Title: Changing practice by changing pressures: A role for oscillating Positive Expiratory Pressure in Chronic Obstructive Pulmonary Disease

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Introduction

Positive expiratory pressure (PEP) is an airway clearance technique involving a series of exhalation manoeuvres against a positive pressure that seeks to promote sputum clearance. It is often prescribed for people with Chronic Obstructive Pulmonary Disease (COPD) who experience sputum production, and clinical interest regarding its importance has existed for many years. Most randomised controlled trials (RCTs) in this field pertain to non-oscillatory PEP, however high quality RCTs of oscillatory PEP (a variation of the technique involving rapid pressure fluctuations within the airways) are emerging. One such example is published in this issue of Thorax, by Alghamdi et al (1).

Dr Alghamdi et al (1) provide important data on the efficacy of the 'Acapella' Oscillating Positive Expiratory Pressure (OPEP) device to reduce cough burden for patients with COPD who regularly produce sputum. The intervention group in this study were encouraged to use an Acapella alongside their Active Cycle of Breathing Techniques (ACBT) while the control group performed ACBT only. Participants were encouraged to perform interventions three times per day for three months. The strengths of this study are the methodology, particularly the recruitment of patients with a chronic bronchitic phenotype who are most likely to benefit from ACBT and OPEP. The authors also collected triangulated cough and sleep data involving both questionnaire-based and objectively quantified data which enhances the rigour of conclusions relating to improved cough frequency, quality of life and fatigue. The authors also observed reduced odds of exacerbations in the OPEP group. This is significant considering the high numbers of individuals who hadn't exacerbated in the

previous year at baseline, however longer term follow-up data in future studies will be required to confirm this. The results from Dr Alghamdi et al (1) are clinically relevant and relate well to current provision restrictions during COVID.

Current National Institute for Health and Care Excellence COPD guidance (2) for people with excessive sputum supports that individuals should be taught how to use PEP devices and perform ACBT. No advice specific to OPEP is provided. ACBT is commonly used as a first line treatment in clinical practice due to its simplicity, effectiveness and cost (free). In clinical practice, ACBT is ideally tailored to the individual needs of each patient involving different dosages and intensities adapted in response to changing breathlessness and sputum location, guided by the equal pressure point theory. Such approaches are, however, associated with high treatment variability – something that is not ideal for controlled RCT environments. But pragmatism helps to mirror real life practice. Alghamdi et al (1) delivered their intervention via video-conferencing. On the one hand, this might be perceived as limiting the external validity of a face-to-face clinical intervention, but again was very appropriate considering COVID-19 restrictions.

Will these new data influence clinical use of OPEP?

The comparatively low focus on airway clearance techniques in guidelines is intriguing compared to comprehensive guidance provided for oral and inhaled medications, pulmonary rehabilitation and lung volume reduction. PEP/OPEP devices are sub-optimally prescribed in clinical practice, with a 100-fold difference in the rate of prescription between carbocisteine and OPEP devices previously reported in the UK (3). According to

openprescribing.net (4), prescription costs across all clinical commissioning groups in NHS England for Carbocisteine between July 2021 and June 2022 totalled £11,706,841 for 3,017,150 items. By contrast, during the same time period prescriptions and costs for OPEP devices were: Acapella Choice (Blue devices only), n=1831 and £69,719; Aerobika n=2980 and £128,287; and Flutter n=1364 and £51,656. Interestingly, while a lack of convincing clinical trial data till recently may have contributed to the limited use of OPEP devices within public health systems (as well as possible environmental concerns regarding plastic device use), evidence for mucolytic therapy in chronic lung diseases is also unconvincing (2,5), meaning therapy choices are not always straight-forward.

Comparison with other studies

Devices and trials in this field differ substantially. The oscillatory mechanism of Acapella is thought to reduce sputum viscoelasticity (6) and has been proposed as an important feature contributing to sputum expectoration during acute exacerbations of COPD (7). The findings from Alghamdi et al's study (1) may not, however, automatically transfer to non-oscillatory or even other oscillatory PEP devices due to device differences (a phenomena analogous to different inhaler devices). Indeed, different PEP trials, including Alghamdi et al's work, have shown different effects. Osadnik et al (8) found no difference in clinical outcomes between people who performed PEP-mask therapy and those who received usual care during an AECOPD. In this example, usual care comprised face-to-face physiotherapy but no structured airway clearance. Dr Alghamdi et al (1) examined people with stable disease who were sputum producers and compared OPEP to another airway clearance technique (ACBT),

and found evidence of clinical benefits. The longer duration of the OPEP intervention and the ongoing indication for airway clearance therapy in such patients likely accounts for some of this disparity. Exacerbations were an a priori secondary outcome of this study(1), recorded as adverse events collected at six weeks and 3 months. The recent TIDe Trial (9) may offer closer comparison. In this study, Daynes at al performed an RCT using an Aerosure OPEP device combined with an inspiratory muscle trainer and compared a 3 x daily intervention with a sham device for 8 weeks. The primary outcome for this trial was the dyspnoea domain of the CRQ, a well-suited outcome for the hybrid airway clearance / inspiratory muscle training intervention. Alghamdi et al (1)utilised the Leicester Cough Questionnaire (10), another subjective patient reported outcome measure which is arguably more specific to the issues associated with excessive sputum production. The LCQ has a known Minimal Clinical Important Difference(MCID) of 1.3 from 12 weeks of PR (11), and a responsiveness of 4.3(SD2.5) in COPD patients followed up for 12 weeks reporting global rating scores of their cough being moderately to a great deal better(12). The authors of the original validation study (10)recommend a change in score of more than 2.56 is clinically significant. Numbers of participants in these responsiveness studies remains small, and MCIDs are specific to interventions. Therefore, there remains uncertainty regarding what is a clinically significant change in cough burden from the additional use of OPEP devices when performing ACBT as standard care. This was the context of Alghamdi et al's study (1), where a lower threshold of clinical significance could be accepted. Moreover, a strength of the data included correlations between subjective and objective cough measures as well as improvements in other clinically meaningful outcome measures. The authors (1) adopted interesting eligibility criteria that combined COPD Assessment Test scores with questions regarding sputum production frequency. This approach is sensible as those more burdened

with sputum retention are more likely to derive benefit from a suitable treatment. Daynes et al (9) did provide the control group with a sham intervention which is an important strength that is rarely observed in RCTs of airway clearance therapy, including the present study by Alghamdi et al (1) . Further trial comparisons are summarised in table 1.

	Population	**Intervention**	**Control**	**Outcome (primary endpoint)**
Alghamdi et al (2022) (1)	People with Stable COPD and sputum producers (OPEP naïve)	Acapella OPEP and ACBT x 3 daily 3 months	ACBT X 3 daily 3 months	Leicester cough questionnaire at 3 months
Daynes et al (2022) (9)	People with Stable COPD with MRC Dyspnoea 2-5 (device naïve)	Aerosure High-Frequency Oscillating device (inspiratory and expiratory training) X 3 daily	Aerosure High-Frequency device (internal mechanism removed) X 3 daily 8 weeks	Self-Reported Chronic Dyspnoea Domain at 8 weeks

		8 weeks		
Milan et al (2019) (7)	People with severe AECOPD	Acapella OPEP 3 x daily during admission	Acapella PEP (oscillatory component removed) 3 x daily during admission	Hospital Length of stay.
Osadnik et al (2014) (8)	People with severe AECOPD and sputum producers (airway clearance and device naïve)	Astra Tech PEP-Mask X 3 daily during admission	Up to 30mins Physical exercise training during admission. No ACBT.	Breathlessness, Cough and Sputum Scale at discharge

Table 1: Comparisons between prominent RCTs involving PEP therapy in COPD

Self-reporting sputum producers are not the majority of people with COPD. 29.1% of people with COPD have been classified as Chronic Bronchitis Exacerbators (1). Previous related

studies have shown difficulty in patient recruitment, screening hundreds of patients in order to meet recruitment targets based on meeting eligibility criteria rather than predominantly declining the intervention (7,8). It would be interesting to know how many people out of the 379 screened for eligibility were excluded due to failure to be sputum producers and exactly how patients were referred to the study team for assessment. This is important considering the patients recruited to this study (1) are a specific phenotype recruited from a single tertiary centre, who are likely to have more severe COPD , worse FACIT score, and a higher percentage of non-smokers than a general COPD population (13).

Future Research and Recommendations regarding PEP therapy

Long-term follow-up is essential to accurately monitor specific important study endpoints such as patient adherence, changes in health-related quality of life over time, exacerbation rates and healthcare utilisation. Primary outcomes of trials need to be comparable, chosen specifically in relation to the inclusion criteria of patients and likely mechanism of benefit of the devices, and ideally be used for health economic evaluation purposes. Future studies may consider combining clinically convenient questionnaire measures alongside quantifiable outcomes such as sputum rheology, Computer-Aided Lung Sound Analysis, actigraphy and lung imaging. There also remains high scope for qualitative inquiry within this area of COPD care.

In consideration of all these factors and despite more research being warranted, Alghamdi et al (1) have provided robust evidence that should strongly encourage clinicians to consider recommending OPEP for people with stable COPD and chronic sputum production, who remain disabled with their cough, despite using ACBT.

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