We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,500
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Airways Clearance Techniques in Cystic Fibrosis: Physiology, Devices and the Future

Adrian H. Kendrick
Department of Respiratory Medicine, University Hospitals, Bristol
England

1. Introduction

The appearance of the lungs of a cystic fibrosis (CF) patient at post mortem is typically one of consolidation, with areas of bronchiectasis filled with mucopurulent material and of mucus plugging of the small airways (Yankaskas et al., 2004). The airways of the upper respiratory tract have increased secretion production, whilst in the lower respiratory tract there is increased mucus production and an increase in sputum. This sputum is usually thick and tenacious, becoming thicker and more abundant during an exacerbation and leading to progressive lung damage. It is therefore essential that in patients with CF the process of airway clearance is enhanced, where needed, to attempt to reduce these long-term effects.

The purpose of this chapter is to outline 1) the normal structure and function of the airways, 2) the process of mucus clearance in normal airways, 3) the effects that CF has on both the physiology and mucus clearance, 4) the current understanding of airway clearance device in terms of how they work and their application and finally 6) to look towards the future.

2. Structure and function in normal airways

The structure of the airways, and hence the function of the airways is affected by disease (Ranga & Kleinerman, 1978). Understanding the structure of the normal airways and how CF changes the airway function is essential in understanding the potential application of airway clearance techniques in clinical practice.

2.1 Normal airway structure

The airways start at the trachea and terminate at the alveolar sacks where gas exchange takes place (Fig 1).

There are about 23 branches of the airways from trachea to alveoli. The first 15 generations do not play a role in gas exchange and constitute the anatomical dead space (~150 ml). Gas exchange commences from generation 15 onwards, with alveolar ducts appearing at generations 19 – 22. Generation 23 is the last generation of the airways, constituting the alveolar sacs. The total number of alveoli ranges from 200 to 600 million (mean 300 million), the number correlating with the standing height of the subject (Angus & Thurlbeck, 1972).
Fig. 1. Resin cast of a human lung showing the branching pattern of the bronchial tree (B) which originates from the trachea (T). In the left lung, the pulmonary arteries (A) and veins (V) are marked. The inset shows the peripheral airway branching at higher power. Reproduced with permission from Wiebel ER, The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System. Harvard University Press, London, England, 1984

The bronchi contain cartilage which maintains airway patency, whilst the bronchioli have no cartilage (Fig 2). Histologically, the airway epithelium becomes thinner towards the alveoli, where the distance between the air in the alveoli and blood in the pulmonary capillaries is about 0.2 µm.

Fig. 2. A) Organization of the airway tree, divided into conducting zones, the transitional and respiratory zones where alveolar begin to appear before leading to the alveolar ducts and sacs. Based on Weibel ER. Morphometry of the human Lung. Heidelberg: Springer. New York Academic, 1963. B) Ciliated epithelia cells and goblet cells occur in the larger airways, decreasing towards the smaller airways. Goblet cells are replaced in the transitional and conducting zones by Clara cells. Pores of Kohn appear in the alveolar walls and are important in terms of collateral ventilation.
Ciliated epithelial cells decrease in number and shape from the large airways towards the small airways. Goblet cells abound in the larger airways, with around 6000 mucus secreting cells/mm², and are responsible, along with the submucosal secretory cells, for producing the thick layer of mucus that lines all but the smallest of conducting airways. Mucin is rapidly released from the mucus-secreting cells in response to a range of stimuli including direct chemical irritation, inflammatory cytokines and neural activity (Rogers, 1994). The number of Goblet cells and their secretions increases significantly in CF.

In the smaller airways, Goblet cells are replaced by Clara cells which constitute about 80% of the cell population. Clara cells may play a role in the Cystic Fibrosis transmembrane conductance regulator (CFTR) gene-dependant regulation of epithelial electrolyte and water secretion in addition to their roles of surfactant production, protection against oxidative stress and suppression of inflammation (Kulaksiz et al, 2002). CFTR expression is significantly greater in the respiratory and terminal bronchioles compared to the proximal airways and alveoli (Engelhardt et al, 1994). Smooth muscle in the airway wall gradually increases so that in the terminal bronchioles it constitutes around 20% of the wall thickness.

2.2 Normal function

The normal lung maintains sterility below the first bronchial division despite breathing in 450 l.h⁻¹ at rest of air contaminated with viruses and bacteria. To move this volume of gas, the ventilatory pump must create negative and positive pressures within the thorax for air to enter and leave, respectively. In addition, the pump must provide a system of distributing the inhaled gas to the alveoli, where blood supplied to the alveoli by the pulmonary circulation will come into contact with the alveolar gas. Hence, for gas exchange to take place 1) the lungs must be ventilated, 2) the pulmonary circulation must be perfused, and 3) the ventilation and perfusion must be matched.

The airways present a major challenge to the movement of air from the atmosphere to the alveoli. The airways narrow with each branching, decreasing from about 18 mm in the trachea, to 0.7 mm at generation 14 and 0.3 mm at the alveolar ducts. Hence, there is a significant increase in the surface area for gas exchange, which may be as great as 143 m² in the average male (Weibel, 1984).

As the airways narrow, the resistance (pressure ÷ flow) to airflow increases along a single airway. In reality though, the highest resistance is found in the large central airways, whilst the resistance in the peripheral airways accounts for only 20% of the total resistance due to the increased cross-sectional area of the millions of peripheral airways in parallel. In the large airways, where air moves by bulk flow, a turbulent airflow pattern predominates, thus increasing resistance, whilst in the peripheral airways, diffusion is the predominant means for moving gas (Fig 3).

As the respiratory bronchioles and alveolar ducts contribute little to the overall resistance of the lungs as a whole, the distribution of gas within these units is determined principally by the compliance of the lungs (C_l) – a measure of stiffness or floppiness of the object (C_l = Δvolume ÷ Δpressure). In normal lungs, the pressure-volume relationship is such that each tidal breath occurs at the steep part of the relationship, where compliance is high (Fig 4).
Fig. 3. The relationship of airway cross-sectional area and airflow velocity to airway generation in the human lung. As the airways branch, the total cross-sectional area increases from 2.5 cm$^2$ in the trachea, to around 13 cm$^2$ at the tenth generation (1024 airways) with a final cross-sectional area of around 300 cm$^2$ in the acinar region. The airflow velocity falls by more than 100-fold from the trachea down to the acinus (1 m.s$^{-1}$ to 1 cm.s$^{-1}$). In exercise, the airflow velocity may be up to ten times greater and so greater airflow is observed within the acinus. Data from various sources.

Fig. 4. Schematic of pressure volumes curves in normal subjects (N) and in patients with CF. In normal subjects, for the change in pressure ($\Delta P_1 = \Delta P_2$) there is a greater change in volume at $\Delta P_1$ than for $\Delta P_2$ demonstrating that the compliance of the lungs is greater at $\Delta P_1$ than at $\Delta P_2$. Normal tidal breathing occurs on the steeper portion of the pressure-volume curve. In CF, the pressure volume curve is altered – there is normal compliance of the lungs over the normal tidal volume range, but reduced compliance at high lung volumes (summary data from Mansell et al, 1974)
When we breathe in close to maximum, the pressure-volume relationship is much flatter (more pressure needed to increase a given volume) and so it is much harder to breathe, making the work of breathing greater. On the other hand, when we breathe fully out, the pressure-volume curve is much steeper, indicating that full exhalation is not limited by lung compliance. One key point on this curve is the end-expiratory lung volume (EELV) or functional residual capacity (FRC). This is the equilibrium point in the relationship between the outward pull of the chest wall and the inward collapse of the lungs, where the relative magnitudes are equal, but opposite.

If we apply this observation to an individual alveolus, then the larger it is at the start of tidal inhalation, the stiffer (less compliant) it is and so less air enters the alveoli. This is observed by looking at the distribution of inspired air, which goes preferentially to the more compliant lung bases. In addition to the compliance, ventilation is further distributed within the alveolar units by the pores of Kohn, which connect the alveoli within a lobe; this is referred to as collateral ventilation. (Desplechín et al, 1983). This should permit equilibrium of gas pressures in different lung regions, but this only appears to apply in diseased lungs, as in normal lungs the flow resistance of the collateral pathways is high, and so movement of gas via this route is minimal. (Macklem, 1971). These pores allow transfer of gas between alveoli and function to minimize the collapse of lung units if a more central airway becomes blocked. (Hogg et al, 1969).

One aspect of ventilation that is affected by respiratory disease is the work of breathing. (Campbell et al, 1957; Milic-Emili, 1991). During the passive expiration of a normal resting tidal breath, the work of breathing is performed entirely by the inspiratory muscles. Approximately 50% of the work during inspiration is dissipated as heat in overcoming the frictional forces that oppose inspiration. The remaining 50% is stored as potential energy in the deformed elastic tissues of the lungs and chest wall, as they are at a point above the EELV and hence are not in equilibrium. This potential energy is available for expiration and is dissipated as heat in overcoming the frictional forces that resist expiration.

Energy that is stored in the deformed elastic tissue allows the work of expiration to be transferred to the inspiratory muscles. The actual work performed by the respiratory muscles is very small (~ 3 ml.min⁻¹ O₂), compared to the average resting oxygen uptake of 250 ml.min⁻¹, and so accounts for only about 1 – 2% of the resting metabolic rate.

The work of breathing overcomes two main problems—the elastic recoil of the lungs and chest wall, and the airway resistance to gas flow. The total work of breathing is the sum of the elastic and resistive work and may be related to lung volume or breathing frequency (Fig 5). It is likely that each individual selects the most appropriate breathing frequency in order to minimize the work of breathing.

3. Mucus clearance mechanisms

When the lungs are ventilated they are exposed to a vast range of particulate matter, bacteria and viruses. The main defence mechanism against these is the viscous mucus layer, which provides a physical protective barrier to chemical damage of the epithelium (Foster, 2002; Rubin, 2002).
Fig. 5. Schematic diagram of the relationships of work of breathing against lung volume (A) and breathing frequency (B). The total work of breathing is the summation of the elastic properties of lungs and chest wall and airway resistance components. In normal subjects, there will be an optimal lung volume and optimal breathing frequency which is probably set for each individual. The effects of obstructive and restrictive lung disorders are shown for both relationships.

Airway mucus is a complex substance that lines the respiratory tract. Bacteria and other airborne particles become trapped in this sticky mucus and then are swept upwards and outwards by the tiny hair-like structures - cilia. The interaction between normal mucus, cilia and associated structures make up the mucociliary clearance system (MC).

Many inhaled irritants simply dissolve in the mucus, whilst inhaled particles are deposited in the airways either by impaction or sedimentation. These particles are then degraded by the proteases in the mucus or removed intact by the mucus. In the smaller airways sedimentation occurs due to the low airflow, so the particles are deposited and removed by macrophages.

For bacteria and viruses, the first line of defence is the physical removal by the mucus. Within the mucus, humoral defences include immunoglobulins, protease inhibitors and endogenous antibiotics. The airway provides numerous defence mechanisms to prevent microbial colonization by the large numbers of bacteria and viruses present in ambient air. Important components of this defence are the antimicrobial peptides and proteins present in the airway surface fluid—the mucin-rich fluid covering the respiratory epithelium (Rose & Voynow, 2006; Voynow & Rubin, 2009). Recently, evidence has indicated that within the airways of normal subjects is an endogenous antibiotic—human defensins, which is believed to play an important role as part of the airway defence mechanisms (Schneider et al, 2005). Human β-defensin gene (HBD-2) represents the first human defence that is produced following stimulation of epithelial cells by contact with micro-organisms, such as *Pseudomonas aeruginosa*, or cytokines, such as tumour necrosis factor-α (TNF-α) and Interleukin-1β (IL-1β) (Laube et al, 2006). Cellular immunity is also in evidence throughout the epithelium with macrophages, neutrophils and lymphocytes commonly occurring during infections in the normal lung.
Respiratory health is dependent on consistent clearance of airway secretions (Wanner et al., 1996; Houtmeyers et al., 1999). A healthy MC moves respiratory secretions to central airways, with the final clearance achieved by a combination of coughing and swallowing.

3.1 Cough and expiratory flow

Cough may be increased in respiratory infection and assists in clearing the airways from generations 7 - 8 upwards, augmenting the MC when overwhelmed by copious secretions.

Cough is a normal reflex mechanism that commences with a brief rapid inspiration usually greater than the resting tidal volume, this volume being sufficient for expiratory activity. (Ross et al., 1955; Bennett et al., 1990; Bennett & Zeman, 1994). The glottis closes for about 200 ms. There is an associated sharp rise in both pleural and abdominal pressure to between 6.6 to 13.3 kPa, resulting from expiratory muscle and diaphragmatic contraction; lung volume is held constant. Glottal closure limits expiratory muscle shortening, so promoting the isometric contraction of the expiratory muscles. This allows the expiratory muscles to maintain a much more advantageous force-length relationship, resulting in the generation of greater positive intra-abdominal and intrathoracic pressures, which may be up to 40 kPa.

Once the glottis is opened, the expiratory phase of cough occurs. The high intrathoracic pressures developed during the compressive phase promote high expiratory flow rates. Initially, there is a very brief blast of turbulent flow. This initial peak of expiratory flow lasts for between 20 ms to 50 ms and the cough Peak Expiratory Flow (cPEF) may exceed 720 L.min\(^{-1}\) (Fig 6). This burst of air is due to the additive effects of the gas expired from the distal parenchymal units and the gas displaced by the more central airways, which are compressed by the high intrathoracic pressures. (Knudson et al., 1974). Although glottal closure enhances this phase of cough, it is not essential for an effective cough. (Von Leden & Isshiki, 1965). After the initial explosive burst of air, a period of between 200 to 500 ms occurs with much lower expiratory flows of between 180 to 240 L.min\(^{-1}\). During this period, lung volume, transpulmonary pressure and cough expiratory flows all decrease.

As expiratory flow rate decreases, the airflow velocity changes—the relationship being dependent on the cross-sectional area of the airways (velocity = flow ÷ cross-sectional area). As shown in Fig 3, the peripheral airways have the largest cross-sectional area, whilst the larger bronchi and trachea have a much lower cross-sectional area. Hence as the cross-sectional area of the airways decreases, the velocity of air increases for a given expiratory flow rate. In other words, the velocity of the gas increases as the air moves from the peripheral to the central airways.

Gas velocity may be further enhanced in the central airways due to dynamic airway compression, where the airway narrows due to the pressure surrounding it being greater than the pressure within it. Narrowing the airway reduces the cross-sectional area, and so velocity increases for a given flow rate.

In normal airways, and during resting tidal breathing, the velocity of air is around 500 cm.s\(^{-1}\) down to the airway generations 7 to 8 (Fig 3). At the peak of cough the velocity of air may exceed 16,000 cm.s\(^{-1}\). The cough lasts for approximately 0.5s: up to 1 litre of air may be expelled and the cough is ended either by glottal closure or respiratory muscle relaxation, with a consequent fall in pleural pressure (Fig 6). Often there are further small coughs, which diminish in intensity as lung volume declines towards residual volume.
In relation to mucous clearance, the actual velocity of airflow through the airways alters the kinetic energy (KE) available. As KE = \( \frac{1}{2} mv^2 \), where \( m \) is the mass of the object and \( v \) the velocity, a doubling of the velocity will result in a fourfold increase in the KE. So, the effects of dynamic compression are such that a narrowing of the airways results in an increase in velocity, which in turn results in increases in kinetic energy, thus enhancing the removal of mucus adhering to the airway wall. Zahm et al (1991), using a simulated cough device, found that the displacement of artificial mucus following a simulated cough was greater at smaller airway diameters. Hasani et al (1994) observed that during expiratory flow, mucus transport was more efficient in the central rather than the peripheral airways.

In order to understand how airway clearance devices may be used to assist in the removal of these secretions, we need to understand how cough works in reality. Cough is effective in removing mucus and particulates if the secretions lining the airways are dispersed into the expiratory gas. The high velocity of airflow interacts with the bronchial secretions, resulting in ‘two-phase air-liquid flow’ by which energy is transferred from the air to the liquid, resulting in a shearing effect on the liquid secretions, thus aiding the expectoration of sputum (Clarke et al, 1970; Kim et al, 1986). At velocities of between 1000 – 2500 cm.s\(^{-1}\) an annular type of two-phase flow occurs, whilst at a velocity of > 2500 cm.s\(^{-1}\) a mist flow with aerosol formation occurs (Fig 7).
A number of factors may be observed -

1. Airways are collapsible structures and so may vibrate and their walls may approximate each other, further aiding the loosening of mucus and promoting clearance (McCool & Leith, 1987);

2. Shearing and expectoration are affected by the viscosity, elasticity and surface tension of the bronchial secretions in a highly complex manner. (Scherer, 1981).

3. Waves of mucus have been observed in the range of airflow occurring during a cough (King et al, 1985) which may further enhance particle clearance (Kim et al, 1983);

4. The physical properties of mucus also affect cough efficiency. Mucus clearance is directly proportional to the depth of the mucus, and is inversely proportional to its viscosity and elasticity (King et al, 1985; King, 1987; King et al 1989; King et al, 1990; Albers et al, 1996)

5. Through use of radiographic methods to measure flow and tracheal cross-section during coughing, an index of ‘scrubbing action’ has been derived (Harris & Lawson, 1968). In healthy subjects during the first cough, around 59% of the scrubbing action occurs, with only 26% and 16% for the second and third coughs in a sequence of coughs.

6. During a forced expiration, high expiratory flow develops within about 100 ms and results in a high shear rate. Mucus transport varies inversely with shear rate, referred to as pseudoplastic flow or shear thinning. This observed decrease in viscosity can be explained by a temporary realignment of macromolecular glycoproteins due to the applied force (Lopez-Vidriero, 1981). Therefore, repeated forced expirations with short time intervals between each forced expiration may result in a reduction of the mucus viscosity and hence improve mucus transport (Zahm et al, 1991).

In healthy individuals, the rate of mucus secretion is carefully balanced with mucus clearance. The consistency of mucus is maintained such that it is thick enough to trap bacteria and other inhaled particles but thin enough to be moved easily by cilia. When airways are kept free of bacteria, other particles and excess mucus, airways remain open and permit normal gas exchange.

When mucus secretion and mucus clearance are not in balance, excessive airway mucus can cause serious problems. Excess, often sticky mucus may accumulate in the airways, resulting in an increase in the work of breathing. Regardless of the causes, the consequences for the patients are the same—a vicious cycle of recurrent, worsening episodes of inflammation, pulmonary infection, increased production of excess mucus, and airway obstruction, lung damage and respiratory failure.

The consequences of uncleared airway secretions in the airways are a clear link between mucus hypersecretion/secretion retention, exacerbation of illness, hospitalization, a sharply declining one second forced expiratory volume (FEV₁) and death (Annesi & Kauffmann, 1986; Lange et al, 1990; Prescott et al, 1995; Vestbo et al, 1996). The recognition of the clinical significance of excessive, abnormal, or retained airway secretions provides the rationale for improving mucociliary clearance as a logical treatment goal in order to avoid mucus retention and to prevent or break the life-destroying cycle of recurrent infection and progressive pulmonary deterioration.
4. Cystic fibrosis

There are a number of significant changes that occur in patients with CF in terms of the respiratory physiology and the mucociliary clearance mechanisms.

4.1 Respiratory physiological changes in CF

The changes that occur to the normal physiology are principally airflow obstruction, which worsens as the disease progresses. In patients with virtually normal spirometry, evidence of mild airways disease is observed by changes in airflow within the small airways, as measured by the Maximal Expiratory Flow (MEF) with 25% of the Forced Vital Capacity (FVC) remaining. This is known as the MEF_{25\%FVC} (Zapatal et al, 1971). In terms of gas exchange function there is widening of the alveolar-arterial PO$_2$ (AaPO$_2$) and an increased dead space to tidal volume ratio (V$_D$/V$_T$) (Lamarre et al, 1972). Whilst the total lung capacity (TLC) is often normal (Reis et al, 1988), the static pressure-volume curve (compliance) shows a loss of recoil pressures at low lung volumes with normal recoil pressures at high lung volumes. (Mansell et al, 1974). This results in a normal compliance of the lungs over the normal tidal volume range, but reduced compliance at high lung volumes (Fig 4).

---

5. Cystic fibrosis – Renewed Hopes Through Research

Fig. 7. Effects of gas flow rates on a mixture of gas and liquid flowing through a horizontal tube. At low flows, bubbles of gas may be dispersed in the liquid (bubble flow). As the gas flow rate increases, the bubbles become larger and fill most of the tube cross section; these gas ‘slugs’ alternate with volumes of liquid and are displaced toward the top of the tube (slug flow). At higher flows the gas slugs merge randomly, leading to the liquid occupy the lower part of the tube with a fairly smooth surface (stratified flow), which as the flow-rate increases further lead to marked surface roll waves appear (wavy flow). With continued increases in flow rates the film of liquid is covered by a dense array of small waves and the surface may appear smoother although there is extreme agitation of the liquid (annular flow). At extreme flow rates, the liquid waves are entrained and blow through the tube in the form of droplets (mist flow). (From Clarke et al, 1970 with permission).

---

1The MEF_{25\%FVC} is obtained from a maximal expiratory flow volume curve. The subject inhales fully and then forcibly exhales. The volume of air exhaled in total is the forced vital capacity (FVC). With 25% of the FVC remaining, the flow rate at this point can be obtained and hence is the MEF_{25\%FVC}. In the US this is referred to as the forced expiratory flow (FEF) after 75% of the FVC has been exhaled (FEF_{75\%FVC}).
Despite malnutrition being common in CF patients, respiratory muscle weakness is not common, and, if present, is generally mild. (Mier et al, 1990). This is important as cough is common in CF with median rates being 21.2 coughs.h⁻¹ (interquartile range [IQR] 14 – 34.9) at the time of exacerbation, but reducing to a median of 9.0 coughs.h⁻¹ (IQR 5.8–12.8). (Smith et al, 2006) The other major abnormality of note is that exercise capacity is often limited by the combined effects of airflow obstruction and muscle wasting due to malnutrition. (Lands et al, 1992). As indicated above, the small airways may have reduced function ($\downarrow$MEF₂₅%FVC).

The causes of this small airways disease are possibly the result of significant increases in the inner wall and the smooth muscle areas of the peripheral airways. (Tiddens HA, et al, 2000) Changes in the airway dimensions of CF patients compared to chronic obstructive lung disease (COPD) patients showed that, for airways of 1.9 mm diameter (12th generation), there was an approximately fivefold increase in the smooth muscle area and a threefold increase in the inner wall area without epithelium. In the larger airways (35 mm diameter) there was a ~1.5 increase in smooth muscle area with an almost identical inner wall area without epithelium. These changes may also be related to age (Soboya & Tausig, 1986). Finally, the work of breathing is increased, although the increase is not solely explained by changes in lung function and lung mechanics (Fig 8), but also by the effects of TNF-α and CFTR (Bell et al, 1996).

These pathological studies demonstrate the variability of the destructive processes in the lungs of CF patients. Airway wall thickening is a marked feature of CF and is likely to extend into the small airways and be associated with airways inflammation and obstruction.

### 4.2 Mucus and mucociliary clearance in CF

In CF, there is increased mucus retention and bacterial colonization, due to the viscous nature of the mucus. However, there is inhibition of antimicrobial peptide activity or gene expression can result in an increased susceptibility to infections where the CF phenotype leads to reduced antimicrobial capacity of peptides in the airway. (Goldman et al, 1997; Rosenstein & Zeitlin, 1998). Thus in CF, bacterial colonization and mucus hypersecretion occur as a consequence, leading to progressive lung damage (Tiddens et al, 2000)

---

**Fig. 8.** Summary data on resting energy expenditure and oxygen cost of breathing in control subjects and patients with CF. The data shown (means only) shows that CF patients have a significantly higher respiratory rate (RR; breaths.min⁻¹: p<0.05), minute ventilation (VE; l.min⁻¹: p<0.001); oxygen uptake/kg (VO₂/kg; l.min⁻¹.kg⁻¹: p<0.001) and resting energy expenditure/kg (REE; kJ.min⁻¹.kg⁻¹: p<0.001) and O₂ cost (ml.l⁻¹ VE). (From Bell et al, 1996).
Patients with CF have impaired airway clearance due to the following problems:

1. **Ineffective ciliary clearance**: Normal cilia beat in a coordinated unidirectional fashion to mobilize mucus and clear particulate matter from the airways. Damaged cilia perform this function inadequately or not at all;
2. **Excessive or abnormal mucus production**: CF results in excess mucus production and the mucus is abnormally thick and sticky. Large quantities of mucus, or mucus with altered physical properties, may overwhelm the mucociliary apparatus, inhibiting normal airway clearance (Rose & Voynow, 2005; Voynow & Rubin, 2009);
3. **Ineffective cough**: Cough function may be weak or ineffective if the muscles have become weak or fatigued;
4. **Obstructive lung disease**: The airway size is decreased as a result of structural changes, bronchospasm and excess mucus, limiting the ability to exhale. These effects result in much slower clearance of mucus than in normal subjects, (Regnis et al, 1994; Matthys & Kohler, 1986; Yeates et al, 1976; Wood et al, 1975) with a correlation between the lung function and mucociliary clearance (Robinson et al, 2000; Fig 9).

Because at-risk individuals are prone to recurrent episodes of respiratory inflammation, infection and, eventually, irreversible lung damage, improvement of MC is an essential goal of any treatment plan. Importantly, it is a goal that can be achieved by the individual and must include effective airway clearance therapy.

Fig. 9. Percentage of radioactivity cleared from different regions of the right lung at 60 minutes in normal subjects (black columns) and in patients with CF (grey columns). In A), the differences are observed for the whole lung (WL), Central (C), Intermediate (Int) and peripheral (Periph) airways. In B), the same regions as in A) are shown in relation to the degree of airway dysfunction in CF patients – normal small airway function (NSA; FEV\(_1\) ≥ 80\%pred and FEF\(_{25-75}\) ≥ 80\%pred), normal spirometry (NSP; FEV\(_1\) ≥ 80\%pred and FEF\(_{25-75}\) < 80\%pred), moderate (Mod; 40\% ≤ FEV\(_1\) < 80\%pred) and severe (Sev; FEV\(_1\) < 40\% pred) lung disease. There is no data for NSP – peripheral. Redrawn from Robinson et al, 2000)

\(^2\)The FEF\(_{25-75}\%\) is the flow rate during a maximal forced exhalation and represents the averaged flow rates between 75\% and 25\% of the FVC.
5. Airway clearance devices

A number of adjunctive techniques and devices have been used to assist those who are unable, for whatever reason, to clear pulmonary secretions effectively and have been extensively reviewed (Cystic Fibrosis Trust, 2003; Yankaskas et al 2004; Kendrick, 2007; van der Schans, 2007; Bott et al, 2009; Flume et al, 2009; Daniels, 2010).

5.1 Criteria for airway clearance devices

The key to any device used to clear secretions is that it meets a number of criteria, based on the physiology. These criteria are:

1. Increase absolute peak expiratory flow (PEF) to move secretions towards the oropharynx;
2. Use of two-phase gas-liquid flow, both in closed and open airways. In the latter, mucus transport can be achieved by expiratory airflow during forced expiration, as well as tidal breathing. The peak expiratory flow/peak inspiratory flow ratio (PEF/PIF) needs to be > 1.1 to achieve this (Kim et al, 1986; Kim et al, 1986a; Kim et al, 1987) and the frequency of oscillation needs to be between 3 – 17 Hz, with the ideal frequency being around 13 Hz (Gross et al, 1985)
3. Decrease the mucus visco-elasticity in the airway, and hence improve mucus transport (App et al, 1998)
4. Elicit spontaneous coughs by mechanical stimulation of the airways to remove mucus from the trachea, inner and intermediate regions of the lungs (Laube et al, 2006; Hasani et al 1994)
5. Increase expectorated mucus volume (Konstan et al, 1994).

However, what all of these are dependent upon is the mechanical properties of the lungs of CF patients, which may deteriorate with disease progression (Arora & Gal, 1981; van der Schans, 1997). This might mean alternative approaches have to be adopted, and although these above criteria are the “ideal” criteria, there are alternative approaches which use different criteria and which may work as well or better. What is important is that we understand the criteria that each device achieves, how it may be adapted to an individual patient’s needs and that changing the device as the disease progresses should always be an option worth considering.

5.2 Physiological aspects of airway clearance devices

Perhaps surprisingly, there are virtually no studies that have investigated exactly how these devices work from the physiological viewpoint and hence our understanding of how we are applying these devices into clinical practice is limited. Recently, McCarren et al (2006a, b, c) have provided evidence of how a variety of techniques work physiologically. These three studies conclude:

1. Chest wall circumference changed by 0.8 cm, the frequency of vibration was 5.5 Hz, the PEF was 58.2 l.min⁻¹ and the PEF/PIF ratio was 0.75, all of which are well below the ideal criteria for removing mucus (McCarren et al 2006a). What this study demonstrated was that the PEF during vibration was 50% greater than from a relaxed TLC manoeuvre and was composed of the flow rate due to a) elastic recoil, b) chest wall compression and c) chest wall oscillation. When summed, these three contributors
equated to the PEF observed during vibration, the proportional contributions being 67%, 15% and 14%, respectively;

2. There were clear relationships between the external chest wall force applied, chest wall circumference, intrapleural pressure (Fig 10) and expiratory flow (McCarren 2006b). Similar to the previous reference (McCarren et al 2006a), the intrapleural pressure observed was composed of the sum of the lung recoil, compression and oscillation components, the proportional contributions being 75%, 13% and 12%, respectively.

These two studies (McCarren et al 2006a; McCarren et al 2006b) have demonstrated some important relationships between the mechanics of the lung and the potential to remove sputum. The flow rates generated by vibration would be insufficient to augment secretion clearance by annular flow, since the PEF/PIF ratio was 0.75 and needs to exceed 1.1 (Kim et al, 1987). Why the inspiratory flow bias occurred is unclear, but may be related to the way in which physiotherapists ask the patient to take a deep breath. The frequency of vibration is also much lower than the ideal of between 11–15 Hz (Gross et al, 1985). It is currently unknown whether this vibration frequency would have a significant influence on the sputum rheology, but any decrease that may occur is likely to enhance the ability of cilia to move mucus (Wanner et al, 1996).

Fig. 10. A) The time course of the expiratory flow of the interventions in one subject. The eight traces have been separated vertically for clarity. Huff-high: huff from high lung volumes; TLC_relax: total lung capacity passive expiration; PEP: positive expiratory pressure. B) Summary of data comparing measured data for PEF/PIF ratio and frequency of oscillation in various methods of airway clearance. The vertical dashed line is the ideal frequency range for the methods, whilst the horizontal dashed line is the minimum ideal PEF/PIF ratio. From McCarren et al, 2006b, with permission.

In normal subjects, expiratory flows are enhanced by lung recoil due to the additional forces applied to the chest wall during vibration by manual compression and oscillation. Where there is increased mucus and more viscous secretions, the airways will have a reduced airway radius and airway resistance will be increased.

Physiologically, these observations can be explained using Poiseuille's Equations (Resistance $\propto \frac{1}{\text{airway radius}^4}$ and Flow $\propto \text{radius}^4$). If the airway narrows (smaller radius), there will be an increase in the resistance to airflow, and a reduction in airflow. Furthermore, Poiseuille's Equation includes a term for viscosity ($\eta$) on the denominator, and therefore changes in the viscosity of the mucus will potentially further alter the resistance and flow rates of air.
The third study in CF patients, (McCarren et al, 2006c) investigated vibration, percussion, PEP device, flutter, VRP valve and Acapella PEP. In addition, forced expiratory manoeuvres were voluntary cough and huff from high lung volumes (huff\textsuperscript{HIGH}). The important new measurements were inspiratory and expiratory flow rates recorded during the manoeuvres and the oscillation frequency determined by frequency spectral analysis. The key findings of this study were –

1. The PEF of vibration (1.58 ± 0.73 l.s\textsuperscript{-1}) was greater by 1.4 (flutter: 1.13 ± 0.3 l.s\textsuperscript{-1}) to 3.6 times (PEP: 0.44 ± 0.15 l.s\textsuperscript{-1}), but cough PEF was 4.67 ± 1.19 l.s\textsuperscript{-1} and huff\textsuperscript{HIGH} PEF was 5.04 ± 2.3 l.s\textsuperscript{-1};

2. The frequency of oscillation ranged 6.5–18.3 Hz, with flutter and Acapella devices having the higher oscillation frequencies (Fig 10).

None of these devices achieved the ideal combination. Vibration did not achieve the critical PEF/PIF of > 1.1, nor the critical optimal frequency (8.4 Hz). PEF was reduced due to the added resistance presented to expiration. However, the added resistance may result in stabilization of collapsible airways and allow for collateral ventilation to occur between alveoli via the Pores of Kohn, resulting in an increase in gas volume behind the mucus and hence aiding the movement of the secretions (Fink, 2002; Delaunois, 1989). As with the devices assessed, cough and huff\textsuperscript{HIGH} do not achieve the ideal intervention status, as they do not oscillate airflow; increasing cilia beat frequency and/or decrease mucus viscosity.

Previous studies looking at the oscillation frequency using bench testing have noted that, for the Acapella and Flutter devices, the frequencies range from 8 – 25 Hz (Acapella blue), 13 – 30 Hz (Acapella green) and 15 - 29 Hz (Flutter) (Volsko et al, 2003). More recently, Alves et al (2008) has demonstrated that the angle of use of the Flutter VRP1 may influence the outcome and treatment application.

With the limited physiological studies, the remaining question that has been answered to some extent is whether or not these devices alter sputum rheology (App et al, 1998). Using the flutter device and comparing changes in the characteristics of sputum, this study showed that the elastic properties of CF sputum samples were affected significantly by application of oscillations generated by the flutter at 15 and 30 min (Fig 11). The median frequency of the flutter-generated oscillations was 19 Hz.

These findings suggest that applied oscillations are capable of decreasing mucus visco-elasticity within the airways at frequencies and amplitudes achievable with the flutter device, and provide direct evidence of changes in the visco-elasticity of sputum.

Whilst the ideal frequency may be around 13 Hz, there is new evidence that suggests that a combination of 1) a higher frequency causing the airways to vibrate, resulting in the loosening (shearing) of the mucus from the airways, and 2) applying minimal positive pressure (+ 1 cmH\textsubscript{2}O) via the Pores of Kohn and hence through the use of collateral ventilation, aids mucus clearance (Clini, 2009). This is clearly demonstrated in Fig 12 using lung ventilation scintigraphy (Fazzi et al, 2009)

One of the other ways of removing excess sputum from the airways is by increasing airflow along the airways. During normal tidal breathing the airflow can be artificially increased by applying a venturi effect within a breathing circuit, and this increase in the velocity of the air can enhance the movement of sputum. This is achieved because the movement of air above
a layer of mucus develops a shearing force over the surface of this liquid layer. When the shearing force exceeds the surface tension in the mucous layer, the mucus starts to move in the direction of the air flow (Kim et al, 1987). As the mucus moves up the bronchial tree, it will eventually be swallowed. Importantly, this effect can be achieved with minimal discomfort and without the need to cough. Where a patient’s clinical condition is deteriorating and they have fatigued muscles, the cough PEF may well be reduced to the extent that clearing secretions is inhibited significantly. A device that removes excessive airway secretions only under tidal breathing conditions would obviate the need for cough.

![Fig. 11. Studies using Autogenic Drainage (AD) and Flutter therapy after an acute session at the start and end of 4 weeks of therapy, followed by a crossover to 4 weeks of treatment with the other therapy. A) Changes in sputum visco-elasticity and B) Mucus clearability indices, where the mucociliary clearance index (M.C.I.) and cough clearability index (C.C.I.) were calculated from sputum viscoelastic data. From App et al, 1998, with permission.](image)

![Fig. 12. Dynamic ventilation obtained using lung ventilation scintigraphy (anterior scan) over 30 min during Temporary Positive Expiratory pressure (TPEP) therapy in a patient with COPD. Note how the central deposition of mucus plugs (dark areas) progressively clears over time. From Fazzi et al, 2008.](image)
5.3 Do airway clearance techniques work in reality? (Cochrane reviews)

The range of techniques has recently been evaluated in six Cochrane reviews (Van der Schans, et al, 2000; Elkins et al, 2004; Main et al, 2005; Moran et al, 2009; Morrison & Agnew, 2009; Robinson et al, 2010). The conclusions from these Cochrane reviews are that:

1. Airway clearance is important in the short term for patients with CF, but the long-term effects of no airway clearance is unknown;
2. Conventional chest physiotherapy is as effective as other forms of airway clearance;
3. Patients like their independence, and therefore any technique which they themselves can use is preferred;
4. Oscillation devices were no more or no less effective than other forms of physiotherapy;
5. There is not enough evidence to conclude, one way or the other, that Active Cycle of Breathing Techniques (ACBT) are any better or worse than any other technique.
6. Non-Invasive Ventilation (NIV) appears to help patients clear sputum more easily than other airway clearance techniques, and particularly in those patients who have difficulty in expectorating sputum.

What is somewhat disheartening in all of these reviews is the almost complete lack of really good quality research, and it is important to ensure data is collected appropriately and the primary and secondary outcome measures are available in order to fully understand the effects of any intervention.

These findings are confirmed in the review by McCool and Rosen (2006) where much of the level of evidence for airway clearance devices is fair to low and the benefits were intermediate to conflicting.

What is consistent in these studies is that, regardless of the device used, or the way in which the trial was conducted, there appears to be little change in the observed primary, and in many cases secondary, outcome measures. However, what makes these studies difficult to compare is the complete lack of commonality between recruitment, methodology, primary and secondary outcome measures, severity of disease, etc. This makes setting evidence-based practice guidelines interesting and limited in their conclusiveness.

5.4 Mathematical modelling

Whilst considerable work has been undertaken with studies on patients, other work has looked at bench testing and modelling some of the airway clearance techniques.

High Frequency Chest Compression (HFCC) has been investigated in such a way. Milla et al. (2004) investigated the actual waveform used in HFCC, which previously had been a sine wave. Changing to a triangular waveform significantly increased sputum production (4%–41%, mean 20%). From this small study of eight patients, the authors concluded that further investigation in patients using the sine and triangular waveform should be undertaken to determine the best frequencies for each waveform, disease and patient. They also pointed out that the original, and now neglected, square wave should be reassessed.

In a subsequent study (Milla et al, 2006), they investigated which frequency was appropriate to use for HFCC in order to ‘tune’ the device with the patient. In 100 patients, they found that the highest airflows for the sine waveform occurred between 13 – 20 Hz, with the
largest volumes occurring between 6 – 10 Hz. For the square waveform, the highest flows and volumes occurred between 6 – 14 Hz. The authors provided a ‘tuning’ protocol for prescribing frequencies with the various HFCC machines, because they are different from one another.

Sohn et al (2005) used a computational model to investigate the non-linear effects of airway resistance, lung capacitance, and inertness of air on respiratory airflow, with airways resistance contributing the greatest effect.

Bench testing of other devices has been limited to oscillating Positive Expiratory Pressure (PEP) devices (Volsko et al, 2003) and HFCC (Lee et al, 2008). In the study of Volsko et al (2003), there was a statistically significant difference, but probably not a clinically significant difference between mean pressure, pressure amplitude and frequency over a range of experimental conditions. At medium flows, there were similar pressure waveforms, and hence overall similar performance characteristics.

Lee et al (2008) investigated the effects of different frequency and pressure waveforms using three different HFCC devices, bench tested using a mannequin. They concluded that a better understanding of the differences in frequency and pressure amplitude when applying devices to patients would allow clinicians and patients to optimize the efficacy of HFCC.

5.5 Which device to use?

Whatever technique is used to aid airway clearance, its application to a given patient must be such that we achieve a balance between the treatment demands and the patient’s lifestyle. It is known that there are adherence issues as a result of the increasing time and effort required by patient self-management strategies, particularly when adults have to try and balance family, work, education etc with managing a chronic disease (Boyle, 2003). Whilst adherence to antibiotic treatment is high (80% - 95%), adherence to physiotherapy is low (40% - 55%; Kettler et al, 2002: 30%; Myers & Horn, 2006). Of note, airway clearance techniques, in adult CF patients, are perceived as a higher treatment burden with only 49% of patients performing airway clearance (Sawicki et al, 2009).

In selecting which airway clearance technique or combination of techniques to use, there are a number of key questions that should be taken into consideration –

1. Is the technique appropriate for the patient’s clinical state and environment?
2. Is the technique compatible with the patient’s lifestyle?
3. What does the patient like and dislike about each technique appropriate for use at that stage of their clinical status?
4. Does the patient perceive that the technique actually works?
5. What is the balance between the cost of the technique and the benefits, efficacy and preference of the technique?

Taking all of these questions into account and listening to the patient and their needs and preferences should allow the most appropriate airway clearance technique to be used, with or without the addition of behavioural techniques that increase adherence (Bernard & Cohen, 2004).
6. The future

Parents of children and adult patients want treatments that will help them achieve optimal health and quality of life goals. To make appropriate choices, they require accurate information, including a clear description of the theory and technique of available airway clearance methods. Additionally, they need information to allow them rule out treatments that are likely to be unsuitable based on particular physical or mental limitations and upon the psychological, social and economic circumstances of the entire family. Useful decision making criteria may include:

1. What the patient and medical team want to achieve;
2. The clinical effectiveness of the technique;
3. Medical contraindications;
4. The ease of teaching/learning the technique by the patients and/or by the carer;
5. The likely acceptability and hence adherence with the technique;
6. The likely effort/work required by the technique compared to its likely benefit;
7. The patient’s age, motivation, cognitive ability, concentration level and caregiver situation;
8. The degree of independence that a given technique gives the patient from the carer or the medical teams.

Airway clearance techniques are an essential part of the management of patients with CF. However, our understanding of how these devices work from bench testing and from physiological studies is limited to a very small number of studies. The studies themselves have used different populations (adults, children, mixed), with a range of disease severity and in general used the FEV$_1$ as the primary outcome measure. Whilst the FEV$_1$ is useful for assessing the respiratory well-being of patients, it presents only a limited picture of airway function. The FEF$_{25\%-75\%}$ has been used, and is thought to be sensitive to abnormalities in the small airway (McFadden & Linden, 1972; Landau et al, 1973). This, however, is only true when both the elastic recoil of the lungs and airways resistance are normal (Woolcock, 1998).

This may not be the case in CF, and is probably overlooked when interpreting results. The other key point about the FEF$_{25\%-75\%}$ is that it is very dependent on a true FVC being achieved on every occasion, which in itself may also be a significant variable. Furthermore, if the FVC increases or decreases then interpretation of this index becomes difficult. An alternative is to use the MEF$_{25\%FVC}$ which is similarly believed to be sensitive to small airway abnormalities. Again, however, if the FVC changes, the MEF$_{25\%FVC}$ cannot be compared post intervention to pre-intervention. Both these indices need careful analysis pre-to-post intervention and this can be achieved by using the iso-volume method of assessment (Boggs et al, 1982a; Boggs et al, 1982b).

Assessing the inhomogeneity of ventilation can be assessed either by nitrogen washout (Paiva & Engel, 1981) or by the use of the Lung Clearance Index (LCI) and the mixing ratio using the inert gas sulphur hexafluoride (SF6). The second method has been shown to be a more sensitive index than spirometry, (Gustafsson et al, 2003) does not require the respiratory gymnastics needed for forced expiratory manoeuvres and also appears to be age independent (Aurora et al, 2004), thereby making it highly useful for longitudinal studies. It is being increasingly used in both adult and paediatric CF patients (Horsley et al, 2008; Horsley, 2009; Kieninger et al (2011)).
Whilst these physiological measurements are important guides to the course of disease, they do not present the whole picture. As stated above, what matters to the patient is how much independence they have and how much they themselves can actually do. Techniques which give the patient greater independence in the management of their own disease may well improve adherence to treatment and therapies. Including in studies, measures of patient adherence and patient acceptability are equally important.

Few studies have investigated health-related quality-of-life measures, the number of exacerbations or hospital days per year, the costs or harm associated with intervention, or mortality rates. These need to be included along with the appropriate physiological measurements in any properly randomized control trial of airway clearance techniques to ensure that we fully understand how these techniques benefit or otherwise patients with CF. Furthermore, in our increasingly cost sensitive society, there needs to be a cost-benefit analysis included.

There are new techniques emerging and modifications of existing techniques which will improve the already difficult lives of patients with CF. As observed in all of the Cochrane reviews there is a clear need for properly controlled randomized trials and sensible and carefully selected primary and secondary outcomes that present the whole picture, provide the much needed evidence-based information needed to understand and apply these techniques. It is therefore incumbent on all researchers and clinicians working with CF patients to ensure that this good quality research is undertaken and published.

7. References

Albers GM, Tomkiewicz RP, May MK, et al (1996). Ring distraction technique for measuring surface tension of sputum: relationship to sputum clearability. *J Appl Physiol*, 81, 2690 – 2695.

Alves L, Pitta F, Brunetto AF (2008). Performance analysis of the Flutter VRP1 under different flows and angles. *Respir Care*, 53, 316 – 323.

Angus GE, Thurlbeck WM (1972). Number of alveoli in the human lung. *J Appl Physiol*, 32, 483 – 485.

Annesi I, Kauffmann F (1986). Is respiratory mucus hypersecretion really an innocent disorder? A 22-year mortality survey of 1,061 working men. *Am Rev Respir Dis*, 134, 688 – 693.

App EA, Kieselmann R, Reinhardt D, et al (1998). Sputum rheology changes in cystic fibrosis lung disease following two different types of physiotherapy. *Chest*, 114, 171 – 177.

Arora NS, Gal TJ (1981). Cough dynamics during progressive expiratory muscle weakness in healthy curanized subjects. *J Appl Physiol*, 51, 494 – 498.

Aurora P, Gustafsson PM, Bush A, et al (2004). Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis. *Thorax*, 59, 1068 – 1073.

Bell SC, Saunders MJ, Elborn JS, Shale DJ (1996). Resting energy expenditure and oxygen cost of breathing in patients with cystic fibrosis. *Thorax*, 51, 126 – 131.

Bennett WD, Foster WM, Chapman WF (1990). Cough-enhanced mucus clearance in the normal lung. *J Appl Physiol*, 69, 1670 – 1675.
Bennett, WD, Zeman KL (1994). Effect of enhanced supra-maximal flows on cough clearance. *J Appl Physiol*, 77, 1577 – 1583.

Bernard RS, Cohen LL (2004). Increasing adherence to cystic fibrosis treatment: a systematic review of behavioural techniques. *Pediatr Pulmonol*, 37, 8 – 16.

Boggs PB, Bhat KD, Vekovius WA, Debo MS (1982). Volume-adjusted maximal mid-expiratory flow (Iso-volume FEF\textsubscript{25-75%}): definition of "Significant" responsiveness in healthy, normal subjects. *Ann Allergy*, 48, 137 - 138.

Boggs PB, Bhat KD, Vekovius WA, Debo MS (1982). The clinical significance of volume-adjusted maximal mid-expiratory flow (Iso-volume FEF\textsubscript{25-75%}) in assessing airway responsiveness to inhaled bronchodilator in asthmatics. *Ann Allergy*, 48, 139 - 142.

Bott J, Blumenthal S, Buxton M, et al (2009). Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Joint BTS/ACPRC Guideline. *Thorax*, 64, Suppl 1, 1 – 52.

Boyle MP (2003). So many drugs, so little time: the future challenge of cystic fibrosis care. *Chest*, 123, 3 – 5.

Campbell EJM, Westlake EK, Cherniack RM (1957). Simple methods of estimating oxygen consumption and the efficiency of the muscles of breathing. *J Appl Physiol*, 11, 303 – 308.

Clarke S, Jones JG, Oliver DR (1970). Resistance to two-phase gas-liquid flow in airways. *J Appl Physiol*, 29, 464 – 471.

Clini E (2009). Positive expiratory pressure techniques in respiratory patients: old evidence and new insights. *Breathe*, 6, 153 – 159.

Cystic Fibrosis Trust (2003). Association of Chartered Physiotherapists in Cystic Fibrosis. Clinical Guidelines for the Physiotherapy Management of Cystic Fibrosis. Kent: Cystic Fibrosis Trust.

Daniels T (2010). Physiotherapeutic management strategies for the treatment of cystic fibrosis in adults. *Journal of Multidisciplinary Healthcare*, 3, 201 - 212.

Delaunois L (1989). Anatomy and physiology of collateral respiratory airways. *Eur Respir J*, 2, 893 – 904.

Desplechain C, Foliguet B, Barrat E, et al (1983). The Pores of Kohn in pulmonary alveoli. *Bull Eur Physiopathol Respir*, 19, 59 – 68.

Elkins M, Jones A, van der Schans CP (2004). Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD003147. DOI: 10.1002/14651858.CD003147.pub3.

Engelhardt JF, Zepada M, Cohn JA, Yankaskas JR, Wilson JM (1994). Expression of cystic fibrosis gene in adult human lung. *J Clin Invest*, 93, 737 - 749.

Fazzi P, Girolami G, Albertelli R, et al (2008). IPPB with temporary expiratory (TPEP) in surgical patients with COPD. *Eur Respir J*, 32, Suppl 52, 577s.

Fazzi P, Albertelli R, Grana M, Paggiaro FL (2009). Lung ventilation scintigraphy in the assessment of obstructive lung diseases. *Breathe*, 5, 252 – 262.

Fink JB (2002). Positive pressure techniques for airway clearance. *Respir Care*, 47, 786 – 796.

Flume PA, Robinson KA, O’Sullivan BP, et al (2009). Cystic Fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care*, 54, 522 – 537.
Foster WM (2002). Mucociliary transport and cough in humans. *Pulm Pharmacol Ther*, 15, 277 - 282.

Goldman MJ, Anderson GM, Stolzenberg ED, et al (1997). Human β-defensin-1 is a salt-sensitive antibiotic in the lung that is inactivated in cystic fibrosis. *Cell*, 88, 553 - 560.

Gross D, Zidulka A, O’Brien C, et al (1985). Peripheral mucociliary clearance with high-frequency chest wall compression. *J Appl Physiol*, 58, 1157 - 1163.

Gustafsson PM, Aurora P, Linblad A (2003). Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J*, 22, 972 - 979.

Harris RS, Lawson TV (1968). The relative mechanical effectiveness and efficiency of successive voluntary coughs in healthy young adults. *Clin Sci*, 34, 569 - 577.

Hasani A, Pavia D, Agnew JE, Clarke SW (1994). Regional lung clearance during cough and forced expiration technique (FET): effects of flow and viscoelasticity. *Thorax* 49, 557 - 561.

Hogg JC, Macklem PT, Thurlbeck WM (1969). The resistance of collateral channels in excised human lungs. *J Clin Invest*, 48, 421 - 431.

Horsley AR, Macleod KA, Robson AG, et al (2008). Effects of cystic fibrosis lung disease on gas mixing indices derived from alveolar slope analysis. *Respir Physiol*, 162, 197 - 203.

Horsley A (2009). Lung clearance index in the assessment of airways disease. *Respir Med*, 103, 793 - 799.

Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M (1999). Regulation of mucociliary clearance in health and disease. *Eur Respir J*, 13, 1177 - 1188.

Kendrick AH. (2007). Airway clearance techniques in cystic fibrosis: physiology, devices and the future. *J R Soc Med*, 100, Suppl 47, 3 - 23.

Kettler LJ, Sawyer SM, Winfield HR, Greville HW. (2002). Determinants of adherence in adult cystic fibrosis. *Thorax*, 57, 459 - 464.

Kieninger E, Singer F, Fuchs O, et al (2011). Long-term course of lung clearance index between infancy and school-age in cystic fibrosis subjects *J Cyst Fibros*, 10, 487 - 490.

King M, Brock G, Lundell C. (1985). Clearance of mucus by simulated cough. *J Appl Physiol*, 58, 1776 - 1785.

King M. (1987). The role of mucus viscoelasticity in cough clearance. *Biorheology*, 24, 89 - 97.

King M, Zahm JM, Pierrot D, Vaquez-Girod S, Puchelle E (1989). The role of mucus gel viscosity spinnability and adhesive properties in clearance by simulated cough. *Biorheology*, 26, 747 - 752.

King M, Zidulka A, Phillips DM, Wight D, Gross D, Chang HK (1990). Tracheal mucus clearance in high-frequency oscillation: effect of peak flow rate bias. *Eur Respir J*, 3, 6 - 13.

Kim CS, Brown LK, Lewars GG, Sackner MA (1983). Deposition of aerosol particles and flow resistance in mathematical and experimental airway models. *J Appl Physiol*, 55, 154 - 163.

Kim CS, Rodriguez CR, Eldridge MA, Sackner MA (1986) Criteria for mucus transport in the airways by two-phase gas-liquid flow mechanism. *J Appl Physiol*, 60, 901 - 907.
Kim CS, Greene MA, Sankaran S, Sackner MA (1986a). Mucus transport in the airways by two-phase gas-liquid flow mechanism: continuous flow model. *J Appl Physiol*, 60, 908 – 917.

Kim CS, Iglesias AJ, Sackner MA (1987). Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. *J Appl Physiol*, 62, 959 – 971.

Knudson RJ, Mead J, Knudson DE (1974). Contribution of airway collapse to supramaximal expiratory flows. *J Appl Physiol*, 36, 653 – 667.

Konstan MW, Stern RC, Doershuk CF (1994). Efficacy of the Flutter device for airway mucus clearance in patients with cystic fibrosis. *J Pediatr*, 124, 689 – 693.

Kulaksiz H, Schmid A, Hanschied M, Ramaswamy A, Cetin Y (2002). Clara cells impact in air-side activation of CFTR in small airways. *Proc Natl Acad Sci*, 99, 6796 – 6801.

Lamarrre A, Reilly BJ, Bryan AC, Levison H (1972). Early detection of pulmonary function abnormalities in cystic fibrosis. *Pediatrics*, 50, 291 – 298.

Landau LI, Hill DJ, Phelan PD (1973). Factors determining the shape of maximum expiratory flow-volume curves in childhood asthma. *Aust N Z J Med*, 3, 557 – 564.

Lands LC, Heigenhauser GJF, Jones NL (1992). Analysis of factors limiting maximal exercise performance in advanced cystic fibrosis. *Clin Sci*, 83, 391 – 397.

Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. (1990). Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax*, 45, 579 – 585.

Laube DM, Yim S, Ryan LK, Kisch KO, Diamond G (2006). Antimicrobial peptides in the airway. *Curr Top Microbiol Immunol*, 306, 153 – 182.

Lee YW, Lee J, Warwick WJ (2008). The comparison of three high-frequency chest compression devices. *Biomed Instrum Technol*, 42, 68 – 75.

Lopez-Vidriero MT (1981). Airway mucus; production and composition. *Chest*, 80 (Suppl), 799 – 804.

Macklem PT (1971). Airway obstruction and collateral ventilation. *Physiol Rev*, 51, 368 – 436.

Main E, Prasad A, van der Schans CP (2005). Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD002011. DOI: 10.1002/14651858.CD002011.pub2.

Mansell A, Dubrawsky C, Levison H, Bryan AC, Crozier DN (1974). Lung elastic recoil in cystic fibrosis. *Am Rev Respir Dis*, 109, 190 – 197.

Matthys H, Kohler D (1986). Bronchial clearance in cystic fibrosis. *Eur J Respir Dis*, 146, 311 – 318.

McCarren B, Alison JA, Herbert RD (2006a). Vibration and its effect on the respiratory system. *Aust J Physiother*, 52, 39 – 43.

McCarren B, Alison JA, Herbert RD (2006b). Manual vibration increases expiratory flow rate via increased intrapleural pressure in healthy adults: and experimental study. *Aust J Physiother*, 52, 267 – 271.

McCarren B, Alison JA (2006c). Physiological effects of vibration in subjects with cystic fibrosis. *Eur Respir J*, 27, 1204 – 1209.

McCool FD, Leith DE. (1987). Pathophysiology of cough. *Clin Chest Med*, 2, 189 – 195.
McCool FD, Rosen MJ. (2006). Non-pharmacologic airway clearance therapies: ACCP evidence-based clinical practical guidelines. Chest, 129, 2505 – 2595.

McFadden ER, Linden DA. (1972). A reduction in maximum mid-expiratory flow rate. A spirometric manifestation of small airway disease. Am J Med, 52, 725 – 737.

Mier A, Ridington A, Brophy C, Hudson M, Green M (1990). Respiratory muscle function in cystic fibrosis. Thorax, 45, 750 – 752.

Milic-Emili J (1991). Work of breathing. In: Crystal RG, West JB, Eds. The Lung: Scientific Foundations. New York: Raven, 1065 – 1075.

Milla CE, Hansen LG, Weber A, Warwick WJ (2004). High-frequency chest compression: effect of the third generation compression waveform. Biomed Instrum Technol, 38, 322 – 328.

Milla CE, Hansen LG, Warwick WJ (2006). Different frequencies should be prescribed for different high frequency chest compression machines. Biomed Instrum Technol, 40, 319 – 324.

Moran F, Bradley JM, Piper AJ (2009). Non-invasive ventilation for cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD002769. DOI: 10.1002/14651858.CD002769.pub3.

Morrison L, Agnew J (2009). Oscillating devices for airway clearance in people with cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD006842. DOI: 10.1002/14651858.CD006842.pub2.

Myers LB, Horn SA (2006). Adherence to chest physiotherapy in adults with cystic fibrosis. J Health Psychol, 11, 915 – 926.

Paiva M, Engel LA (1981). The anatomical basis for the sloping N₂ plateau. Respir Physiol, 44, 325 – 337.

Prescott E, Lange P, Vestbo J (1995). Chronic mucus hypersecretion in COPD and death from pulmonary infection. Eur Respir J, 8, 1333 – 1338.

Ranga V, Kleinerman J (1978). Structure and function of small airways in health and disease. Arch Pathol Lab Med, 102, 609 – 617.

Regnis JA, Robinson M, Bailey DL, et al (1994). Mucociliary clearance in patients with cystic fibrosis and in normal subjects. Am J Respir Crit Care Med, 150, 66 – 71.

Reis AL, Sosa G, Prewitt L, Friedman PJ, Harwood IR (1988). Restricted pulmonary function in cystic fibrosis. Chest, 94, 575 – 579.

Robinson KA, Mckoy N, Saldanha I, Odelola OA (2010). Active cycle of breathing technique for cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 11. Art. No.: CD007862. DOI: 10.1002/14651858.CD007862.pub2.

Robinson M, Eberl S, Tomlinson C, Daviskas E, Regnis JA, Bailey DL, Torzillo PJ, Menache M, Bye PT (2000). Regional mucociliary clearance in patients with cystic fibrosis. J Aerosol Med, 13, 73 - 86.

Rogers DF (1994). Airway goblet cells: responsive and adaptable frontline defenders. Eur Respir J, 7, 1690 – 1706.

Rose MC, Voynow JA (2006). Respiratory Tract Mucin Genes and Mucin Glycoproteins in health and Disease. Physiol Rev, 86, 245 – 278.

Rosenstein BJ, Zeitlin PL (1998). Cystic Fibrosis. Lancet, 351, 277 – 282.
Ross BB, Gramiak R, Rahn H. (1955). Physical dynamics of the cough mechanism. *J Appl Physiol*, 8, 264 – 268.

Rubin BK (2002). Physiology of airway mucus clearance. *Respir Care*, 47, 761 – 768.

Sawicki GS, Seller DE, Robinson WM (2009). High treatment burden in adults with Cystic Fibrosis: Challenges to Disease Self-Management. *J Cyst Fibros*, 8, 91 – 96.

Scherer PW (1981). Mucus transport by cough. *Chest*, 805, 830 – 833.

Schneider JJ, Unholzer A, Schaller M, Schäfer-Korting M, Korting HC (2005). Human Defensins. *J Mol Med (Berl)*, 83, 587 – 585.

Smith JA, Owen EC, Jones AM, Dodd ME, Webb AK, Woodcock A (2006). Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis. *Thorax*, 61, 425 – 429.

Soboya RE, Tausig LM. (1986). Quantitative aspects of lung pathology in cystic fibrosis. *Am Rev Respir Dis*, 134, 290 – 295

Sohn K, WJ Warwick, Lee YW, Lee J, Holte JE (2005). Investigation of non-uniform airflow signal oscillation during high frequency chest compression. *Biomed Eng Online* 2005 [http://www.biomedicalengineering-online.com/content/4/1/34]

Tiddens HA, Koopman LP, et al (2000). Cartilaginous airway wall dimensions and airway resistance in cystic fibrosis. *Eur Resp J*, 15, 735 – 742.

van der Schans CP (1997). Forced expiratory manoeuvres to increase transport of the bronchial mucus: a mechanistic approach. *Monaldi Arch Chest Dis*, 52, 367 – 370.

van der Schans CP, Prasad A, Main E (2000). Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD001401. DOI: 10.1002/14651858.CD001401

van der Schans CP (2007). Conventional chest physical therapy for Obstructive Lung Disease. *Respir Care*, 52, 1198 – 1206.

Vestbo J, Prescott E, Lange P (1996). Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med*, 153, 1530 – 1535

Volsko TA, DiFiore JM, Chatburn RL (2003). Performance comparison of two oscillating positive expiratory pressure devices: Acapella versus Flutter. *Respir Care*, 48, 124 – 130.

Von Leden H, Isshiki N (1965). An analysis of cough at the level of the larynx. *Arch Otolaryngol*, 81, 616 – 625.

Voynow JA, Rubin BK. (2009). Mucins, mucus and sputum. *Chest*, 135, 505 – 512.

Wanner A, Salathe’ M, O’Riordan TG (1996). Mucociliary clearance in the airways. *Am J Respir Crit Care Med* 154, 1868 – 1902

Weibel ER (1984). The Pathway of Oxygen. Cambridge, Mass: Harvard University Press.

Wood RE, Wanner A, Hirsch J, Di Sant’Agnese (1975). Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. *Am Rev Respir Dis*, 111, 733 – 738.

Woolcock AJ (1998). Effects of drugs on small airways. *Am J Respir Crit Care Med*, 157 (Suppl 5), S203 – S207

Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D (2004). Cystic fibrosis adult care: consensus conference report. *Chest*, 125, 1 (Suppl), 1S - 39S.
Yeates DB, Sturgess JM, Kahn SR, Levison H, Aspin N. (1976). Mucociliary transport in trachea of patients with cystic fibrosis. *Arch Dis Child*, 51, 28 – 33.
Zahm JM, King M, Duivivier C, Pierrot D, Girod S, Puchelle E. (1991). Role of simulated repetitive coughing in mucus clearance. *Eur Respir J*, 4, 311 – 315.
Zapatal A, Motoyama EK, Gibson LE, Bouhuys A. (1971). Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics*, 48, 64 – 72.
Living healthy is all one wants, but the genetics behind creation of every human is different. As a curse or human agony, some are born with congenital defects in their menu of the genome. Just one has to live with that! The complexity of cystic fibrosis condition, which is rather a slow-killer, affects various organ systems of the human body complicating further with secondary infections. That's what makes the disease so puzzling for which scientists around the world are trying to understand better and to find a cure. Though they narrowed down to a single target gene, the tentacles of the disease reach many unknown corners of the human body. Decades of scientific research in the field of chronic illnesses like this one surely increased the level of life expectancy. This book is the compilation of interesting chapters contributed by eminent interdisciplinary scientists around the world trying to make the life of cystic fibrosis patients better.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Adrian H. Kendrick (2012). Airways Clearance Techniques in Cystic Fibrosis: Physiology, Devices and the Future, Cystic Fibrosis - Renewed Hopes Through Research, Dr. Dinesh Sriramulu (Ed.), ISBN: 978-953-51-0287-8, InTech, Available from: http://www.intechopen.com/books/cystic-fibrosis-renewed-hopes-through-research/airway-clearance-techniques-in-cystic-fibrosis-physiology-devices-and-the-future
