Positive Expiratory Pressure via Mask Does Not Improve Ventilation Inhomogeneity More than Huffing and Coughing in Individuals with Stable Chronic Obstructive Pulmonary Disease and Chronic Sputum Expectoration

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Key Words

Chronic obstructive pulmonary disease · Ventilation heterogeneity · Airway clearance · Physical therapy modalities · Positive expiratory pressure

Abstract

Background: Positive expiratory pressure (PEP) has been used to promote airway clearance in individuals with chronic obstructive pulmonary disease (COPD) for many years; however, its mechanism of action and benefits are unclear. Previous authors have suggested that PEP improves collateral ventilation via changes in lung volumes. **Objectives:** It was the aim of this study to determine whether PEP improves ventilation inhomogeneity more than controlled huffing and coughing in individuals with stable COPD. **Methods:** Twelve participants with COPD (mean forced expiratory volume in 1 s 45% predicted) and chronic sputum expectoration performed PEP therapy (10–20 cm H₂O) or controlled huffing and coughing in random order on alter-

nate study days with a 48-hour washout. Measures of acinar and conductive airway ventilation (S_{acin} , S_{cond}), lung volumes, spirometry and sputum wet weight were recorded before, immediately after and 90 min following treatment. Ease of expectoration [visual analogue scale (VAS)] and oxyhaemoglobin saturation were assessed immediately following treatment. **Results:** There were no significant differences between the effect of either test condition at any time point for any test parameter. Mean S_{acin} immediately following PEP and control conditions was 0.465 and 0.438 litre⁻¹, respectively ($p = 0.45$ for comparison between conditions) and mean S_{cond} was 0.042 and 0.039 litre⁻¹ ($p = 0.55$). PEP therapy did not significantly enhance total mean sputum expectoration compared to controlled huffing and coughing (7.06 vs. 6.15 g; $p = 0.51$) and did not improve ease of expectoration (VAS PEP 4.8 cm vs. control 4.1 cm; $p = 0.53$). **Conclusion:** Any therapeutic benefits of PEP in individuals with COPD and chronic sputum expectoration are unlikely to be mediated by improvements in ventilation or lung volumes.

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Introduction

Airway clearance techniques (ACTs) involve the application of external forces and manipulation of lung volumes, pulmonary pressures and gas flow in order to clear sputum from the airways [1]. They are frequently prescribed for patients with chronic obstructive pulmonary disease (COPD) [2, 3]. However, convincing evidence of significant clinical benefits is limited [4]. Factors such as disease severity [5], the degree of elastic lung recoil [6] or the presence of other co-existing respiratory conditions such as bronchiectasis [1] (reported in 29–50% of patients with COPD) [7, 8] may influence the response to ACTs.

Positive expiratory pressure (PEP) therapy involves breathing with a slightly active expiration against a mild expiratory resistance (typically 10–20 cm H₂O). It is conventionally performed via a small hand-held mask as part of a cycle that includes huffing and coughing. It has been postulated to assist sputum clearance: by splinting open airways prone to dynamic compression during forced expiratory manoeuvres [9]; reducing gas trapping [10]; improving ventilation and gas flow via recruitment of collateral channels [11, 12], possibly due to an increase in functional residual capacity (FRC). Rapid increases in FRC have been demonstrated in adults without respiratory disease [13]; however, the effect of PEP may differ in individuals with COPD where FRC can be significantly elevated. For example, in healthy lungs, there is typically a uniform (homogenous) distribution of ventilation, due to equal rates of filling and emptying of individual lung units. In COPD, ventilation is often non-uniform (inhomogenous) due to asynchronous filling and emptying of lung units.

Ventilation inhomogeneity can be quantified from multiple-breath nitrogen washout (MBNW) tests. The lung clearance index (LCI) is a global measure of ventilation inhomogeneity in both the small and large airways and is calculated as the number of lung turnovers (cumulative expired volume divided by FRC) required to reduce end-tidal nitrogen concentration to below a fixed value. This is usually 2% absolute or 1/40th of the starting nitrogen concentration [14, 15]; however, differing end-tidal values such as 5% or 1/20th of the starting nitrogen concentration have also been used [16]. Ventilation inhomogeneity can be further partitioned into two distinct distal airway regions based on different modes of gas transport (convection and diffusion) within the lung [17]. Ventilation inhomogeneity due to uneven distribution of convective gas flow is termed ' S_{cond} ' whilst the interaction between diffusive and convective gas flow, occurring at

the acinar entrance, is assessed by the index S_{acin} . Elevation of both these indices has been shown to correlate to the worsening of ventilation inhomogeneity [18].

Evaluation of the effect of ACTs using measures of ventilation distribution offers considerable advantage over widely used spirometric outcomes as the sensitivity to detect change, particularly in the small airways (the 'quiet zone') [19], is significantly enhanced [17, 18, 20, 21]. Despite this, the use of such procedures in ACT studies is rare. In a study by Darbee et al. [22], 5 children with cystic fibrosis demonstrated that measurements of ventilation distribution via a single-breath helium dilution technique worsened following PEP mask therapy whilst small improvements in the forced expiratory volume in 1 s (FEV₁) were detected. However, this study did not standardize the frequency of coughing and huffing across both test conditions despite their known influence on sputum clearance [6, 23, 24]. Controlling for this effect is crucial in order for the effect of PEP to be isolated.

Aim

The principal aim of the study was to identify whether PEP mask therapy improves ventilation inhomogeneity (S_{acin} , S_{cond}) and increases FRC compared to controlled huffing and coughing in individuals with stable COPD and chronic sputum expectoration. The influence of disease severity, co-existing bronchiectasis and the amount of sputum expectorated on PEP mask therapy effectiveness was also explored.

Material and Methods

Ethics

This study was approved by the Human Ethics Committees of Alfred Health (359/09) and La Trobe University (09-060).

Participants

Individuals with at least moderate [25], stable COPD (no history of an exacerbation requiring medical treatment for the previous 4 weeks) [26] and usual sputum expectoration ('regular expectoration of sputum on most days') were recruited from a tertiary hospital in Melbourne, Australia, between April 2010 and October 2011. Individuals were ineligible if they had severe or widespread bullous disease affecting >50% of any lobe, a history of recent (<6 months) pneumothorax or resting oxyhaemoglobin saturation (SpO₂) <90% on room air [21] or were unable to provide informed consent.

Study Design

This was a randomized crossover trial comparing the effect of 15 min of PEP mask therapy to 15 min of controlled huffing and coughing (fig. 1). The primary outcomes were S_{acin} and S_{cond} , and the secondary outcomes were FRC, residual volume (RV), total lung capacity (TLC), RV/TLC, inspiratory capacity (IC), FEV₁,

Fig. 1. Study design.

forced vital capacity (FVC), FEV_1/FVC , LCI at 5 and 2%, SpO_2 , sputum wet weight and self-reported ease of expectoration.

Test Protocol

The baseline assessment comprised pre- and post-bronchodilator spirometry, gas transfer factor and a high-resolution computed tomography of the chest to identify significant bullous disease (sharply demarcated areas of emphysema of ≥ 1 cm diameter possessing a thin epithelialized wall of ≤ 1 mm) and/or co-existing bronchiectasis [localized irreversible bronchial dilatation as identified by a bronchoarterial ratio (internal bronchial diameter/accompanying artery diameter) >1 , a visible airway within 1 cm of the costal pleural surface, or direct contact of an airway with the mediastinal pleural surface]. Modified Bhalla criteria [27, 28] were used to quantify the degree of bronchiectasis as a score from 0 to 54 (the higher the score, the more severe the disease), with total extent scores ≥ 2 deemed clinically significant [8]. Further details are provided in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000348546).

Participants then performed a control or PEP mask intervention (order randomized) at the same time of day on 2 study days, with at least 48-hour washout between visits. Tests of lung function (MBNW, spirometry and lung volumes, in order) were performed before (T1), immediately after (T2) and 90 min following treatment (T3) (fig. 1). Participants took their usual respiratory medications but were administered bronchodilator therapy (300 μ g salbutamol via metered dose inhaler with spacer) prior to baseline testing to enhance standardization. Block randomization was performed via a web-based sequence generator, and treatment order (group allocation) was concealed using sealed, sequentially numbered opaque envelopes.

Experimental Conditions

Control

Participants sat in an upright position and breathed normally for 15 min. At 3-min intervals, they performed two huffs through standard mouthpiece tubing. The first was from a low lung volume (small inspiration, prolonged expiration) and the second from a mid-lung volume (moderate inspiration, moderate expiration). This was followed by two strong coughs (five cycles total).

Intervention

Participants sat in a forward lean position with elbows rested on a table and held a PEP mask (Astra-tech AB[®]) over the nose and mouth to create an airtight seal. A valve on the front directed inspiration through a one-way inlet and expiration through a one-way outlet connected to a small expiratory resistor (internal diameter range 1.5–5.0 mm). Participants took 10 tidal volume breaths with a slightly active expiration to achieve a stable expiratory pressure of 10–20 cm H_2O [29] (monitored via a pressure manometer), followed by two huffs through standard mouthpiece tubing and two strong coughs. This cycle was repeated five times over a 15-min period.

Outcomes and Equipment

MBNW testing was performed using a double ‘bag-in-box’ system with participants seated upright and instructed to breathe at 1 litre tidal volumes (visual assistance provided via a computer display). Following a period of stable air breath, participants were switched to breathing of 100% O_2 . Nitrogen concentration was continuously monitored at the mouth (AU9240-4032, Medical Graphics Corporation, St. Paul, Minn., USA) while flow and volume were calculated by volume displacement from within the double bag-in-box system and measured by pneumotachography (Fleish type, flow range 0–5 litres s^{-1}). Participants continued to breathe O_2 until nitrogen was washed out to below 2%. This test was repeated three times at each time point (total 9 MBNWs/day), with sufficient time allowed for complete re-equilibration of nitrogen within the lung FRC before subsequent testing was commenced [30]. Further details of the equipment set-up and test protocol are described by Stuart-Andrews et al. [31].

Analysis of the MBNW tests was undertaken using a previously described automated technique, whereby the slope of the alveolar (or phase III) portion of each breath recorded during the wash-out was calculated [31]. Indices of ventilation inhomogeneity (S_{acin} and S_{cond}) were determined and interpreted as described by Verbanck et al. [17, 32], and LCI was calculated as previously described [14–16]. Spirometry and lung volumes (via constant volume body plethysmography) were performed using standard lung function equipment (Platinum Elite series, Medical Graphics Corporation) interfaced with MedGraphics Breeze software in accordance with

American Thoracic Society/European Respiratory Society guidelines [33, 34].

Oxyhaemoglobin saturation was measured using a portable pulse oximeter (Massimo, Radical 7) and digital probe before and immediately after treatment. Sputum wet weight (g) was recorded using a calibrated digital weighing scale before and after lung function testing. Participants rated their ease of sputum expectoration immediately after treatment using a 10-cm visual analogue scale (VAS; 0 = extremely easy; 10 = extremely difficult) which asked 'how easy was it to cough and expectorate sputum?'

Blinding

The assessors responsible for conducting and analysing the MBNWs (C.S.-A.) and chest high-resolution computed tomographies (S.E.) were blind to the participants' treatment order throughout the study. The outcome assessor responsible for collecting and analysing all other secondary outcomes was the treating therapist (C.O.) who was not blind to group allocation.

Statistical Analysis

The effect of the test conditions on ventilation inhomogeneity (S_{cond} , S_{acin} , LCI5%, LCI2%) and lung function (FRC, TLC, RV, RV/TLC, IC, FEV₁, FVC) at T2 and T3 was analysed using separate linear mixed-model analyses for each outcome. Each model comprised allocation sequence, test day and test condition as fixed effects and participants as random effects. A sensitivity analysis was performed to investigate the effect of incorporating baseline data (T1) as a fixed effect covariate in the model for the primary outcomes. Paired *t* tests (two-tailed) were used to compare the effect of treatment on SpO₂, sputum wet weight and VAS scores. The effect of disease severity, co-existing bronchiectasis and sputum production on S_{acin} and S_{cond} were explored via correlation coefficients. Cronbach's α was set at 0.05. *P* values less than 0.05 were considered statistically significant.

Results

Ninety-three individuals with COPD were screened for study eligibility. Most were excluded due to not regularly expectorating sputum (40/93, 43%). Thirteen participants were recruited and randomized (6 PEP first); however 1 subject [male, 71 years old, FEV₁ 0.95 litre (33.5% predicted)] did not return after the first study day (PEP) and was excluded from all analyses. Another could not perform acceptable manoeuvres for calculation of lung volumes and was excluded from analysis of these data only. Key demographic data for the 12 participants are presented in table 1. Data from the quantitative analysis are presented in table 2. Further individual data are available in the online supplementary material.

Primary Outcomes

There were no statistically significant within-group changes or between-group differences in S_{acin} or S_{cond} at

Table 1. Baseline characteristics of participants

Participant characteristics	n = 12
Age, years	66.1 ± 8.6
Gender, male:female	8:4
Body mass index	27.1 ± 3.9
Smoking status, current:former	2:10
Smoking, pack-years	67.4 ± 60.9
Previously diagnosed respiratory comorbidity	5 (42)
Radiological evidence of significant bronchiectasis	8 (66.7)
Self-reported usual daily sputum expectoration	
≤1 teaspoon	2 (17)
1–3 tablespoons	7 (58)
≥1/2 cup	3 (25)
Post-bronchodilator lung function	
FEV ₁ , litre	1.3 ± 0.5
FEV ₁ , % predicted	45.2 ± 18.5
FVC, litre	3.4 ± 0.8
FVC, % predicted	85.9 ± 17.1
FEV ₁ /FVC	0.38 ± 0.12
T _L CO _{Hb} , % predicted	51.1 ± 19.2
FRC, litre ^a	4.87 ± 1.08
FRC, % predicted	139 ± 22
RV, litre ^a	3.59 ± 0.99
RV, % predicted	158 ± 40
TLC, litre ^a	7.36 ± 1.36
TLC, % predicted	124 ± 13
RV/TLC ^a	48.7 ± 8.6
IC, litre ^a	2.43 ± 0.62
S_{acin} , litre ⁻¹	0.498 ± 0.11
S_{acin} , % predicted	426 ± 88
S_{cond} , litre ⁻¹	0.041 ± 0.02
S_{cond} , % predicted	97 ± 53
GOLD stage, 1:2:3:4	0:5:4:3

Data are the mean ± SD, or the number of patients, with percentages in parentheses. T_LCO_{Hb} = Transfer factor of carbon monoxide adjusted for haemoglobin; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

^aMeasured on 11 participants only.

any time point (fig. 2, 3). Results from the sensitivity analysis did not differ. No statistically significant correlations with disease severity, extent of co-existing bronchiectasis or sputum wet weight existed.

Secondary Outcomes

No statistically different between-group differences in LCI2% or LCI5% existed at T2 or T3. Despite very small within-group increases in FRC following both test conditions (fig. 4), no statistically significant differences were evident between test conditions at T2 or T3 for FRC or any other lung volume or spirometric parameter. A non-significant trend towards greater improvement in FEV₁ following PEP compared to controlled coughing was observed (42 vs. 5 ml).

Table 2. Results of linear mixed-model analysis

	T2					T3				
	difference between treatments			end treatment		difference between treatments			end treatment	
	mean PEP – control	lower CI	upper CI	PEP	control	mean PEP – control	lower CI	upper CI	PEP	control
S_{acin} , litre ⁻¹	0.026	-0.048	0.101	0.465	0.438	0.001	-0.069	0.070	0.453	0.452
S_{cond} , litre ⁻¹	0.002	-0.005	0.010	0.042	0.039	-0.003	-0.016	0.010	0.031	0.034
LCI5% (TO)	0.078	-0.092	0.247	5.847	5.770	-0.021	-0.253	0.210	5.735	5.756
LCI2% (TO)	0.024	-0.648	0.695	13.450	13.427	0.144	-0.536	0.247	13.093	13.237
FRC, litre	-0.06	-0.21	0.09	5.07	5.13	0.02	-0.20	0.25	5.14	5.12
RV, litre	-0.02	-0.20	0.17	3.74	3.76	0.09	-0.07	0.25	3.84	3.75
TLC, litre	-0.08	-0.21	0.03	7.55	7.63	0.04	-0.20	0.29	7.63	7.59
RV/TLC	0.00	-0.02	0.02	0.49	0.49	0.01	-0.01	0.03	0.50	0.49
IC, litre	-0.03	-0.23	0.18	2.40	2.43	0.02	-0.32	0.34	2.40	2.38
FEV ₁ , litre	-0.02	-0.11	0.07	1.35	1.37	-0.02	-0.13	0.10	1.30	1.32
FVC, litre	-0.03	-0.14	0.10	3.53	3.56	-0.04	-0.25	0.17	3.49	3.53
FEV ₁ /FVC	-3.26	-8.90	2.37	0.38	3.64	0.01	-0.02	0.03	0.38	0.37

Data are the mean difference between treatments immediately after (T2) and 90 min following treatment (T3), and least square mean values for PEP and control conditions at T2 and T3. CI = Confidence interval; TO = turnovers (cumulative expired volume divided by FRC).

Fig. 2. Mean (standard error) S_{acin} over time. T1 = Before treatment; T2 = immediately after treatment; T3 = 90 min following treatment. **Fig. 3.** Mean (standard error) S_{cond} over time. T1 = Before treatment; T2 = immediately after treatment; T3 = 90 min following treatment.

Complete pre- and post-treatment SpO_2 data from both test conditions were obtained from 9 participants only. Mean (SD) end-treatment SpO_2 was 93.6% (1.7) and 93.7% (2.5) following PEP and control, respectively ($p = 0.84$). Mean (SD) sputum wet weight immediately following treatment was 3.87 g (4.7) (PEP) and 3.77 g (4.3) (control), increasing to 7.06 g (7.9) (PEP) and 6.15 g (6.1)

(control) by the end of T3 ($p = 0.51$). VAS scores were not significantly different (4.8 cm PEP vs. 4.1 cm control; $p = 0.53$). No adverse events occurred throughout the study. Data of individual participants are available in the online supplementary material.

Fig. 4. Mean (standard error) FRC over time. T1 = Before treatment; T2 = immediately after treatment; T3 = 90 min following treatment.

Discussion

This was the first study to investigate the effect of PEP on ventilation inhomogeneity and FRC in individuals with COPD and regular sputum expectoration. No clinically or statistically significant differences were found for any measure of ventilation or lung function between the two test conditions. The lack of change in S_{acin} , S_{cond} , FRC and RV/TLC fails to support two of the three mechanisms proposed to explain how PEP benefits sputum clearance, namely improvement in pulmonary ventilation and gas flow and a reduction in gas trapping. The ability of PEP to create a protective splinting effect during active expirations was not directly examined in the present study; however, no anticipated reduction in RV was observed. This raises questions regarding the effectiveness and rationale for using PEP in this patient group.

The primary outcomes used in this study (S_{acin} , S_{cond}) have typically been utilized to characterize lung disease severity and progression [17, 18, 35, 36] due to their capability to detect subtle change in the structure and function of the small airways. Their limited use in studies of ACTs means comparison of our findings to existing literature is not possible. One PEP session may have been insufficient to alter small airway structure; however, the absence of change in small airway function was likely due to a true absence of effect given the high sensitivity of these parameters [37]. The novel application of MBNW technology in this study was warranted by the specific physiological aims and proved both feasible and well tolerated by participants.

Mean sputum expectoration was generally low throughout this study and did not significantly correlate with the extent of bronchiectasis or the severity of COPD. The importance of the within-group changes in sputum wet weight from baseline were difficult to ascertain as no minimally important difference exists in clinical practice, and comparisons between conditions were confounded by the effect of repeated forced expiratory manoeuvres during serial lung function tests. This may have contributed to the lack of observed benefit of PEP on sputum expectoration and contrasts the notion that ACTs may be more important in 'wet' versus 'dry' COPD phenotypes.

The findings of this study are consistent with previous literature in stable COPD that reported endpoints including FEV₁ [38, 39], RV [40] and SpO₂ [41]. Whether the MBNW findings have implications for individuals with acute exacerbations of COPD, where ACTs appear to differ in their effects compared to stable disease [4] and are more frequently prescribed [2, 3], remains unclear. Replicating this study in an acute environment would be challenging as the washout duration is likely to coincide with significant clinical improvement, and tolerance to repeated lung function tests may be low. The use of MBNW tests as a sole outcome is limited by its present lack of accuracy to measure changes in lung volumes, particularly FRC.

Results from this study indicate that a single PEP mask treatment does not improve ventilation inhomogeneity or increase FRC more than huffing and coughing in individuals with COPD and regular sputum expectoration. Therefore, any benefits derived from PEP therapy in this patient group do not appear to be mediated by improvements in ventilation due to changes in lung volumes.

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Financial Disclosure and Conflicts of Interest

None of the authors has a conflict of interest related to the content of the manuscript.

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