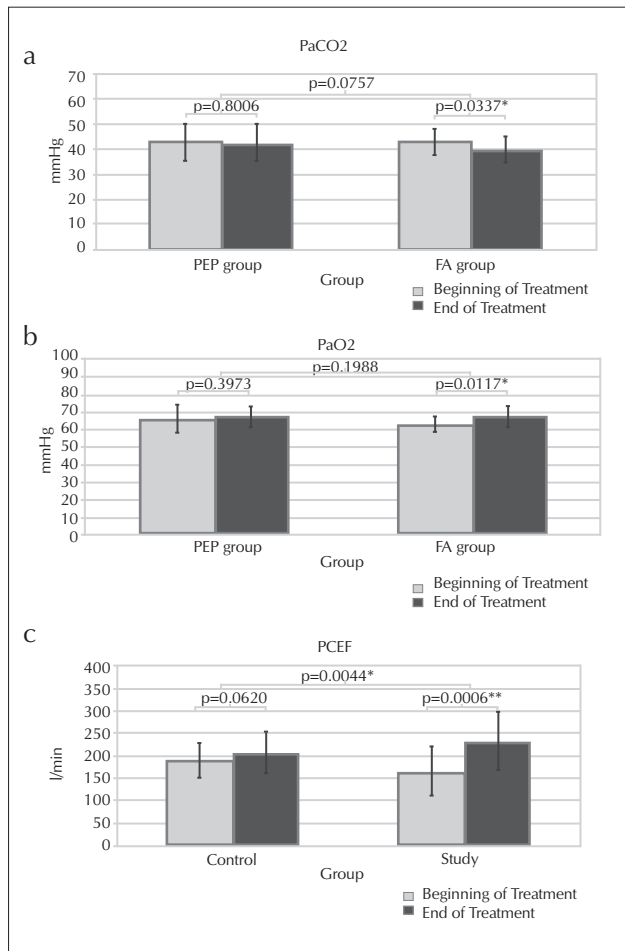[a]Data are expressed as mean ± standard deviation

Figure 3.a-c. Results for primary outcomes
PCEF: peak cough expiratory flow; PaO$_2$: arterial partial pressure of oxygen; PaCO$_2$: arterial pressure of carbon dioxide; FEV$_1$: forced expiratory volume in 1 s

was considered as significant. The statistical power analysis was not performed because a small sample of patients was considered in this pilot study, required to have a preliminary estimate on the results. However, selecting a maximum level of significance equal to 0.05 allows to ensure a high level of protection from the possibility to make type I error.

RESULTS

The two groups were matched with respect to age and disease severity, as well as respiratory function parameters. The baseline characteristics of the two groups are reported in Table 1.

Primary Outcomes
Arterial blood gases showed a significant pre- and post-improvement in EFA for both PaO$_2$ (pre: 62.92 (4.70) mmHg vs. post: 67.36 (6.01) mmHg, p=0.0117) and PaCO$_2$ (pre: 42.97 (5.37) mmHg vs. post: 40.09 (4.99) mmHg, p=0.0337), but the intergroup difference was not significant (Figure 3a-c). The change in PCEF between the start and end of treatment was greater in EFA (166 (54.81) cm H$_2$O vs. 233 (65.16) cm H$_2$O, p=0.0006) than in BP (190 (39.16) cm H$_2$O vs. 206.90 (46.98) cm H$_2$O, p=0.0620), and the difference between the groups was significant (p=0.0044) (Table 2).

Secondary Outcomes
Expiratory flow accelerator showed larger variations in MIP and MEP than BP (Figure 4a-c). In EFA, MIP significantly increased (5.89 (2.3) cm H$_2$O vs. 7.53 (2.38) cm H$_2$O, p=0.0153), whereas there was no variation in BP. The difference between the two groups was significant (p=0.0191). MEP increased in both groups (9.37 (2.22) vs. 10.62 (3.03) in the BP group and 9.03 (3.49) vs. 11.12 (3.19) in the EFA

Table 2. Comparison of outcome parameters within each group (pre-post) and between the two groups

Outcome	Groups				Differences within groups		Difference between group
	Pre		Post				
	PEP bottle (n=10)	Free aspire (n=10)	PEP bottle (n=10)	Free aspire (n=10)	PEP bottle	Free aspire	Free aspire Vs PEP bottle
PaO$_2$	66.05	62.92	67.33	67.36	0.3973	0.0117**	0.1988
(mmHg)	(8.11)	(4.70)	(6.38)	(6.01)			
PaCO$_2$	42.82	42.97	42.60	40.09	0.8006	0.0337*	0.0757
(mmHg)	(7.51)	(5.37)	(7.62)	(4.99)			
PCEF	190.00	166	206.90	233	0.0620	0.0006**	0.0044**
(cmH$_2$O)	(39.16)	(54.81)	(46.98)	(65.16)			
MEP	9.37	9.03	10.62	11.12	0.2413	0.1306	0.1212
(cmH$_2$O)	(2.22)	(3.49)	(3.03)	(3.19)			
MEP	7.28	5.89	6.85	7.53	0.4165	0.0153*	0.0191*
(cmH$_2$O)	(1.43)	(2.31)	(1.15)	(2.38)			
6MWT	316.23	287.47	331.43	373.00	0.8798	0.1509	0.0492*
(mt)	(124.22)	(192.75)	(113.12)	(297.43)			
MRC	3.30	2.30	2.40	1.10	0.0521	0.0466*	0.701
	(1.16)	(1.34)	(1.07)	(0.99)			

paO$_2$: arterial partial pressure of oxygen; paCO$_2$: arterial pressure of carbon dioxide; PCEF: peak cough expiratory flow; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; 6MWT: 6-min walk test; MRC: medical research council dyspnea scale
*Significantly different p<0.05 (95% confidence interval); **Significantly different p<0.01 (95% confidence interval)
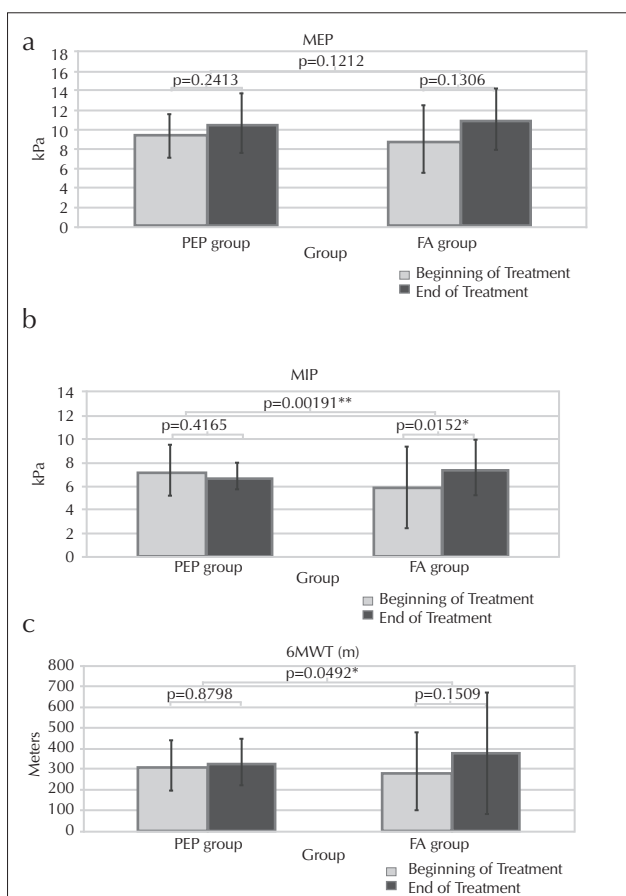
Figure 4.a-c. Results for secondary outcomes
PEP: positive expiratory pressure; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; 6MWT: 6-minute walk test

group) but without a significant difference between pre–post within each group or between the groups. The 6MWT demonstrated a difference between the groups; patients in EFA showed an average increase of 86 m (+92.99%, p=0.1509) in the distance walked compared with baseline, whereas those in BP showed only a 15 m increase (+17.37%, p=0.8798). The difference between the two groups was significant (p=0.0492). Dyspnea decreased in both groups without a significant difference between the groups (p=0.70), although in EFA the pre–post difference was significant (p=0.0466). EFA showed a lower impact of disease on the quality of life than BP, with the average score on the SGRQ being 30.73±9.61 in EFA versus 34.06±9.98 in BP. A comparison of the outcomes measured at the start and end of treatment is summarized in Table 2.

DISCUSSION

Airway obstruction is one of the pathological components of diverse chronic obstructive airway diseases. Therefore, ACTs are regularly used in patients who have these diseases. ACTs aim to decrease airway resistance, improve gas exchange, and reduce respiratory load by improving airway clearance. While its efficiency is often debated, ACTs remain widely prescribed in the treatment of many chronic obstructive airway diseases [30]. Given the heterogeneity of COPD, it is likely that there is a cohort of patients who can benefit from the prescription of an ACT. Little attention has been focused on the physiological mechanisms of individual ACTS in COPD.

PEP is an ACT that works by splitting open collapse airways, and its use is particularly suited in patients where airway collapsibility is suspected. PEP is well suited for patients with increased pulmonary compliance or marked pulmonary hyperinflation [29, 31]. This preliminary study compared an EFA technology tool with a widely used PEP ACT (BP) as an adjunctive therapy in patients with severe COPD. The results showed particularly improved gas exchanges for EFA, probably due to a better airway clearance and pulmonary hygiene. Even if EFA does not apply a positive pressure, it may be beneficial to improve the recruitment of non-ventilated areas; thus, the ventilation/perfusion rate was improved, as confirmed by the improvement of ABG (PaO_2 and $PaCO_2$). Indeed, the ABG variation between the beginning and end of treatment was significant only in the EFA group; $PaCO_2$ decreased and PaO_2 increased significantly. We also observed in the EFA group an improvement in MIP and PCEF, which may be related to a reduction of the bronchial intrinsic resistances and work of breathing (WOB) [19, 31]. This can explain the better performance of respiratory muscles (MIP) and cough efficacy (PCEF), which resulted significantly improved in the EFA group. The improvement of PCEF not only depends on expiratory muscle action but also depends on the generation of a sufficient preliminary volume obtained through a more efficient inspiration [32]. Therefore, the reduction of WOB is one of the key elements in reducing dyspnea and increasing exercise tolerance in patients with COPD. A positive trend was also found and subsequently in the perception of dyspnea, but no significant intergroup difference between EFA and BP. Further investigation is needed to confirm that EFA, by improving the airway clearance and reducing WOB, can have an effect on reducing dyspnea and its impact on activities of daily life (ADL). Studies have shown that an improved respiratory performance with respect to a lower degree of obstruction and increased airflow influences ADL and health-related quality of life (HRQoL) [12, 16]. Patients in the EFA group also showed a significant increase in the distance walked on the 6MWT, although a greater variability of data was observed in this group. Regarding the HRQoL measured by SGRQ at the end of treatment in both groups, the EFA group showed a lesser impact of the disease on HRQoL. Several studies using similar devices were published in the last few years [29, 33-35]. The conclusions of these studies have been consistent with our study; ACTs reduce dyspnea and cough through the modification of lung functional parameters. Further consideration about EFA is required. In contrast to other devices, the breathing required during its use did not call for any additional respiratory effort or physical or mental effort. This constitutes an important advantage because most clearance techniques require the active participation of the patient, and when this is not possible, the use of invasive and uncomfortable techniques is necessary [9]. As a pilot preliminary study, the comparative analysis between the two ACTs has some limitations: the small number of patients, the lack of statistical power analysis, and a limited number of outcomes analyzed (e.g., changes in volume of produced sputum and patient-reported symptoms, such as encumbrance or cough). In addition, regarding the short-term effects of the techniques, no inferences can be made about the maintenance of these results in the long term.

This pilot study investigated the efficacy of EFA technology compared with PEP technique in facilitating airway clearance in patients with severe COPD as an adjunctive therapy of a pulmonary rehabilitation program. The EFA group showed an improvement in gas exchange with use of the EFA device and significant differences compared with BP in the increase of expiratory cough flow, respiratory muscle strength, exercise capacity, and perceived dyspnea. Based on these findings, we conclude that the use of EFA can be included with benefit in a program of respiratory rehabilitation for patients with COPD with severe obstruction and ineffective cough. However, further studies in a broader population sample are necessary to statistically confirm and extend our findings. The results of this preliminary study will be used to determine the sample size required for the main definitive trial with a suitable statistical power.

REFERENCES

1. National Institute for Clinical Excellence (NICE): Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE 2018, p.5-60.
2. GOLD Global Initiative for Chronic Obstructive Lung Disease 2018, p.1-123.
3. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46. **[CrossRef]**
4. Van Durme YMTA, Verhamme KMC, Stijnen T, et al. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. Chest 2009;135:368-77. **[CrossRef]**
5. Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J 2006;27:188-207. **[CrossRef]**
6. Celli BR, Halbert RJ, Isonaka S, et al. Population impact of different definitions of airways obstruction. Eur Respir J 2003;22:268-73. **[CrossRef]**
7. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011;155:179-91. **[CrossRef]**
8. Russi EW, Karrer W, Brutsche M, et al. Diagnosis and management of chronic obstructive pulmonary disease: the Swiss guidelines. Official guidelines of the Swiss Respiratory Society. Respiration 2013;85:160-74. **[CrossRef]**
9. Osadnik CR, McDonald CF, Jones AP, et al. Airway clearance techniques for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012;3:CD008328. **[CrossRef]**
10. Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. Cochrane Database Syst Rev 2015; CD008351. **[CrossRef]**
11. Hill K, Patman S, Brooks D. Effect of airway clearance techniques in patients experiencing an acute exacerbation of chronic obstructive pulmonary disease: a systematic review. Chron Respir Dis 2010;7:9-17 **[CrossRef]**
12. Garuti G, Verucchi E, Fanelli I, et al. Management of bronchial secretions with FREE ASPIRE in children with cerebral palsy: impact on clinical outcomes and healthcare resources. Ital J Pediatrics 2016;42:7 **[CrossRef]**
13. Bertelli L, Di Nardo GD, Cazzato S, et al. Free-Aspire: a new device for the management of airway clearance in patients with ineffective cough. Pediatric Rep 2017;9:7270. **[CrossRef]**
14. Kim CS, Rodriguez CR, Eldridge MA, et al. Criteria for mucus transport in the airways by two-phase gas-liquid flow mechanism. J Appl Physiol 1986;60:901-907. **[CrossRef]**
15. Kim CS, Iglesias AJ, Sackner MA. Mucus clearance by two phase gas-liquid flow mechanism: asymmetric periodic flow model. J Appl Physiol 1987;62:959-71. **[CrossRef]**
16. Venturelli E, Tonelli R, Righi D, et al. Efficacy of Vakum technology in patients with chronic hypersecretion: a multicenter randomized clinical trial. Abstract at 5th European Respiratory Care Congress March 26-28, 2015, Lyon.
17. D'Abrosca F, Belli S, Carai C, et al. Noninvasive management of tracheobronchial secretions in tracheostomized patients. Abstract at 5th European Respiratory Care Congress March 26-28, 2015,Lyon.
18. Miller MR, Hankinson J, Brusasco V, et al. Standardization of spirometry. Eur Respir J 2005;26:319-38. **[CrossRef]**
19. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Resp Crit Care Med 2002;166:518-624. **[CrossRef]**
20. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Resp Crit Care Med 2002;166:111-7. **[CrossRef]**
21. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American thoracic Society technical standard: field walking test in chronic respiratory disease. Eur Respir J 201:4;1428-46. **[CrossRef]**
22. Özmen İ, Yıldırım E, Öztürk M, et al. Pulmonary rehabilitation reduces emergency admission and hospitalization rates of patients with chronic respiratory diseases. Turk Thorac 2018;19:170-5. **[CrossRef]**
23. Stenton C. The MRC breathlessness scale. Occup Med 2008;58:226-7. **[CrossRef]**
24. Jones PW, Quirk FH, Baveystock CM, et al. A Self-complete Measure of Health Status for Chronic Airflow Limitation: The St. George's Respiratory Questionnaire. Am J Resp Crit Care Med 1992;145:1321-7. **[CrossRef]**
25. Santos MD, Milross MA, Eisenhuth JP, et al. Tubing internal diameter affects the pressure and oscillation frequencies generated by the therapist-made bubble-positive expiratory pressure device. Physioth Theory Pract 2018;13:1-7. **[CrossRef]**
26. Santos MD. Therapist-made bubble positive expiratory pressure : a survey of physiotherapists in Australia. Cardiopulm Phys Ther J 2016;27:3-10. **[CrossRef]**

27. Mestriner RG, Fernandes RO, Steffen LC, et al. Optimum design parameters for a therapist-constructed positive-expiratory-pressure therapy bottle device. Respir Care 2009;54:504-8.

28. Fagevik Olsén M, Lannefors L, Westerdahl E. Positive expiratory pressure - Common clinical applications and physiological effects. Respir Med 2015;109:297-307. **[CrossRef]**

29. Nicolini A, Mascardi V, Grecchi B, et al. Comparison of effectiveness of temporary expiratory pressure versus oscillatory positive expiratory pressure in severe COPD patients. Clin Resp J 2018;12:1274-82. **[CrossRef]**

30. Reychler G, Debier E, Contal O, et al. Intrapulmonary Percussive Ventilation as an Airway Clearance Technique in Subjects With Chronic Obstructive Airway Diseases. Respir Care 2018;63:620-31. **[CrossRef]**

31. Hess DR. Airway clearance: physiology, pharmacology, techniques, and practice. Respir Care 2007;52:1392-6.

32. McCool FD. Global physiology and pathophysiology of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129(Suppl 1):48S-53S. **[CrossRef]**

33. Liao LY, Chen KM, Chung WS, et al. Efficacy of respiratory rehabilitation exercise training package in hospitalized elderly patients with acute exacerbations of COPD : a randomized control trial. Int J Chron Obstruct Pulmon Dis 2015;10:1703-9. **[CrossRef]**

34. Ides K, Vos W, De Becker L, et al. Acute effects of intrapulmonary percussive ventilation in COPD patients assessed by using conventional parameters and a novel computational fluid dynamic technique. Int J Chron Obstruct Pulmon Dis 2012;7:667-71. **[CrossRef]**

35. Kodric M, Garuti G, Colomban M, et al. The effectiveness of bronchial drainage technique (ELTGOL) in COPD exacerbations. Respirology 2009;14:424-8. **[CrossRef]**