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REVIEW

Improving mucociliary clearance in chronic obstructive pulmonary disease

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Summary

Patients with COPD usually experience mucus hypersecretion as a result of airway inflammation and response to noxious stimuli. These in turn lead to worsening airway resistance, impaired airflow, increased work of breathing, dyspnoea and exercise intolerance. Mucus hypersecretion may also lead to increased exacerbations and poor health related quality of life (HRQL). Institution based pulmonary rehabilitation programs incorporating airway clearance techniques have been shown to improve HRQL, reduce dyspnoea and improve exercise tolerance but are often difficult to provide due to restricted accessibility and resource implications. This review examines the current evidence base and best clinical practice in the area of airway clearance. Mechanical devices such as the flutter valves, positive end expiratory pressure and high frequency chest wall oscillation (HFCWO) may be able to provide the benefits of improved airway clearance in the patient's home potentially with reduced demands on healthcare resources.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic obstruction of expiratory flow affecting peripheral airways, associated with chronic bronchitis (mucus hypersecretion with goblet cell and submucosal gland hyperplasia) and emphysema (destruction of pulmonary parenchyma), together with fibrosis and tissue damage, and inflammation of the small airways.¹ In 1959, Fletcher hypothesized that recurrent respiratory infections might lead to chronic bronchitis and the chronic mucus production caused by this might lead to chronic airway obstruction. When this hypothesis was tested, a causal relationship between respiratory infections and sputum production was not found and it was concluded that smoking caused both chronic bronchitis and COPD, but the two did not have a causal relationship.² However, more recent study has demonstrated that among smokers chronic sputum production³ and increased airway bacterial counts may be associated with a more rapid decline in lung function.^{4,5}

Pathophysiology

Mechanisms of airway mucus production

Cigarette smoke results in increased numbers of goblet cells in the small airways.⁶ A wide variety of stimuli (e.g., bacteria, viruses, allergens, cigarette smoke, foreign

bodies, reactive oxygen species, various cytokines, and activated leukocytes) cause goblet cell precursors to differentiate into mucin-producing goblet cells via activation of an epidermal growth factor receptor (EGFR) cascade.⁷ Neutrophil elastase and cell surface adhesion molecules have been implicated in the process by which neutrophils stimulate the production of mucus from goblet cells.⁸

Methods of clearance of airway mucus

Airway secretions are cleared by mucociliary clearance (MCC), in addition to other mechanisms such as cough, peristalsis, two-phase gas–liquid flow and alveolar clearance. MCC comprises the cephalad movement of mucus caused by the cilia lining the conducting airways which is determined by the structure, number, movement and coordination as well as the amount, composition and rheological properties of the periciliary and mucus layers.⁹ MCC is a vital mechanism of lung defence, enabling efficient clearance of inhaled particles, including microorganisms, from the respiratory tract.^{10,11} Inherited defects in ciliary motility as well as the effects of neutrophil products may impair ciliary beating [Table 1](#).¹²

Effects of mucus hypersecretion and retention

Chronic mucus hypersecretion is significantly and consistently associated with both an excess FEV₁ decline and an

Table 1 Modalities and mechanisms of mucociliary clearance.

Modalities	Agents	Mechanisms
Mucolytics	Carbocisteine Erdosteine N acetyl cysteine DNase Gelsolin Dextran LMW heparin	Breaking down mucus strands and increased fluidity; destabilization of chemical structure of disulfide bonds; hydrolysis of DNA molecules and DNA length
Expectorants	Guaifenesin	Clearance of large airways, unlikely to be of any clinical benefit
Mucoactive	Bronchodilators	Increased mucus clearance through improved ciliary movement, reducing airway obstruction
Mucus reduction	Erdosteine Anticholinergics Indomethacin (NSAIDs) Corticosteroids Macrolide antibiotics	Reducing inflammation and mucus production
Non-specific	Airway humidification Aerobic exercise	Increasing airway humidity and water content of mucus; unlikely to be of any clinical benefit Shear stress improves mucus mobility and opening of smaller airways; unlikely to be of any clinical benefit Percussion and shear stresses with aids to mobilization
Mucociliary clearance	Conventional chest physiotherapy Chest physiotherapy (autogenic drainage, active cycle breathing) Resistive measures Flutter valve Positive end expiratory pressure High frequency chest wall oscillation	Effective clearance of smaller, peripheral airways
Osmolar agents	Mannitol Amiloride Hypertonic saline	Increasing mucosal water content, reducing viscosity

increased risk of subsequent hospitalization because of COPD.³ Excess mucus in the airways causes severe cough and discomfort, and can lead to further obstruction and inflammation.⁸ Hogg et al. reported that the increase in peripheral airway wall thickness and volume of inflammatory cells in the mucous exudate were directly predictive of the stage of advancement of COPD, based on a study of surgically resected lung tissue.¹³ The airways of patients with COPD are often found to be colonized by bacteria, and it is now recognized that higher airway bacterial loads are associated with increased airway inflammation¹⁴ more frequent exacerbation¹⁵ and faster lung function decline¹⁶ in smokers.¹⁷ In addition, severe airflow limitation is associated with an increased number of neutrophils, macrophages, NK lymphocytes, and MIP-1 α + epithelial cells in the bronchial mucosa.¹⁸ Airway infections and ciliary dysfunction can lead to impaired mucus transport and can thereby increase the retention of particles, including microorganisms in the airways.^{19,20} Hence techniques of efficient clearance of peripheral airways may reduce airway occlusion by excess mucus and inflammatory cells, improving lung function, exercise capacity and reducing exacerbation frequency.

Therapeutic approaches to airway mucus hypersecretion and retention

Non-pharmacological

Air humidification

Although cold air and mist humidification are commonly used, they have been shown not to be useful in achieving adequate air humidification nor in aiding sputum clearance. There is, in fact, a higher risk of bacterial infection with mist humidification systems.²¹ Warm air humidification may help in intubated patients but does not help to improve airway clearance in non-intubated adults.²²

Exercise

Aerobic exercise leads to more rapid and deep breathing leading to shearing force along the airway walls hence improving clearance of secretions but although exercise may improve functional capacity, it has not been shown to be a replacement for physiotherapy in adequate airway clearance in cystic fibrosis (CF).²³

Conventional chest physiotherapy (CCPT)

Although CCPT is still considered the gold standard of treatment in clinical practice, a Cochrane review in 2000 concluded that the evidence for this was not robust.²⁴ This is possibly due to a lack of appropriate trials rather than any evidence of lack of benefit. A systematic review carried out in 2004 to look at airway clearance techniques in all disorders of airway clearance to produce American College of Chest Physicians (ACCP) guidelines, found that although some techniques improved sputum expectoration, there was no high quality evidence for long term outcomes with these techniques.²⁵ They recommended the use of CCPT in CF but noted that manually assisted cough might be detrimental in COPD and recommended that this technique not be used in these patients. CCPT requires active intervention from a trained assistant or therapist.

ACBT

The active cycle breathing technique (ACBT) is a cycle of breathing control, thoracic expansion exercises and forced expiration techniques (one or two huffs combined with periods of breathing control). Huffing to low lung volumes helps to clear the secretions from peripheral airways and when they reach the more proximal airways, a huff or cough from a high lung volume can be used to clear them.²⁶ This technique has been recommended for both CF and COPD in the ACCP guidelines for airway clearance therapies.²⁵ Various other techniques have been used as adjuncts to "standard" physiotherapy for patients with CF. Forced expiration²⁷ and inspiration against resistance have demonstrated better sputum expectoration than standard therapy.²⁸

Autogenic drainage

Autogenic drainage is the use of exhalation at different lung volumes – from low lung volume to high lung volume – to gradually mobilize the airway secretions from the peripheral to the proximal airways. It has been shown to have at least equal efficacy to ACBT in a cohort of 30 patients with COPD.²⁹

Resistive inspiratory manoeuvres (RIM)

Inspiration against a fixed inspiratory resistance is thought to improve sputum clearance. RIM was shown in CF to improve sputum expectoration compared to standard physiotherapy alone.²⁸ There are no studies looking at this technique in COPD.

Flutter

This is a pipe-shaped device with a high density stainless steel ball-bearing enclosed in a cone in the bowl of the "pipe". During expiration through the flutter device, the rise and fall of the ball and its movement along the surface of the cone creates a positive expiratory pressure and oscillatory vibration of the air within the airways. This phenomenon helps to loosen secretions, which are mobilized to the central airways and cleared by deep exhalations through the device with the aid of subsequent coughing and/or huffing. It has been shown that oral high frequency oscillation improves mucociliary clearance in normal individuals.³⁰ A flutter device was compared to standard chest physiotherapy in CF patients and found to

be equivalent in its effects on spirometry, 6 min walk distance and oxygen saturations.³¹ However, another study using the VRP1 flutter device, was found to be less efficient than ACB techniques at clearing the airway and concerns were raised about sputum retention with this device.³² There is little evidence for improved airway clearance with the flutter device in patients with COPD, but one study of 23 patients with COPD found that the bronchodilator response to salbutamol and ipratropium was improved after the use of a flutter device.³³

Positive expiratory pressure (PEP)

The PEP device consists of a face mask or mouthpiece and a one-way valve to which expiratory resistors can be attached. A manometer is inserted into the system between the valve and the resistance to monitor the pressure. This should be 10–20 cmH₂O at mid-expiration. Tidal breathing, with a slightly active expiration, is used and the lung volume is retained at a higher level than the usual residual volume by avoiding complete expiration.²⁶ A Cochrane review of the use of PEP devices for CF patients concluded that there was no objective evidence that PEP devices were either better or worse than other airway clearance techniques. Some patients reported a preference for PEP over standard therapy, but these studies were not of very high quality.³⁴ The ACCP guidelines²⁵ have recommended the use of PEP in CF because it is approximately as effective as CCPT, is safe and can be self-administered. However, there is no evidence available on the use of PEP to aid sputum expectoration in COPD.

HFCWO

High frequency chest wall oscillation devices allow positive pressure air pulses to be applied to the chest wall, for example by means of an inflatable vest. It was hypothesized that chest wall oscillation might increase the expiratory flow bias and this would lead to increased mucus clearance.³⁵ Chest wall oscillation at 13 Hz using an inflatable cuff around the lower thorax was demonstrated in early canine studies to improve tracheal mucus clearance more effectively than in the control group or in subjects given high frequency oscillation at the airway opening.^{36,37} Following this, it was recognized that the use of a mechanical chest wall oscillatory device might be more convenient for patients as they would be able to perform their airway secretion clearance manoeuvres at home and this would in turn improve compliance and efficacy.³⁸ Most studies of HFCWO have been performed in patients with cystic fibrosis (CF). Darbee et al. used a protocol using a chest wall oscillation frequency of 10 Hz for 15 min and 15 Hz for another 15 min as six cycles of 5 min of treatment followed by expiratory and expectoration manoeuvres. This was compared to positive expiratory pressure (PEP) breathing at 10–20 cmH₂O. Nebulized salbutamol and normal saline were administered in both arms. FEV₁ and FVC improved with both treatments. Ventilation was more uniformly distributed throughout the lungs and inspired gases were better mixed with existing pulmonary gases after both treatments. However, the oxygen saturation fell slightly lower during treatment with HFCWO.³⁹ Perry et al. showed that the addition of PEEP to HFCWO at 10 Hz with a mean chest wall pressure of 16 cm of water increased end

expiratory lung volume and mean oscillatory flow rates during inspiration and expiration in patients with COPD. They therefore suggest that PEEP should be used in conjunction with HFCWO to maximize the sputum clearance obtainable with this technique.⁴⁰ HFCWO has been used in other disease conditions to attempt the improvement of clearance of airway secretions. Chaisson et al. found no benefit in FVC, oxygenation or adverse events with HFCWO in addition to BIPAP compared with BIPAP alone with standard therapy in patients with amyotrophic lateral sclerosis, but there were only nine subjects.⁴¹ An instrument to measure satisfaction levels and patient rated efficacy levels was validated by Oermann et al. This showed that conventional physiotherapy techniques (postural drainage, percussion and vibration) seemed to be considered by patients with cystic fibrosis to be less efficacious than HFCWO and less comfortable or convenient than flutter devices. They also observed that greater satisfaction was associated with greater compliance with therapy.⁴² There are no satisfactory studies to demonstrate the effect of HFCWO on exacerbations and quality of life in patients with COPD.

Pharmacological

Reduced airway surface liquid volume has been shown to be an important predictor of mucosal stasis and hence efficiency of mucociliary clearance. Studies in CF patients have demonstrated clearly the disease progression when this is impaired severely due to impaired CF transmembrane regulator (CFTR) gene expression. Recent studies from patients with COPD and asthma have shown that airway surface liquid volume homeostasis is linked to activation of adenosine receptor (A2B).⁴³ Therapeutic strategies that increase airway surface liquid content through osmosis may improve hydration and hence efficiency of mucociliary clearance. The mucus factors that favour mucociliary transport (e.g., thin mucus gel layer, "ideal" sol depth, and elasticity greater than viscosity) are opposite to those that favour cough effectiveness (thick mucus layer, excessive sol height, and viscosity greater than elasticity), which indicates that different mucoactive drugs are likely to be required for treatment of mucus obstruction in proximal versus distal airways, or in patients with an impaired cough reflex.⁴⁴

Hypertonic saline

A significant inhibition of luminal sodium conductance has been shown as a result of high luminal sodium concentrations. This mechanism may be involved in the regulation of fluid transport across the respiratory epithelium and in the improvement of mucociliary clearance with inhalation of hypertonic saline.⁴⁵ Of the various agents that are currently in favour, hypertonic saline has probably the maximum interest amongst researchers in COPD (with mucus hypersecretion). Saline (1.21 M) was used in 1978 to demonstrate more rapid clearance of secretions in patients with COPD.⁴⁶ Hypertonic saline has been demonstrated to improve sputum expectoration in CF in a dose dependent way, improving with increasing concentrations of saline within a range of 0.9–12%.⁴⁷ Daviskas et al. demonstrated increased mucociliary clearance in asthmatics and normal

controls using 14.4% hypertonic saline, but there was a fall in FEV₁ of 22% in the asthmatic group.⁴⁸ However, the technique of sputum induction using 3% saline has been shown to be safe in patients with COPD suggesting that lower concentrations of saline may have a role in improving mucociliary clearance in these patients.⁴⁹

Mannitol

As mannitol is thought to have a similar osmotic effect to hypertonic saline, inhalation of dry powder mannitol via an inhaler has been used to improve sputum expectoration in asthmatics as well as healthy volunteers.⁵⁰ Similar results were obtained in bronchiectasis.⁵¹ But again, there was a significant fall in FEV₁ in the asthmatic patients of 22 ± 3% raising the possibility of similar falls in COPD, which might be unsafe.

Amiloride

Amiloride has been shown to improve sputum clearance, but is not currently recommended for clinical use.⁵²

Mucolytics

While an early study of S-carboxymethylcysteine in patients with chronic bronchitis found no benefit on sputum expectoration,⁵³ subsequent work has demonstrated reduced sputum viscosity and increased mucociliary transport after a short treatment.⁵⁴ A recent study in Chinese patients with COPD showed a reduction in frequency of exacerbations in patients treated with Carbocysteine.⁵⁵ Erdosteine has been found in animal studies to have several possible mechanisms of action as an expectorant.⁵⁶ It has been shown to improve sputum clearance in elderly patients with bronchiectasis and chronic mucus hypersecretion.⁵⁷ A study of 8 months of daily erdosteine improved exacerbation and hospitalization rates and quality of life scores.⁵⁸ Overall, mucolytics have been shown to slightly reduce the frequency of exacerbations and the total number of days of disability.⁵⁹ Although these drugs fell out of favour in the UK for many years, the NICE guidelines for the management of COPD have recommended their use in selected patients.⁶⁰

Conclusions

Many techniques have been used to aid sputum expectoration and improve mucociliary clearance in patients with a variety of chronic mucus hypersecretory conditions. The majority of literature deals with cystic fibrosis. Novel therapies in development are targeted at correcting the ion transport deficiency of CF. The goal is to hydrate airway surfaces by stimulating secretion (through activation of the CFTR and calcium-activated chloride channels),⁶¹ and/or inhibiting absorption (through the epithelial sodium channel)⁶² thereby stimulating healthy mucociliary clearance.⁶³

However, these novel techniques are likely to take sometime before reaching the realms of clinical practice. As of now there is only limited evidence to show that some of the techniques described have been used with benefit in patients with COPD. Further study is required in this group of patients as the number of people suffering from COPD is

enormous and exacerbations of COPD consume a large portion of healthcare resources. We propose that HFCWO is a technique of self-managed efficient clearance of peripheral airways that should be studied in patients with COPD because there is some good evidence showing its benefits in airway clearance in cystic fibrosis and compared with other approaches such as hypertonic saline, erdos-teine and NAC. This is important as many patients with COPD have restricted mobility and may find it difficult to attend physiotherapy sessions on a regular basis.

Financial and conflict of interest statement

GA and KC have conducted a pilot study of HFCWO devices in COPD patients sponsored by Electromed Inc. USA in 2007, under IC as Principal Investigator. The project was funded to 16,000 GBP but no personal payments were received.

Originality and relevance statement

This article brings together the latest research and expert opinion in the emerging impact of physiotherapy techniques using adjuncts, which add the ability of self-management and empowerment to patients with COPD. The role of techniques employing flutter valves and high frequency chest wall oscillation to traditional chest physiotherapy is discussed and evidence reviewed.

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