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Personalising airway clearance in chronic lung disease

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To the Editors of the European Respiratory Review

RE: Personalising airway clearance in chronic lung disease.

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We are pleased to submit the manuscript titled, "Personalising airway clearance in chronic lung disease" for consideration as a, "State of the Art Review" for publication in European Respiratory Review.

This review describes a framework for providing a personalised approach to selecting the most appropriate airway clearance technique (ACT) for the individual patient. It is based on a synthesis of the physiological evidence that supports the modulation of ventilation and expiratory airflow as a means of assisting airway clearance. This provides the basis for clinical reasoning in selecting the most appropriate ACT.

The authors of this paper, believe that this review will have an impact on how clinicians personalise airway clearance techniques in clinical practice in patients with bronchiectasis and other chronic suppurative lung diseases from any cause including CF. While a few papers have attempted to describe the physiological theories on which airway clearance techniques are based, this is the first paper to collate the physiological evidence to support these theories and to provide clinical reasoning for use of the different approaches to airway clearance.

Thank-you for your consideration.

Maggie McIlwaine

Yours

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ABSTRACT

This review describes a framework for providing a personalised approach to selecting the

most appropriate airway clearance technique (ACT) for the individual patient. It is based on a

synthesis of the physiological evidence that supports the modulation of ventilation and

expiratory airflow as a means of assisting airway clearance. By possessing a strong

understanding of the physiological basis for ACTs, it will enable clinicians to decide which

ACT best aligns with the individual patient's pathology in diseases with anatomical

bronchiectasis and mucus hyper-secretion.

The physiological underpinning of postural drainage is that by placing a patient in various

positions, gravity enhances mobilisation of secretions. Newer ACTs are based on two other

physiological premises: the ability to ventilate behind obstructed regions of the lung; and the

capacity to achieve the minimum expiratory airflow bias necessary to mobilise secretions.

After reviewing each ACT to determine if it utilises both ventilation and expiratory flow,

these physiological concepts are assessed against the clinical evidence to provide a

mechanism for the effectiveness of each ACT. This paper provides the clinical rationale

necessary to determine the most appropriate ACT for each patient, thereby improving care.

Physiological Basis of Airway Clearance Techniques

INTRODUCTION. Personalised medicine has been used to describe the application of genomics, proteomics and biomarkers to precisely tailor therapy according to various characteristics of an individual patient[1] This concept of personalised medicine can also be applied to a variety of therapies, such as airway clearance, by taking into account individual patients' lung pathology, clinical, functional, environmental and social factors, as well as the physiological concepts underlying airway clearance techniques (ACTs). [2] Personalised medicine results in resources being more effectively directed to the most appropriate patients, thereby ensuring that patients receive the specific technique that optimises the likelihood of benefit in terms of lung health and time commitment. The use of ACT's can be further enhanced by the appropriate use of inhaled medications such as mucoactive agents, however these medications are not within the scope of this review.[3]

This paper provides an overview of the physiological principles underlying ACTs and links these physiological principles to the evidence base of commonly used ACTs. This will facilitate clinicians to personalise airway clearance techniques specific to patients underlying lung pathology as well as other clinical, functional, environmental and social factors. While some patients with chronic lung disease are ventilated, the vast majority are breathing spontaneously. As the physiological mechanisms described differ in ventilated patients, it must therefore be emphasised that this paper is written only for the spontaneously breathing patient.[4]

Background

ACTs are used to supplement the body's mucociliary clearance system when it is impaired by disease. This system is an important lung defence mechanism consisting of: airway surface

liquid comprising of mucus and periciliary layers (PCL); ciliary epithelium; and, a cough mechanism.[5] In healthy people, cilia beat at a mean frequency of between 11 - 13 Hz,[6] propelling mucus proximally up the airways at a rate of between 4 -5 mm/min.[7,8] The rate of clearance is strongly influenced by the mucus's hydration state, rigidity, and viscosity to elasticity ratio.[9,10]

The mucociliary transport system is impaired in chronic suppurative lung diseases, such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD) and bronchiectasis not caused by CF (BE). This is due to the occurrence of one or more of the following conditions: dehydration of the PCL; absence of lubricant activity which prevents adhesion of mucus to airway surfaces;[11] an inherent defect within the cilia; or, immunodeficiencies including cellular defects. Any one of these may cause a failure of ciliary beat frequency and reduced mucociliary clearance. Once this mechanical defence system is breached, the lung is more susceptible to infection and inflammation that can result in further airway damage, eventually leading to bronchiectasis.[12]

To be effective, ACTs should assist the body's natural mucociliary clearance system to transport secretions proximally up the airways. Historically, to achieve mucociliary clearance, postural drainage positions were utilized primarily for drainage by relying on gravity.[13] However, there is little supporting evidence that postural drainage utilising gravity, effectively mobilises secretions.[14,15] In CF patients, gravity in a head-down position increased the mucociliary clearance rate only from 0 mm/min to 3 – 5 mm/min[8]. Based on the assumption that mucociliary clearance rates in gravity dependant positions remain the same in different lung regions, to mobilise secretions from a sub-segmental airway in the lower lobe would require a patient to be placed in a head down position for approximately one hour. Thus, positioning a patient in a head-down position alone for 3- 5 minutes (as historically

used in CF centres), is expected to be ineffective and may even do harm by promoting gastro-oesophageal reflux.[13,16-20] Two studies, one in CF adults and the other in patients with chronic bronchitis using radiolabeled tracer gases demonstrated that in the side-lying position more secretions are mobilised from the dependent lung than from the non-dependent lung, which suggests that the impact of body position on ventilation plays a greater role than gravity in mobilising secretions.[21-23] Since this data was published there has been limited translation of these findings into clinical practice, suggesting why perhaps that in many countries, positioning for drainage remains a key ACT. Positioning for ventilation will be discussed later in this paper.

Newer ACTs rely on two over-riding physiological principles. First, a mechanism to allow air to move behind obstruction and ventilate the regions distally, and second, modulation of expiratory airflow in such a way as to propel secretions proximally up the airways. This paper describes the physiological theories and evidence underlying the use of individual ACTs in the non-ventilated spontaneously breathing patient.

1. Principles for optimising ventilation to obstructed regions of the lung.

In normal healthy individuals, during inspiration, airflow takes the path of least resistance, ventilating all areas of the lung, although there may be some asynchronous ventilation secondary to regional and stratified inhomogeneity.[24] In patients with obstructed airways, secretions decrease the diameter of the airway and increase airway resistance, causing preferential ventilation of unobstructed regions and hypoventilation of obstructed regions.[24] Over time, air gradually moves behind the obstruction, but it is not expired, leading to dynamic hyperinflation of the obstructed lung unit. Several mechanisms used in ACTs optimise ventilation to obstructed lung units.

Interdependence during deep inspiration

When tidal volume is increased during a deep inspiration, expanding alveoli exert a traction force on less well expanded alveoli which they surround, thereby assisting in the re-expansion of collapsed alveoli due to the elasticity of the surrounding interstitium. This is known as "interdependence". It results in air moving into the small airways obstructed by secretions, a phenomenon that has been called Pendelluft[25] and which results from the "interdependence". The theory of interdependence was proposed by Mead and a physical model was created to test this hypothesis.[26] The theory was later confirmed in clinical studies on anesthetised dogs.[27]

Collateral ventilation (CV)

Ventilation can also occur between adjacent lung segments through collateral channels.[28,29] In healthy individuals, the importance of CV is negligible due to resistance to airflow being higher in the collateral channels than in the airways. However, if an airway proximal to these collaterals becomes blocked, the collateral channels allow air to move through these pathways due to the pressure differences between adjacent lung units and function to minimise collapse of lung units. Studies have shown that excised human lungs can be re-inflated using collateral channels.[30,31] There are three types of collateral connections: channels of Lambert; pores of Kohn; and, pathways/channels of Martin.

Channels of Lambert represent epithelium-lined tubular communications between distal bronchioles and the adjacent alveoli. These are most likely the primary channels responsible for CV.[32] Pores of Kohn are inter-alveolar connections. There are approximately 50 pores of Kohn varying from 3 to 13μm in diameter in each alveolus.[33,34] *In vivo*, these pores are mostly filled by fluid and act as a pathway for alveolar lining fluid, surfactant components, and cells like macrophages to move between adjacent alveoli.[34] Lastly, there exist Pathways of Martin/channels of Martin, which are interbronchiolar connections. Results of an experiment with excised dogs lungs, pressurised to between $17 - 28$ cms H_2O, indicated connections between respiratory bronchioles and terminal bronchioles from adjacent lung

segments,[35] suggesting that use of collateral ventilation channels forms the basis for use of positive expiratory pressure ACTs .

Three second breath hold

A three second breath hold is another method of ventilating obstructed lung units. When the unobstructed region of the lung has been preferentially ventilated a pause for three seconds alters the time constants and allows air to move from the unobstructed regions, where the pressure gradient is higher, to the obstructed regions of the lung. This transient movement of gas out of some alveoli into another at the end of inspiration is known as Pendelluft flow. Multiple-breath washout tests have shown that a breath hold increases alveolar gas mixing and decreases the inhomogeneity of ventilation in normal subjects.[36] In post-operative clinical practice it has been demonstrated that a three second breath hold is effective in reducing atelectasis.[37]

Positioning to optimise ventilation in adults and children

Positioning may be used to enhance ventilation to specific lung regions where secretions are located, such as in bronchiectasis patients. The increased ventilation to those lung regions can then be used effectively to mobilise secretions.[21,22] There are differences in chest shape and lung mechanics between adults and children which result in differences in ventilation patterns.

When adults are placed in the upright position, optimum ventilation occurs in the mid and lower lobes, while perfusion is greatest in the lower lobes. Theoretically, ventilation/perfusion ratio V/Q = 1 is at the level of the right middle lobe and lingula.[38] When an adult is placed in side-lying, the dependent lung is preferentially ventilated due to the dependent hemi-diaphragm being stretched, causing a greater length to tension ratio, with increased contractility. This creates a greater negative pleural pressure, which clinically results in increased ventilation.[39]

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Perfusion is greater to the dependent lung in both adults and children because it is gravity dependent.

When very young children are placed in side-lying, the non-dependant lung is preferentially ventilated, most likely due to the differences in their lung and chest wall mechanics. This occurs in children up to age 12 years, causing airway closure to occur in the more dependent regions, independent of lung disease.[39]

Supine is the best position to ventilate the upper lobes.[38] However, if this is not suitable, as when taking an inhaled medication, side lying may be an alternative position. Inhaled drug deposition is improved by 13% to the dependent upper lobe when healthy adults were placed in side-lying. Adults with mild CF lung disease improve upper lobe deposition by 4% with the same side lying strategy[40] Table 1 shows optimal positioning for use during airway clearance to optimise ventilation to obstructed regions of the lung, based on changes in ventilation patterns with positioning.

Table 1. Optimal positioning for airway clearance techniques to enhance ventilation to obstructed regions of the lung

	Optimal position	**Alternative, 2nd choice, Position**
Secretions in upper lobes	Supine	Side Lying
Secretions in middle lobe and lingula	Upright	Side Lying or Supine
Secretions in right lung	Adults: place in right side lying Children: place in left side lying	
Secretions in left lung	Adults: place in left side lying Children: place in right side lying	
Secretions lower lobes	Upright	Side Lying

Use of mobilisation to increase ventilation

Moving a patient into different positions affects ventilation in two different ways. First, a change in body position alters regional ventilation as noted above. Second, by increasing the mobility of a patient, oxygen demand increases, resulting in a corresponding increase in minute ventilation and lung volumes.[41] The resultant increase in ventilation allows air to move into obstructed lung units by interdependence and collateral ventilation.

2. **Methods of utilising expiratory airflow to enhance secretion removal**

Increasing the velocity of the expiratory airflow in such a way as to create high shearing forces at the airway walls, and high kinetic energy that enhance the cephalad movement of secretions is a second key mechanism to mobilise airway secretions.

Cough

Coughing is a normal reflex defence mechanism used to clear excessive secretions down to the 7th or 8th generation of airways.[42] During a typical cough, a deep inspiration is followed by closure of the glottis. High intra-thoracic pressures (up to 300 mmHg) builds up, resulting in a high explosive, turbulent expiratory flow rate that may exceed 500 L/min[43] when the glottis is opened. During this time, dynamic compression of the airways occurs, resulting in an increase in velocity and kinetic energy which produces a shear force detaching mucus from the airway walls and enhancing the cephalic movement of mucus proximally up the airways. Distal to the regions where the airways are compressed, there may be a collapse of the airways, especially when airway instability is present.[43]

Cough is an effective method of clearing secretions from the larger airways in healthy individuals. However, in chronic supperative lung disease, where narrowing and "floppy" airways may close prematurely, it can have detrimental effects if used inappropriately over an extended period as the primary method of clearing secretions. When repeated coughs are

used, bronchial wall instability may result due to recurrent compression of the airways, thereby reducing expiratory flow and limiting the effectiveness of the cough.[44] Therefore, we recommend that ACTs be used as the primary method of mobilising secretions from the middle and small airways to the larger airways. Then one effective cough be used to clear secretions from the larger airways, thereby preserving the integrity of the larger airways.

Huff / Forced expiratory manoeuvre

A forced expiration manoeuvre may also be described as a "Huff". It accelerates the expiratory airflow, creating high linear velocities that shear mucus from the airway walls. Unlike a cough that is performed with a closed glottis, a huff is performed with an open glottis. The huff concept is based on the equal pressure point theory (EPP).[45] At the EPP, dynamic compression of the airways occurs, creating an increase in the linear velocity of the expiratory airflow which propels secretions proximally. The site of the EPP is determined by the size of expiratory force, airway stability, and the elastic recoil. Initiating a forced expiration at a low lung volume shifts the EPP to the periphery, targeting secretions in the small airways. Similarly, initiating a forced expiration from a high lung volume will move the EPP centrally towards the thoracic aperture. This is sometimes referred to as a "Huff-Cough".[38]

Two-phase gas-liquid flow mechanism

Mucus clearance can be modelled as a two-phase gas-liquid flow mechnism.[46] This indicates that peak expiratory flow rate (PEFR) must exceed peak inspiratory flow rate (PIFR) by at least 10% for mucus to move proximally. The peak expiratory flow rate must also exceed 30 – 60 L/min to overcome the adhesive strength by which the mucus is attached to the interface. Mucus factors affecting mucociliary clearance are the mucus depth and the viscoelastic properties of mucus. Viscosity is a liquid property of mucus, whereas elasticity is

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described as the energy storage with an applied stress to a solid. The rate of mucus transport is higher with viscoelastic mucus than with non-elastic viscous mucus.[47]

During normal tidal volume breathing at rest, PEFR does not exceed 30 L/min and PIFR is greater than PEFR. The result is that secretions are not mobilised. In order to use airflow to mobilise secretions it is necessary to optimise the expiratory airflow so that the PEFR > PIFR by at least 10%, and the velocity of the expiratory flow rate is at least 30 – 60 L/min, depending on the properties of the secretions. In a clinical study that examined the effect of a cough and a huff on regional lung clearance, PEFR recorded with a cough was 288 (29) l/min and 203 (25) l/min with a huff.[48] Both were sufficient to increase tracheobronchial clearance by 44% and 42% respectively, confirming that an increase in PEFR will enhance lung clearance.[48] Further studies have demonstrated that, in addition to huffing and coughing, manual vibration, oscillating positive expiratory pressure (using the Flutter VRP1) as well as autogenic drainage met the criteria for using expiratory flow to mobilise secretions proximally.[49,50] (Table 2)

Table 2. Effects of airway clearance interventions on peak expiratory flow rates.

Intervention	Subject n	PEFR L/mins	PIFR L/min	PEFR/PIFR Ratio	Frequency Hz
Huff	17	302.4±121.8	124.8±85.2	2.80	
Cough	17	280.2±114.6	100.8±44.4	3.07	
Vibration	17	94.8±43.8	63.6±16.2	1.51	8.4±0.4
Autogenic Drainage	14	85.2±28.8	50.4±13.8	1.69	
Flutter	17	67.8±18.0	63.0±16.2	1.15	11.3±1.5
Percussion	18	49.8±8.4	50.4±6.0	0.99	7.3±0.3
Acapella	18	35.4±4.8	58.8±16.2	0.64	13.5±1.7
PEP	18	26.4±9.0	57.6±12.0	0.47	

Data are represented as mean±SD of each subject. Table adapted from work by McCarren[49] and McIlwaine's own work.[50,51] Peak expiratory Flow Rate (PEFR) and Peak Inspiratory Flow Rate are recorded in Litres per minute.

Effects of expiratory airflow on airway surface liquid

There have been studies on the effect of airflow on the volume of airway surface liquid (ASL), using an oscillatory motion device and a cyclic compressive device.[47,52] The use of these devices caused normal airway cell cultures to double their ASL height with oscillatory motion of 0.3–0.4 Hz, and CF cultures to increase their ASL height to approximately 7µm, thereby being capable of maintaining mucus transport for protracted intervals. It is hypothesised that oscillatory shear stress stimulates Adenosine triphosphate (ATP), which in turn stimulates Ca^{2+} mediated Cl^- secretion and also inhibits the Na^+ absorption.

These important physiological findings provide some basis for the use of airway clearance techniques utilising expiratory airflow and pressure support. However, the oscillation rate of 0.3 – 0.4 Hz, which is defined in these experiments, is only slightly greater than the rate of breathing in an adult, and does not equate to the oscillation rate of 11 – 15 Hz described below as the oscillation rate necessary for effective airway clearance. Further studies are needed to confirm these in vitro experiments.

Oscillation

Oscillation frequencies between 5 to 17 Hz improve tracheal mucus clearance rates in dogs with frequencies between 11 and 15 Hz increasing mucus clearance from 8.2 mm/min to 26 mm/min,[53] which corresponds with the ciliary beat frequency. Oscillations also have an effect on the mucus rheological properties of mucus rigidity (sum of viscosity and elasticity), spinnability (thread forming capacity of mucus), and a derived cough clearance index (CCI). A higher CCI indicates that the mucus is easier to clear with a cough. In an *in vitro* study, oscillations at 19 Hz using an oscillatory positive expiratory pressure device (Flutter VRP1) resulted in only a small non-significant decrease in mucus rigidity and no significant change

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in the CCI.[54] The use of rhDNase had the same effect. However, when oscillations were combined with rhDNase the result was a significant decrease in rigidity and a significant change in the CCI. A 4 week clinical study confirmed the findings from the *in vitro* study and demonstrated a significant decrease in sputum rigidity and spinnability following oscillation with the Flutter compared to autogenic drainage.[55] In another study of CF patients who exercised for 20 minutes on a treadmill, there was also a significant reduction in sputum rigidity.[56] This result may be due to trunk oscillations associated with treadmill exercise.

Vibrations

Vibrations are the application of fine manual oscillatory movements (either back and forth or side to side) applied to the chest wall during expiration. In studies of healthy subjects vibrations increase peak expiratory flow rates (PEFR) by 50% over relaxed expiration.[57,58] The frequency of vibration and its effect on expiratory airflow has been compared to several other airway clearance interventions in clinical studies: Acapella; Positive Expiratory Pressure (PEP); Flutter; and, Percussion.[49] Vibration was applied during expiration after a slow maximal inspiration (Table 2). The resultant PEFR of 1.58 L/s and PEFR/PIFR ratio of 1.51, is sufficient to assist in mucus clearance and was greater than the other interventions, but lower than a huff or cough manoeuvre.[49] This work has added greatly to our understanding of the effects of vibration, particularly its impact on expiratory flow rates. In addition, based on studies demonstrating that oscillation frequencies of between 5–17Hz improves mucocilliary clearance,[52] there is a sound rationale to suggest that vibrations with a frequency of <17 Hz will improve mucociliary transport.[49,58]

3. Applying physiological principles to airway clearance techniques

In order to determine which ACT is most suitable for the individual patient, it is important to understand how each ACT incorporates the physiological elements of ventilation and

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expiratory airflow as described previously. Both are essential for enhancing mucus clearance.

Table 3 gives a synopsis of the physiological basis for each ACT followed by a more detailed

outline of their physiological components. The ACTs included in this section are those which

are evidence based and have randomised controlled long-term clinical trials to support their

use. There are other ACTs and ACT devices in use, which are currently being researched but

have not been included in this review as they lack the rigour of long-term studies.

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Table 3. Physiological basis for each airway clearance technique.

	Interdependence	VENTILATION			EXPIRATORY AIRFLOW		
	Interdependence	Collateral Ventilation (CV)	Breath hold	Huffing[1]	PEFR/PIFR >1.1	PEFR > 30 – 60 L/min	Oscillation
Active Cycle of Breathing Techniques	Thoracic expansion exercises utilise interdependence	Thoracic expansion exercises utilise CV	Sometimes used with this technique if hypo- ventilating	Uses forced expirations at different levels	Ratio = 2.8	Average 302 L/min with huffing	No
Autogenic Drainage	No	Yes with breath hold	Uses 3 second breath hold with each breath	Only used to clear secretions from larger airways if needed	Yes, emphasis is on slow inspiration and increased velocity on expiration	40 – 70 L/min. Depends on level of breathing and degree of airway obstruction	No
Positive Expiratory Pressure	No	As PEP is maintained within the airways during 12 – 15 breaths, use of CV is maximised.	Not necessary as PEP is maintained within the airways during 12 – 15 breaths.	Used at end of each cycle of 12 -15 breaths	No Ratio = 0.47	No Average 26 L/min	No
Oscillating Positive Expiratory Pressure with Flutter	Oscillations between 3-5 Hz may play a role, but frequency used in Flutter is > 5 Hz	Yes with breath hold	Uses 3 second breath hold with each breath	Used at end of each cycle of 8 - 10 breaths	Ratio = 1.15	Average 68 L/min	2 - 32Hz Most often uses 6 - 26 Hz
Oscillating Positive Expiratory Pressure with Acapella	Oscillations between 3-5 Hz may play a role, but frequency used in Acapella is > 5 Hz	As a PEP is maintained within the airways during 12 – 15 breaths, use of CV is maximised	Not necessary	Used at end of each cycle of 12 -15 breaths	No Ratio = 0.64	Average 35.4 L/min Within PEFR range needed, but would depend, on viscoelastic and viscosity properties of secretions.	10 - 18 Hz
High FrequencyChestWallOscillation	Oscillations between 3-5 Hz may play a role, but frequency used in HFCWO is > 5 Hz	No	No	Interspersed with HFCWO	Yes, expiratory flow rate is much higher than inspiratory flow rate.	Average 120 L/min	5-25 Hz

Peak expiratory Flow Rate (PEFR) and Peak Inspiratory Flow Rate are recorded in Litres per minute.

[1] Each technique with the exception of AD incorporates huffing as used at PET.

Active cycle of breathing techniques (ACBT)

ACBT ventilates behind obstructed lung units, using interdependence and collateral ventilation, during thoracic expansion exercises.[59] A three second breath hold is included at the end of inspiration. This increases alveolar gas mixing and decreases the inhomogeneity of ventilation.[36] (Table 3). The main driver of expiratory airflow is huffing, which relies on the use of EPP to enhance mucus clearance. The peak expiratory flow rate, with a huff at high lung volume, is similar to a cough (Table 2), demonstrating that the increase in air flow linear velocity is sufficient to promote cephalic movement of secretions.[60] Both the breathing level at which the huff is performed and the strength of the huff are adjusted to allow the EPP to occur where the secretions are located. As huffing is a forced expiration manoeuvre which can lead to bronchospasm, it is necessary to intersperse it with breathing control i.e. the "Forced Expiration Technique (FET)" which is a combination of huffing and breathing control.[61] ACBT is performed in either upright, recumbent positions or drainage positions.[60]

Autogenic drainage (AD)

In autogenic drainage (AD) ventilation to obstructed lung regions is achieved with a three second breath hold on inspiration during tidal volume breathing, utilising the collateral ventilation channels. The expiratory airflow is modulated so that at each level (unsticking phase, collecting phase, and evacuating phase), tidal volume breathing is performed and the expiratory airflow velocity is maximised without causing dynamic compression of the airways (Figure 1).[62,43] In a study with patients who had obstructive lung disease, when AD was performed, the expiratory airflow varied between 40 – 70 L/min depending on lung volume and level of breathing, thereby moving secretions proximally.[50] A slow inspiratory flow rate is necessary to create an expiratory

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flow rate bias by at least 10%. AD is usually performed in an upright position, an alternate position may be used to enhance ventilation to specific lung regions.

Positive Expiratory Pressure Mask

Positive expiratory pressure, used in the PEP technique, is a flow regulating technique employing positive expiratory pressures between $10 - 20$ cms of H_2O. [63,64] FRC is temporarily increased by breathing through a closed system using a PEP Mask (Figure 2).[65] Usually PEP is performed in a sitting position and the patient is instructed to take $12 - 15$ tidal volume breaths through the PEP mask before it is removed for huffing.[66] If the patient removes the mask prematurely, before completing 12 breaths, or uses a mouthpiece without a good seal, the positive pressure in the airways is lost and FRC returns to normal thereby lessening the effect of the technique. The effect of an application of PEP on collateral channels was demonstrated by Martin[35]. The PEP technique uses a pressure similar to that used in studies on the effect of pressure on ASL.[47,52] Therefore, it may also enhance mucociliary transport.

While ventilation is improved through the use of the PEP mask, the expiratory airflow necessary to mobilise secretions proximally is not achieved as PEP only has a PEFR/PIFR of 0.47.[49] PEP therefore needs to be combined with a manoeuvre such as huffing or autogenic drainage.

Oscillating Positive Expiratory Pressure

Flutter and Acapella devices generate an automatically controlled oscillating PEP, although both operate utilising different physiological bases. They provide similar frequency of oscillation within the range necessary to decrease the viscoelastic and spinnability properties of mucus, and thereby improve mucus clearance.[53,55] Flutter oscillates with frequencies 6-26 Hz, with average PEP pressures of 18-35 cms H_2O. Acapella oscillates with frequencies of $10 - 18$ Hz, with an average pressure between $10 - 25$ cms H_2O.[67] These oscillation frequencies are much higher than

the 0.3–0.4 Hz[47,52] used in *in-vitro* experiments where ASL height was doubled. It has still to be determined what effect frequencies of 6- 26Hz have on ASL.

Oscillating PEP with Flutter

While exhaling through the flutter to ERV, the individual tunes the device to their ventilator abilities, thereby enabling a modulation of both pressure and airflow oscillation frequency increasing expiratory airflow to mobilise secretions proximally.[68] Flutter produces an expiratory flow bias of PEFR/PIFR 1.15, which is sufficient to mobilise secretions.[49] In addition, huffing is added at the end of each breathing cycle. Unlike the PEP Mask, FRC is not increased with the flutter due to the inability to inspire through the device. To overcome ventilatory asynchronism, inspiration is followed by a three second breath hold.

While the Flutter meets the two criteria for mobilising secretions, it raises some concerns. Sometime, expiration is into the ERV where closing volume has the potential to cause airway closure.[69] FRC level is not temporarily increased so that the effect of PEP on opening collateral channels is negated. However, the three second breath has been shown to increase alveolar gas mixing, alter time constants, and allow air to move distal to any obstruction. Another limitation of the Flutter is that due to its pipe-like design, it can only be used in the upright position.

Oscillating PEP with Acapella

Because inspiratory and expiratory manoeuvres are performed through the Acapella in a closed system for 12 to 15 breaths, its physiological basis is similar to the PEP technique, allowing air to move behind secretions through collateral ventilation channels as a result of an increased FRC level. The addition of oscillation should enhance the technique. Similar to PEP, the expiratory flow bias is insufficient with a PEFR/PIFR ratio of 0.64,[49] therefore the Acapella needs to be

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combined with huffing to assist in mucociliary clearance from the larger airways. Acapella is position independent, so it can be used in any position to optimise ventilation

High frequency chest wall oscillation (HFCWO).

During HFCWO (also known as High Frequency Chest Compression) oscillations are created over the chest wall at frequencies between 5–25 Hz. On expiration the oscillations enhance mucociliary transport in three essential ways, similar to the oscillations produced with oscillatory PEP devices: 1) by altering the rheological properties of mucus; [54] 2) by creating an expiratory flow bias that shears mucus from the airway walls and encourages its movement proximally;[53] and, 3) by enhancing ciliary beat frequency.[70] The oscillatory expiration flow generated by compression of the chest wall, (creating a PEFR up to 120 L/min), is sufficient to overcome mucus adhesion from the airway wall and propel it up the airway. However, the HFCWO device provides no means of ventilating behind obstructed airways. Unlike the other oscillatory devices, HFCWO does not provide any PEP, and the end-expiratory volume has been reported to decrease 10-50% during compression.[71] While this may improve expiratory flows through the smaller airways, it may worsen expiratory flows if the airways are smaller and airway resistance is increased, leading to early airway closure.[72] This may lead to a worsening of lung disease. Several short-term randomised controlled trials in CF patients have been unable to demonstrate any significant difference between HFCWO and other ACTs.[73-76] However, in two long term studies, HFCWO was associated with an increased number of respiratory exacerbations in one,[77] and by a decreased in lung function in the other.[78]

Personalising airway clearance strategies

While no one ACT has been found to be more effective than another, as synthesised in five

Cochrane reviews[79-83] on ACT's in CF, traditionally the choice of ACT has been based on: what

is available locally; the training and expertise of the local physiotherapist; and culture.[84]

However, a one size fits all approach based on regional preference may not address specific

patient's needs. An individualised strategy should take into account the patient's disease state,

preference, motivation, and maturity which, together with the physiological knowledge base of

each ACT, apply the most effective airway clearance intervention for that individual. Some

examples of clinical considerations based on the unique physiological principles of each ACT

are as follows:

a) A deep inspiration with a three second breath hold is a particularly effective means of

increasing ventilation in patients with a restrictive component to their lung disease[37]. But

using a 3 second breath hold in a patient with a severe lung disease who is tachypneaic

may lead to hypoxia.

b) A forced expiration, as used in ACBT and with the various PEP devices, needs to be

adapted to the individual's underlying lung pathology. In someone with collapsible

airways, a huff may compress the airways in such a way as to limit expiratory airflow

rather than to increase the velocity of airflow[43]. Alternatively, if bronchospasm is present,

airflow obstruction is greater therefore one needs to reduce the force of the huff.

c) In autogenic drainage the expiratory airflow is gently accelerated avoiding compression

of the airways. This technique is therefore more favourably suited to patients with

bronchospasm, or patients with haemoptysis, where a gentler technique is required. In a

clinical study, patients with bronchospasm responded best to AD.[85] As AD requires a

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self-awareness of one's own respiratory mechanics and concentration to perform, it is generally used in teenagers or adults, unless a caregiver is skilled in its performance.

d) PEP increases FRC during tidal volume breathing, evening out intrapulmonary distribution of ventilation, opening up regions that are otherwise closed off.[65] It is therefore effective in both restricted and obstructed patients. In addition, the positive expiratory pressure splints the airways during expiration thereby avoiding airway collapse, which makes it a favourable technique for patients with unstable airways.

e) Adding oscillations to expiration, either by using a oscillatory PEP device or HFCWO device, has the added advantage of: increasing mucociliary clearance;[53] decreasing the viscoelastic properties of mucus; and, potentially rehydrating mucus. When using oscillation devices, the clinician needs to consider what method they want to use to first ventilate behind the obstructed units. Flutter uses a three second breath hold, Acapella like PEP increases FRC, splinting airways open. HFCWO needs to be combined with either deep inspiratory manoeuvres, three second breath hold, or PEP.

f) Exhaling into ERV, as used during AD, Flutter and HFCWO assists in mobilising secretions from the small airways but has the potential to cause airway closure.[62,69,71] To avoid this, during these techniques, the therapist should ensure patients adequately incorporate methods to ventilate small airways such as three second breath holds, or thoracic expansion exercises.

g) A therapeutic strategy for an individual patient may involve a combination of ACTs. For example, in a patient with unstable large airways, the use of a PEP device will enhance ventilation. But during the huffing phase the airways may be unable to resist

compression. By combining PEP with AD, expiratory flow rates could be increased

without causing airway compression thereby mobilising secretions more effectively

Conclusion

The approach to care of the individual patient needs to be personalised. Sometimes, in clinical

practice more than one ACT may be effective for a patient at a given time in their disease

trajectory and choice of technique may then be dependent on availability and patient preference.

Other considerations include cleaning and durability of an ACT device if one is used. However,

more often than not, due to the varying nature of the underlying disease pathology; phenotypic

characteristics; and, taking into account individual patients' clinical, functional, environmental

and social factors, ACTs needs to be personalised to meet patient's specific needs. This requires

a sound understanding of the physiological basis of each technique

Examining the application of physiological principles to ACTs provides a better understanding

of how to optimise airway clearance strategies to the individual patient's underlying pathology.

This allows for both more personalised and improved patient care. Physiological theories which

support ACTs had previously been identified.[42,43,86] However, this is the first review to present

the physiological evidence supporting methods to ventilate behind obstructed lung units, and

modulation of expiratory airflow, and to collate this physiological evidence in an effort to assist

in translation into practice.

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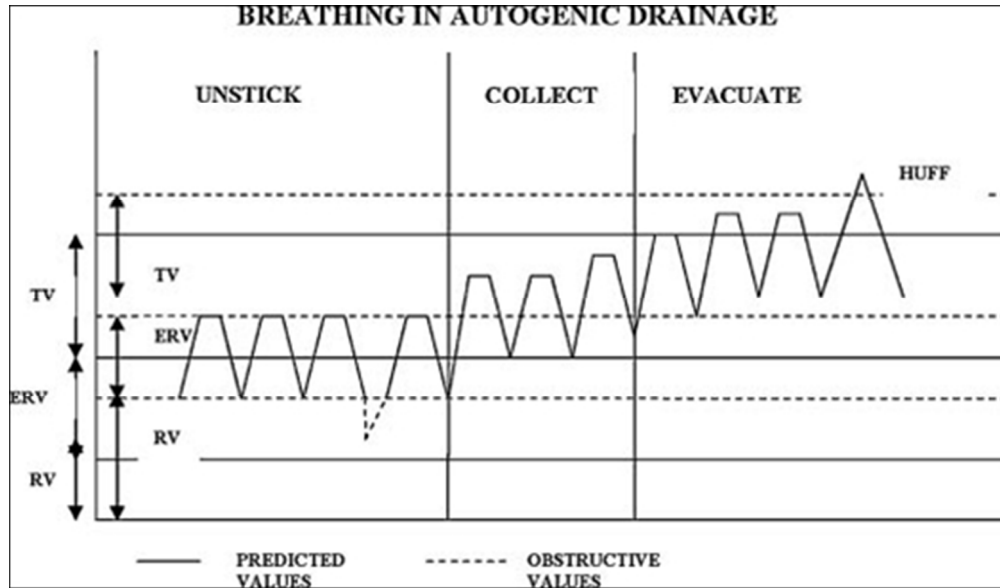
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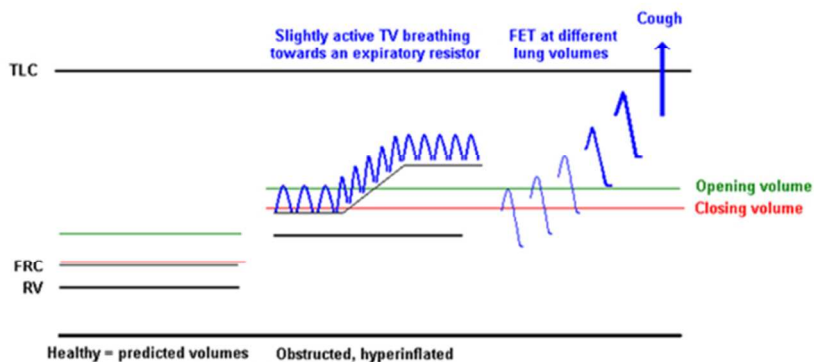
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Airway clearance using PEP in a pulmonary obstructed patient with hypersecretion problems

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Legends for figures

Figure 1. Breathing pattern during autogenic drainage

Figure 2. Schematic representation of breathing levels during PEP in an obstructed patient. Courtesy L. Lannefors

Title page

Title of article: Personalising airway clearance in chronic lung disease.

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ABSTRACT

This review describes a framework for providing a personalised approach to selecting the most appropriate airway clearance technique (ACT) for the individual patient. It is based on a synthesis of the physiological evidence that supports the modulation of ventilation and expiratory airflow as a means of assisting airway clearance. By possessing a strong understanding of the physiological basis for ACTs, it will enable clinicians to decide which ACT best aligns with the individual patient's pathology in diseases with anatomical bronchiectasis and mucus hyper-secretion.

The physiological underpinning of postural drainage is that by placing a patient in various positions, gravity enhances mobilisation of secretions. Newer ACTs are based on two other physiological premises: the ability to ventilate behind obstructed regions of the lung; and the capacity to achieve the minimum expiratory airflow bias necessary to mobilise secretions. After reviewing each ACT to determine if it utilises both ventilation and expiratory flow, these physiological concepts are assessed against the clinical evidence to provide a mechanism for the effectiveness of each ACT. This paper provides the clinical rationale necessary to determine the most appropriate ACT for each patient, thereby improving care.

Physiological Basis of Airway Clearance Techniques

INTRODUCTION. Personalised medicine has been used to describe the application of genomics, proteomics and biomarkers to precisely tailor therapy according to various characteristics of an individual patient[1] This concept of personalised medicine can also be applied to a variety of therapies, such as airway clearance, by taking into account individual patients' lung pathology, clinical, functional, environmental and social factors, as well as the physiological concepts underlying airway clearance techniques (ACTs). [2] Personalised medicine results in resources being more effectively directed to the most appropriate patients, thereby ensuring that patients receive the specific technique that optimises the likelihood of benefit in terms of lung health and time commitment. The use of ACT's can be further enhanced by the appropriate use of inhaled medications such as mucoactive agents, however these medications are not within the scope of this review.[3]

This paper provides an overview of the physiological principles underlying ACTs and links these physiological principles to the evidence base of commonly used ACTs. This will facilitate clinicians to personalise airway clearance techniques specific to patients underlying lung pathology as well as other clinical, functional, environmental and social factors. While some patients with chronic lung disease are ventilated, the vast majority are breathing spontaneously. As the physiological mechanisms described differ in ventilated patients, it must therefore be emphasised that this paper is written only for the spontaneously breathing patient.[4]

Background

ACTs are used to supplement the body's mucociliary clearance system when it is impaired by disease. This system is an important lung defence mechanism consisting of: airway surface

liquid comprising of mucus and periciliary layers (PCL); ciliary epithelium; and, a cough mechanism.[5] In healthy people, cilia beat at a mean frequency of between 11 - 13 Hz,[6] propelling mucus proximally up the airways at a rate of between 4 -5 mm/min.[7,8] The rate of clearance is strongly influenced by the mucus's hydration state, rigidity, and viscosity to elasticity ratio.[9,10]

The mucociliary transport system is impaired in chronic suppurative lung diseases, such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD) and bronchiectasis not caused by CF (BE). This is due to the occurrence of one or more of the following conditions: dehydration of the PCL; absence of lubricant activity which prevents adhesion of mucus to airway surfaces;[11] an inherent defect within the cilia; or, immunodeficiencies including cellular defects. Any one of these may cause a failure of ciliary beat frequency and reduced mucociliary clearance. Once this mechanical defence system is breached, the lung is more susceptible to infection and inflammation that can result in further airway damage, eventually leading to bronchiectasis.[12]

To be effective, ACTs should assist the body's natural mucociliary clearance system to transport secretions proximally up the airways. Historically, to achieve mucociliary clearance, postural drainage positions were utilized primarily for drainage by relying on gravity.[13] However, there is little supporting evidence that postural drainage utilising gravity, effectively mobilises secretions.[14,15] In CF patients, gravity in a head-down position increased the mucociliary clearance rate only from 0 mm/min to 3 – 5 mm/min[8]. Based on the assumption that mucociliary clearance rates in gravity dependant positions remain the same in different lung regions, to mobilise secretions from a sub-segmental airway in the lower lobe would require a patient to be placed in a head down position for approximately one hour. Thus, positioning a patient in a head-down position alone for 3- 5 minutes (as historically

used in CF centres), is expected to be ineffective and may even do harm by promoting gastro-oesophageal reflux.[13,16-20] Two studies, one in CF adults and the other in patients with chronic bronchitis using radiolabeled tracer gases demonstrated that in the side-lying position more secretions are mobilised from the dependent lung than from the non-dependent lung, which suggests that the impact of body position on ventilation plays a greater role than gravity in mobilising secretions.[21-23] Since this data was published there has been limited translation of these findings into clinical practice, suggesting why perhaps that in many countries, positioning for drainage remains a key ACT. Positioning for ventilation will be discussed later in this paper.

Newer ACTs rely on two over-riding physiological principles. First, a mechanism to allow air to move behind obstruction and ventilate the regions distally, and second, modulation of expiratory airflow in such a way as to propel secretions proximally up the airways. This paper describes the physiological theories and evidence underlying the use of individual ACTs in the non-ventilated spontaneously breathing patient.

1. Principles for optimising ventilation to obstructed regions of the lung.

In normal healthy individuals, dDuring inspiration, airflow takes the path of least resistance, ventilating all areas of the lung, although there may be some asynchronous ventilation secondary to regional and stratified inhomogeneity.[24] In patients with obstructed airways, sSecretions decrease the diameter of the airway and increase airway resistance, causing preferential ventilation of unobstructed regions and hypoventilation of obstructed regions.[24] Over time, air gradually moves behind the obstruction due to altered time constants, but it is not expired, leading to dynamic hyperinflation of the obstructed lung unit. Several mechanisms used in ACTs optimise ventilation to obstructed lung units.

Interdependence during deep inspiration

When tidal volume is increased during a deep inspiration, expanding alveoli exert a traction force on less well expanded alveoli which they surround, thereby assisting in the re-expansion of collapsed alveoli due to the elasticity of the surrounding interstitium. This is known as "interdependence". It results in air moving into the small airways obstructed by secretions, a phenomenon that has been called Pendelluft[25] and which results from the "interdependence". The theory of interdependence was proposed by Mead and a physical model was created to test this hypothesis.[26] The theory was later confirmed in clinical studies on anesthetised dogs.[27]

Collateral ventilation (CV)

Ventilation can also occur between adjacent lung segments through collateral channels.[28,29] In healthy individuals, the importance of CV is negligible due to resistance to airflow being higher in the collateral channels than in the airways. However, if an airway proximal to these collaterals becomes blocked, the collateral channels allow air to move through these pathways due to the pressure differences between adjacent lung units and function to minimise collapse of lung units. Studies have shown that excised human lungs can be re-inflated using collateral channels.[30,31] There are three types of collateral connections: channels of Lambert; pores of Kohn; and, pathways/channels of Martin.

 Channels of Lambert represent epithelium-lined tubular communications between distal bronchioles and the adjacent alveoli. These are most likely the primary channels responsible for CV.[32] Pores of Kohn are inter-alveolar connections. There are approximately 50 pores of Kohn varying from 3 to 13μm in diameter in each alveolus.[33,34] *In vivo*, these pores are mostly filled by fluid and act as a pathway for alveolar lining fluid, surfactant components, and cells like macrophages to move between adjacent alveoli.[34] Lastly, there exists Pathways of Martin/channels of Martin, which are interbronchiolar connections. Results of an experiment with excised dogs lungs, pressurised to between $17 - 28$ cms H_2O, indicated connections between respiratory bronchioles and terminal bronchioles from adjacent lung

segments,[35] suggesting that use of collateral ventilation channels forms the basis for use of positive expiratory pressure ACTs .

Three second breath hold

A three second breath hold is another method of ventilating obstructed lung units. When the unobstructed region of the lung has been preferentially ventilated a pause for three seconds alters the time constants and allows air to move from the unobstructed regions, where the pressure gradient is higher, to the obstructed regions of the lung. This transient movement of gas out of some alveoli into another at the end of inspiration is known as Pendelluft flow. Multiple-breath washout tests have shown that a breath hold increases alveolar gas mixing and decreases the inhomogeneity of ventilation in normal subjects.[36] In post-operative clinical practice it has been demonstrated that a three second breath hold is effective in reducing atelectasis.[37]

Positioning to optimise ventilation in adults and children

Positioning may be used to enhance ventilation to specific lung regions where secretions are located, such as in bronchiectasis patients. The increased ventilation to those lung regions can then be used effectively to mobilise secretions.[21,22] There are differences in chest shape and lung mechanics between adults and children which result in differences in ventilation patterns.

When adults are placed in the upright position, optimum ventilation occurs in the mid and lower lobes, while perfusion is greatest in the lower lobes. Theoretically, ventilation/perfusion ratio V/Q = 1 is at the level of the right middle lobe and lingula.[38] When an adult is placed in side-lying, the dependent lung is preferentially ventilated due to the dependent hemi-diaphragm being stretched, causing a greater length to tension ratio, with increased contractility. This creates a greater negative pleural pressure, which clinically results in increased ventilation.[39]

Perfusion is greater to the dependent lung in both adults and children because it is gravity dependent.

When very young children are placed in side-lying, the non-dependant lung is preferentially ventilated, most likely due to the differences in their lung and chest wall mechanics. This occurs in children up to age 12 years, causing airway closure to occur in the more dependent regions, independent of lung disease.[39]

Supine is the best position to ventilate the upper lobes.[38] However, if this is not suitable, as when taking an inhaled medication, side lying may be an alternative position. Inhaled drug deposition is improved by 13% to the dependent upper lobe when healthy adults were placed in side-lying. Adults with mild CF lung disease improve upper lobe deposition by 4% with the same side lying strategy[40] Table 1 shows optimal positioning for use during airway clearance to optimise ventilation to obstructed regions of the lung, based on changes in ventilation patterns with positioning.

Table 1. Optimal positioning for airway clearance techniques to enhance ventilation to obstructed regions of the lung

	Optimal position	**Alternative, 2nd choice, Position**
Secretions in upper lobes	Supine	Side Lying
Secretions in middle lobe and lingula	Upright	Side Lying or Supine
Secretions in right lung	Adults: place in right side lying Children: place in left side lying	
Secretions in left lung	Adults: place in left side lying Children: place in right side lying	
Secretions lower lobes	Upright	Side Lying

Use of mobilisation to increase ventilation

Moving a patient into different positions affects ventilation in two different ways. First, a change in body position alters regional ventilation as noted above. Second, by increasing the mobility of a patient, oxygen demand increases, resulting in a corresponding increase in minute ventilation and lung volumes.[41] The resultant increase in ventilation allows air to move into obstructed lung units by interdependence and collateral ventilation.

2. **Methods of utilising expiratory airflow to enhance secretion removal**

Increasing the velocity of the expiratory airflow in such a way as to create high shearing forces at the airway walls, and high kinetic energy that enhance the cephalad movement of secretions is a second key mechanism to mobilise airway secretions.

Cough

Coughing is a normal reflex defence mechanism used to clear excessive secretions down to the 7th or 8th generation of airways.[42] During a typical cough, a deep inspiration is followed by closure of the glottis. High intra-thoracic pressures (up to 300 mmHg) builds up, resulting in a high explosive, turbulent expiratory flow rate that may exceed 500 L/min[43] when the glottis is opened. During this time, dynamic compression of the airways occurs, resulting in an increase in velocity and kinetic energy which produces a shear force detaching mucus from the airway walls and enhancinges the cephalic movement of mucus proximally up the airways., and overcomes the shear force of mucus attached to the airway walls. Distal to the regions where the airways are compressed, there may be a collapse of the airways, especially when airway instability is present.[43]

Cough is an effective method of clearing secretions from the larger airways in healthy individuals. However, in chronic supperative lung disease, where narrowing and "floppy" airways may close prematurely, it can have detrimental effects if used inappropriately over an

extended period as the primary method of clearing secretions. When repeated coughs are used, bronchial wall instability may result due to recurrent compression of the airways, thereby reducing expiratory flow and limiting the effectiveness of the cough.[44] Therefore, we recommend that ACTs be used as the primary method of mobilising secretions from the middle and small airways to the larger airways. Then one effective cough be used to clear secretions from the larger airways, thereby preserving the integrity of the larger airways.

Huff / Forced expiratory manoeuvre

A forced expiration manoeuvre may also be described as a "Huff". It accelerates the expiratory airflow, creating high linear velocities that shear mucus from the airway walls. Unlike a cough that is performed with a closed glottis, a huff is performed with an open glottis. The huff concept is based on the equal pressure point theory (EPP).[45] At the EPP, dynamic compression of the airways occurs, creating an increase in the linear velocity of the expiratory airflow which propels secretions proximally. The site of the EPP is determined by the size of expiratory force, airway stability, and the elastic recoil. Initiating a forced expiration at a low lung volume shifts the EPP to the periphery, targeting secretions in the small airways. Similarly, initiating a forced expiration from a high lung volume will move the EPP centrally towards the thoracic aperture. This is sometimes referred to as a "Huff-Cough".[38]

Two-phase gas-liquid flow mechanism

Mucus clearance can be modelled as a two-phase gas-liquid flow mechnism.[46] This indicates that peak expiratory flow rate (PEFR) must exceed peak inspiratory flow rate (PIFR) by at least 10% for mucus to move proximally. The peak expiratory flow rate must also exceed 30 – 60 L/min to overcome the adhesive strengthshear force by which the mucus is attached to the interface. Mucus factors affecting mucociliary clearance are the mucus depth and the

viscoelastic properties of mucus. Viscosity is a liquid property of mucus, whereas elasticity is described as the energy storage with an applied stress to a solid. The rate of mucus transport is higher with viscoelastic mucus than with non-elastic viscous mucus.[47]

During normal tidal volume breathing at rest, PEFR does not exceed 30 L/min and PIFR is greater than PEFR. The result is that secretions are not mobilised. In order to use airflow to mobilise secretions it is necessary to optimise the expiratory airflow so that the PEFR > PIFR by at least 10%, and the velocity of the expiratory flow rate is at least 30 – 60 L/min, depending on the properties of the secretions. In a clinical study that examined the effect of a cough and a huff on regional lung clearance, PEFR recorded with a cough was 288 (29) l/min and 203 (25) l/min with a huff.[48] Both were sufficient to increase tracheobronchial clearance by 44% and 42% respectively, confirming that an increase in PEFR will enhance lung clearance.[48] Further studies have demonstrated that, in addition to huffing and coughing, manual vibration, oscillating positive expiratory pressure (using the Flutter VRP1) as well as autogenic drainage met the criteria for using expiratory flow to mobilise secretions proximally.[49,50] (Table 2)

Table 2. Effects of airway clearance interventions on peak expiratory flow rates.

Intervention	Subject n	PEFR L/mins	PIFR L/min	PEFR/PIFR Ratio	Frequency Hz
Huff	17	302.4±121.8	124.8±85.2	2.80	
Cough	17	280.2±114.6	100.8±44.4	3.07	
Vibration	17	94.8±43.8	63.6±16.2	1.51	8.4±0.4
Autogenic Drainage	14	85.2±28.8	50.4±13.8	1.69	
Flutter	17	67.8±18.0	63.0±16.2	1.15	11.3±1.5
Percussion	18	49.8±8.4	50.4±6.0	0.99	7.3±0.3
Acapella	18	35.4±4.8	58.8±16.2	0.64	13.5±1.7
PEP	18	26.4±9.0	57.6±12.0	0.47	

Data are represented as mean±SD of each subject. Table adapted from work by McCarren[49] and McIlwaine's own work.[50,51] Peak expiratory Flow Rate (PEFR) and Peak Inspiratory Flow Rate are recorded in Litres per minute.

Effects of expiratory airflow on airway surface liquid

There have been studies on the effect of airflow on the volume of airway surface liquid (ASL), using an oscillatory motion device and a cyclic compressive device.[47,52] The use of these devices caused normal airway cell cultures to double their ASL height with oscillatory motion of 0.3–0.4 Hz, and CF cultures to increase their ASL height to approximately 7µm, thereby being capable of maintaining mucus transport for protracted intervals. It is hypothesised that oscillatory shear stress stimulates Adenosine triphosphate (ATP), which in turn stimulates Ca^{2+} mediated Cl^- secretion and also inhibits the Na^+ absorption.

These important physiological findings provide some basis for the use of airway clearance techniques utilising expiratory airflow and pressure support. However, the oscillation rate of 0.3 – 0.4 Hz, which is defined in these experiments, is only slightly greater than the rate of breathing in an adult, and does not equate to the oscillation rate of 11 – 15 Hz described below as the oscillation rate necessary for effective airway clearance. Further studies are needed to confirm these in vitro experiments.

Oscillation

Oscillation frequencies between 5 to 17 Hz improve tracheal mucus clearance rates in dogs with frequencies between 11 and 15 Hz increasing mucus clearance from 8.2 mm/min to 26 mm/min,[53] which corresponds with the ciliary beat frequency. Oscillations also have an effect on the mucus rheological properties of mucus rigidity (sum of viscosity and elasticity), spinnability (thread forming capacity of mucus), and a derived cough clearance index (CCI). A higher CCI indicates that the mucus is easier to clear with a cough. In an *in vitro* study, oscillations at 19 Hz using an oscillatory positive expiratory pressure device (Flutter VRP1)

resulted in only a small non-significant decrease in mucus rigidity and no significant change in the CCI.[54] The use of rhDNase had the same effect. However, when oscillations were combined with rhDNase the result was a significant decrease in rigidity and a significant change in the CCI. A 4 week clinical study confirmed the findings from the *in vitro* study and demonstrated a significant decrease in sputum rigidity and spinnability following oscillation with the Flutter compared to autogenic drainage.[55] In another study of CF patients who exercised for 20 minutes on a treadmill, there was also a significant reduction in sputum rigidity.[56] This result may be due to trunk oscillations associated with treadmill exercise.

Vibrations

Vibrations are the application of fine manual oscillatory movements (either back and forth or side to side) applied to the chest wall during expiration. In studies of healthy subjects vibrations increase peak expiratory flow rates (PEFR) by 50% over relaxed expiration.[57,58] The frequency of vibration and its effect on expiratory airflow has been compared to several other airway clearance interventions in clinical studies: Acapella; Positive Expiratory Pressure (PEP); Flutter; and, Percussion.[49] Vibration was applied during expiration after a slow maximal inspiration (Table 2). The resultant PEFR of 1.58 L/s and PEFR/PIFR ratio of 1.51, is sufficient to assist in mucus clearance and was greater than the other interventions, but lower than a huff or cough manoeuvre.[49] This work has added greatly to our understanding of the effects of vibration, particularly its impact on expiratory flow rates. In addition, based on studies demonstrating that oscillation frequencies of between 5–17Hz improves mucocilliary clearance,[52] there is a sound rationale to suggest that vibrations with a frequency of <17 Hz will improve mucociliary transport.[49,58]

3. Applying physiological principles to airway clearance techniques

In order to determine which ACT is most suitable for the individual patient, it is important to understand how each ACT incorporates the physiological elements of ventilation and expiratory airflow as described previously. Both are essential for enhancing mucus clearance. Table 3 gives a synopsis of the physiological basis for each ACT followed by a more detailed outline of their physiological components. The ACTs included in this section are those which are evidence based and have randomised controlled long-term clinical trials to support their use. There are other ACTs and ACT devices in use, which are currently being researched but have not been included in this review as they lack the rigour of long-term studies.

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Table 3. Physiological basis for each airway clearance technique.

		VENTILATION			EXPIRATORY	AIRFLOW	
	Interdependence	Collateral Ventilation (CV)	Breath hold	Huffing[1]	PEFR/PIFR >1.1	PEFR > 30 – 60 L/min	Oscillation
Active Cycle of Breathing Techniques	Thoracic expansion exercises utilise interdependence	Thoracic expansion exercises utilise CV	Sometimes used with this technique if hypo- ventilating	Uses forced expirations at different levels	Ratio = 2.8	Average 302 L/min with huffing	No
Autogenic Drainage	No	Yes with breath hold	Uses 3 second breath hold with each breath	Only used to clear secretions from larger airways if needed	Yes, emphasis is on slow inspiration and increased velocity on expiration	40 – 70 L/min. Depends on level of breathing and degree of airway obstruction	No
Positive Expiratory Pressure	No	As PEP is maintained within the airways during 12 – 15 breaths, use of CV is maximised.	Not necessary as PEP is maintained within the airways during 12 – 15 breaths.	Used at end of each cycle of 12 -15 breaths	No Ratio = 0.47	No Average 26 L/min	No
Oscillating Positive Expiratory Pressure with Flutter	Oscillations between 3-5 Hz may play a role, but frequency used in Flutter is > 5 Hz	Yes with breath hold	Uses 3 second breath hold with each breath	Used at end of each cycle of 8 - 10 breaths	Ratio = 1.15	Average 68 L/min	2 - 32Hz Most often uses 6 - 26 Hz
Oscillating Positive Expiratory Pressure with Acapella	Oscillations between 3-5 Hz may play a role, but frequency used in Acapella is > 5 Hz	As a PEP is maintained within the airways during 12 – 15 breaths, use of CV is maximised	Not necessary	Used at end of each cycle of 12 -15 breaths	No Ratio = 0.64	Average 35.4 L/min Within PEFR range needed, but would depend, on viscoelastic and viscosity properties of secretions.	10 - 18 Hz
High FrequencyChestWallOscillation	Oscillations between 3-5 Hz may play a role, but frequency used in HFCWO is > 5 Hz	No	No	Interspersed with HFCWO	Yes, expiratory flow rate is much higher than inspiratory flow rate.	Average 120 L/min	5-25 Hz

Peak expiratory Flow Rate (PEFR) and Peak Inspiratory Flow Rate are recorded in Litres per minute.

[1] Each technique with the exception of AD incorporates huffing as used at HFT.

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Active cycle of breathing techniques (ACBT)

ACBT ventilates behind obstructed lung units, using interdependence and collateral ventilation, during thoracic expansion exercises.[59] ~~When~~ Aa three second breath hold is included at the end of inspiration. This ~~,~~ increases alveolar gas mixing and decreases the inhomogeneity of ventilation~~time constants are further altered thereby allowing more time for the pressure gradient to equalise in the obstructed units~~.[36] (Table 3). The main driver of expiratory airflow is huffing, which relies on the use of EPP to enhance mucus clearance. The peak expiratory flow rate, with a huff at high lung volume, is similar to a cough (Table 2), demonstrating that the increase in air flow linear velocity is sufficient to promote cephalic movement of secretions.[60] Both the breathing level at which the huff is performed and the strength of the huff are adjusted to allow the EPP to occur where the secretions are located. As huffing is a forced expiration manoeuvre which can lead to bronchospasm, it is necessary to intersperse it with breathing control i.e. the "Forced Expiration Technique (FET)" which is a combination of huffing and breathing control.[61] ACBT is performed in either upright, recumbent positions or drainage positions.[60]

Autogenic drainage (AD)

In autogenic drainage (AD) ventilation to obstructed lung regions is achieved with a three second breath hold on inspiration during tidal volume breathing, utilising the collateral ventilation channels. The expiratory airflow is modulated so that at each level (unsticking phase, collecting phase, and evacuating phase), tidal volume breathing is performed and the expiratory airflow velocity is maximised without causing dynamic compression of the airways (Figure 1).[62;43] In a study with patients who had obstructive lung disease, when AD was performed, the expiratory airflow varied between 40 – 70 L/min depending on lung volume and level of breathing, thereby moving secretions proximally.[50] A slow inspiratory flow rate is necessary to create an expiratory

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flow rate bias by at least 10%. AD is usually performed in an upright position, an alternate position may be used to enhance ventilation to specific lung regions.

Positive Expiratory Pressure Mask

Positive expiratory pressure, used in the PEP technique, is a flow regulating technique employing positive expiratory pressures between 10 – 20 cms of H_2O. [63,64] FRC is temporarily increased by breathing through a closed system using a PEP Mask (Figure 2).[65] Usually PEP is performed in a sitting position and the patient is instructed to take 12 – 15 tidal volume breaths through the PEP mask before it is removed for huffing.[66] If the patient removes the mask prematurely, before completing 12 breaths, or uses a mouthpiece without a good seal, the positive pressure in the airways is lost and FRC returns to normal thereby lessening the effect of the technique. The effect of an application of PEP on collateral channels was demonstrated by Martin[35]. The PEP technique uses a pressure similar to that used in studies on the effect of pressure on ASL.[47,52] Therefore, it may also enhance mucociliary transport.

While ventilation is improved through the use of the PEP mask, the expiratory airflow necessary to mobilise secretions proximally is not achieved as PEP only has a PEFR/PIFR of 0.47.[49] PEP therefore needs to be combined with a manoeuvre such as huffing or autogenic drainage.

Oscillating Positive Expiratory Pressure

Flutter and Acapella devices generate an automatically controlled oscillating PEP, although both operate utilising different physiological bases. They provide similar frequency of oscillation within the range necessary to decrease the viscoelastic and spinnability properties of mucus, and thereby improve mucus clearance.[53,55] Flutter oscillates with frequencies 6-26 Hz, with average PEP pressures of 18-35 cms H_2O. Acapella oscillates with frequencies of 10 – 18 Hz, with an average pressure between 10 – 25 cms H_2O.[67] These oscillation frequencies are much higher than

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the 0.3–0.4 Hz[47,52] used in *in-vitro* experiments where ASL height was doubled. It has still to be determined what effect frequencies of 6- 26Hz have on ASL.

Oscillating PEP with Flutter

While exhaling through the flutter to ERV, the individual tunes the device to their ventilator abilities, thereby enabling a modulation of both pressure and airflow oscillation frequency increasing expiratory airflow to mobilise secretions proximally.[68] Flutter produces an expiratory flow bias of PEFR/PIFR 1.15, which is sufficient to mobilise secretions.[49] In addition, huffing is added at the end of each breathing cycle. Unlike the PEP Mask, FRC is not increased with the flutter due to the inability to inspire through the device. To overcome ventilatory asynchronism, inspiration is followed by a three second breath hold.

While the Flutter meets the two criteria for mobilising secretions, it raises some concerns. Sometime, expiration is into the ERV where closing volume has the potential to cause airway closure.[69] FRC level is not temporarily increased so that the effect of PEP on opening collateral channels is negated. However, the three second breath has been shown to increase alveolar gas mixing, alter time constants, and allow air to move distal to any obstruction. Another limitation of the Flutter is that due to its pipe-like design, it can only be used in the upright position.

Oscillating PEP with Acapella

Because inspiratory and expiratory manoeuvres are performed through the Acapella in a closed system for 12 to 15 breaths, its physiological basis is similar to the PEP technique, allowing air to move behind secretions through collateral ventilation channels as a result of an increased FRC level. The addition of oscillation should enhance the technique. Similar to PEP, the expiratory flow bias is insufficient with a PEFR/PIFR ratio of 0.64,[49] therefore the Acapella needs to be

combined with huffing to assist in mucociliary clearance from the larger airways. Acapella is position independent, so it can be used in any position to optimise ventilation

High frequency chest wall oscillation (HFCWO).

During HFCWO (also known as High Frequency Chest Compression) oscillations are created over the chest wall at frequencies between 5–25 Hz. On expiration the oscillations enhance mucociliary transport in three essential ways, similar to the oscillations produced with oscillatory PEP devices: 1) by altering the rheological properties of mucus;[54] 2) by creating an expiratory flow bias that shears mucus from the airway walls and encourages its movement proximally;[53] and, 3) by enhancing ciliary beat frequency.[70] The oscillatory expiration flow generated by compression of the chest wall, (creating a PEFR up to 120 L/min), is sufficient to overcome mucus adhesion from the airway wall and propel it up the airway. However, the HFCWO device provides no means of ventilating behind obstructed airways. Unlike the other oscillatory devices, HFCWO does not provide any PEP, and the end-expiratory volume has been reported to decrease 10-50% during compression.[71] While this may improve expiratory flows through the smaller airways, it may worsen expiratory flows if the airways are smaller and airway resistance is increased, leading to early airway closure.[72] This may lead to a worsening of lung disease. Several short-term randomised controlled trials in CF patients have been unable to demonstrate any significant difference between HFCWO and other ACTs.[73-76] However, in two long term studies, HFCWO was associated with an increased number of respiratory exacerbations in one,[77] and by a decreased in lung function in the other.[78]

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Personalising airway clearance strategies

While no one ACT has been found to be more effective than another, as synthesised in five

Cochrane reviews[79-83] on ACT's in CF, traditionally the choice of ACT has been based on: what

is available locally; the training and expertise of the local physiotherapist; and culture.[84]

However, a one size fits all approach based on regional preference may not address specific

patient's needs. An individualised strategy should take into account the patient's disease state,

preference, motivation, and maturity which, together with the physiological knowledge base of

each ACT, apply the most effective airway clearance intervention for that individual. Some

examples of clinical considerations based on the unique physiological principles of each ACT

are as follows:

a) A deep inspiration with a three second breath hold is a particularly effective means of
   increasing ventilation in patients with a restrictive component to their lung disease[37]. But
   using a 3 second breath hold in a patient with a severe lung disease who is tachypneaic
   may lead to hypoxia.

b) A forced expiration, as used in ACBT and with the various PEP devices, needs to be
   adapted to the individual's underlying lung pathology. In someone with collapsible
   airways, a huff may compress the airways in such a way as to limit expiratory airflow
   rather than to increase the velocity of airflow[43]. Alternatively, if bronchospasm is present,
   airflow obstruction is greater therefore one needs to reduce the force of the huff.

c) In autogenic drainage the expiratory airflow is gently accelerated avoiding compression
   of the airways. This technique is therefore more favourably suited to patients with
   bronchospasm, or patients with haemoptysis, where a gentler technique is required. In a
   clinical study, patients with bronchospasm responded best to AD.[85] As AD requires a

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self-awareness of one's own respiratory mechanics and concentration to perform, it is generally used in teenagers or adults, unless a caregiver is skilled in its performance.

d) PEP increases FRC during tidal volume breathing, evening out intrapulmonary distribution of ventilation, opening up regions that are otherwise closed off.[65] It is therefore effective in both restricted and obstructed patients. In addition, the positive expiratory pressure splints the airways during expiration thereby avoiding airway collapse, which makes it a favourable technique for patients with unstable airways.

e) Adding oscillations to expiration, either by using a oscillatory PEP device or HFCWO device, has the added advantage of: increasing mucociliary clearance;[53] decreasing the viscoelastic properties of mucus; and, potentially rehydrating mucus. When using oscillation devices, the clinician needs to consider what method they want to use to first ventilate behind the obstructed units. Flutter uses a three second breath hold, Acapella like PEP increases FRC, splinting airways open. HFCWO needs to be combined with either deep inspiratory manoeuvres, three second breath hold, or PEP.

f) Exhaling into ERV, as used during AD, Flutter and HFCWO assists in mobilising secretions from the small airways but has the potential to cause airway closure.[62,69,71] To avoid this, during these techniques, the therapist should ensure patients adequately incorporate methods to ventilate small airways such as three second breath holds, or thoracic expansion exercises.

g) A therapeutic strategy for an individual patient may involve a combination of ACTs. For example, in a patient with unstable large airways, the use of a PEP device will enhance ventilation. But during the huffing phase the airways may be unable to resist

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compression. By combining PEP with AD, expiratory flow rates could be increased without causing airway compression thereby mobilising secretions more effectively

Conclusion

The approach to care of the individual patient needs to be personalised. Sometimes, in clinical practice more than one ACT may be effective for a patient at a given time in their disease trajectory and choice of technique may then be dependent on availability and patient preference. Other considerations include cleaning and durability of an ACT device if one is used. However, more often than not, due to the varying nature of the underlying disease pathology; phenotypic characteristics; and, taking into account individual patients' clinical, functional, environmental and social factors, ACTs needs to be personalised to meet patient's specific needs. This requires a sound understanding of the physiological basis of each technique

Examining the application of physiological principles to ACTs provides a better understanding of how to optimise airway clearance strategies to the individual patient's underlying pathology. This allows for both more personalised and improved patient care. Physiological theories which support ACTs had previously been identified.[42,43,86] However, this is the first review to present the physiological evidence supporting methods to ventilate behind obstructed lung units, and modulation of expiratory airflow, and to collate this physiological evidence in an effort to assist in translation into practice.

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Point by point response to reviewers.

We thank the editors and reviewers for reviewing this paper. We hope we have addressed all the concerns expressed in this letter and have provided a point to point response to each concern

Reviewer 3. Comments to the authors

1. Page 5, line 37: „…non-ventilated spontaneously BREATHING patient". Add "…ly breathing"

Response from authors

Thank-you for your feedback and the manuscript has been changed to, " spontaneously breathing patient both on line 37 and on page 3 line 47.

Reviewer 3. Comments to the authors

2. Page 5, line 41: This sentence is not quite correct. Airflow would be ventilating only those parts of the lungs where airways are not totally obstructed. This reviewer would suggest to add for example "with patent airways" after "…areas of the lung".

Response from authors

The authors agree with the reviewer, that we are discussing partially obstructed airway, that is why the sentence states that, "secretions decrease the diameter of the airway ..." as opposed to totally obstructing an airway.

The authors have also tried to clarify this sentence and the previous sentence by commencing the sentence following the one, ":areas of the lung... "with, "In patients with obstructed airways secretions.." The authors have also added to the previous sentence, "In normal healthy individuals, during.." . This is to differentiate the difference between healthy and obstructed lungs.

Reviewer 3. Comments to the authors

3. Page 5, line 49: Time constants may change if the connections are opened more but most likely, the time itself is what counts. It is strongly suggested to delete "due to altered time constants".

Response from authors

Thank-you for your feedback and as per the suggestion, the authors have deleted, "due to altered time constants".

Reviewer 3. Comments to the authors

4. Page 6, line 54: delete the "s" in "exists".

Response from authors

Thank-you for your feedback and as per the suggestion, the authors have deleted the S in exists.

Reviewer 3. Comments to the authors

5. Page 9, line 39: the sentence "… excessive secretions down to …" may be misleading. Possibly, "…secretions FROM TRACHEA AND BROCHI down to…" is more clear.

Response from authors

Thank-you for your feedback and as per the suggestion, have added, "clear excessive secretions" from the trachea down..."

Reviewer 3. Comments to the authors

6. Page 9, line 51: It should read "adhesion" instead of "shear force", right?

Response from authors

Thank-you for your feedback. Have restructured the sentence to the following, "During this time, dynamic compression of the airways occurs, resulting in an increase in velocity and kinetic energy which produces a shear force detaching mucus from the airway walls and enhancing the cephalic movement of mucus proximally up the airways."

Reviewer 3. Comments to the authors

7. Page 11, line 12/13: again, shear force is the force that detaches mucus. It should be "adhesive strength" or some similar expression.

Response from authors

Thank-you for your feedback and as per the suggestion, have deleted shear force and changed to adhesive strength.

Reviewer 3. Comments to the authors

8. Page 17, line 15/16: the time constants will not allow for more time. The Notion of time constants may be deleted in this context.

Response from authors

Thank-you for your feedback. The authors have removed the words, "time constants" and rephrased the sentence to, "A three second breath hold is included at the end of inspiration. This increases alveolar gas mixing and decreases the inhomogeneity of ventilation.[36] The authors have included a reference for this.

Reviewer 3. Comments to the authors

9. Page 23, line 27: "…ACTs need…", delete the "s" in "needs".

Response from authors

Thank-you for your feedback and as per the suggestion, the authors have deleted the S in needs.

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Reviewer 3. Comments to the authors
10. Page 23, line 35: "This allows…", add an "s" to "allow".

Response from authors

Thank-you for your feedback and as per the suggestion, the authors have added an to allow.