

# Mechanical clearance of human airways using the Frequencer electro-acoustical transducer – a white paper

Dr. André Cantin  
Marc Bacon, P. Eng.

*Abstract: Clearance of mucus from airways is vital in the treatment of pulmonary obstructive diseases, and especially cystic fibrosis (CF). This paper reviews briefly the structure of respiratory system, and then describes mucus rheology and mucus clearance mechanisms. It goes on to describe the operation of the Frequencer electro-acoustical transducer and the unique physical phenomena that allow it to contribute to effective mucus clearance. The paper compares the effectiveness and safety of the Frequencer to chest physiotherapy (CPT) and other mechanical means of airway clearance and provides results of testing showing significant increases in mucus flow rates using the Frequencer.*

## **Respiratory system overview**

Air enters the human respiratory system, is warmed, humidified and filtered as it travels down to the alveoli. There it exchanges oxygen into the blood and removes carbon dioxide from it, and then is exhaled.

The respiratory system below the larynx is constructed as follows:

1. The trachea is a cylinder supported by 16 to 20 C-shaped hyaline cartilage rings embedded in an external fibroelastic membrane. In this and other branches of the airway below it, the rings serve to prevent collapse of the airways under inspiration. The trachealis muscle serves to adjust airflow in the trachea. The trachea is lined with a ciliated pseudostratified epithelium that functions as a mucociliary escalator.
2. A bronchial tree with 23 branching generations of airways in total. The first 16 comprise the conducting zone and serve as fluid conduits. Generations 17-23 form the respiratory zone, which includes the respiratory bronchioles, alveolar ducts, and alveolar sacs. The branches are composed of:
  - Primary bronchi, which are the first part of the airway to enter the lungs. They are supported by C-shaped hyaline cartilage rings. The right bronchus is slightly wider and more vertical than the left.
  - Secondary (lobar) bronchi, which are supported by overlapping plates of hyaline cartilage. There is one secondary bronchus for each lobe (3 for the right lung and 2 for the left)
  - Tertiary (segmental) bronchi, which are supported as well by overlapping plates of hyaline cartilage. There are 10 right, 8 left tertiary bronchi.
  - Bronchioles. They have no cartilage, since they are smaller than about 1mm in diameter. Their smooth muscle layer gives them their rigidity and allows for constriction or dilation. Particles of irritating substances can cause bronchiolar spasms in the bronchioles (as in patients with asthma). The bronchioles are lined with ciliated simple cuboidal epithelium cells that wave constantly towards the pharynx, moving secreted mucus at about 1.4 cm/min. and replacing the entire mucoid coating about every 20 minutes.<sup>1</sup>
  - Alveolar ducts and alveolar sacs. There are approximately 300 million alveoli, each with a radius of 100-300  $\mu\text{m}$  that open onto the lumina of the airways. Alveoli first begin to appear in the respiratory bronchioles, attached to the walls, and their frequency increases in the alveolar ducts until the airways end in grapelike clusters of alveoli.

---

<sup>1</sup> Robert A. Freitas Jr.. *Nanomedicine, Volume 1: Basic Capabilities*. 8.2.2 Navigational Bronchography. 1999, page 2.

Pleural fluid lubricates the outer surface of the lungs. The lobes slide against each other in the same way that the entire lungs slide within the thoracic cavity.<sup>2</sup>

## ***The mucociliary escalator***

The respiratory system is provided with a remarkable system to catch and reject foreign objects, while allowing air to pass with minimal restriction.

When particles and microbes enter the respiratory system, they can irritate and infect it. Transport and deposition of particles larger than 1 $\mu$  in the respiratory system are largely determined by particle size, density, shape, and gas velocity.<sup>3</sup>

Although sneezing and coughing with expectoration can eliminate many inhaled particles, the mucociliary escalator assisted by bronchus-associated lymphoid tissue (BALT) and alveolar macrophages are responsible for clearing the airways. To this is added the surfactant action of secretions.

Bronchial secretions from bronchial glands and goblet cells, together with secretions from deeper in the lungs, form a sheet of fluid which is propelled upwards continuously by the centripetal beat of the cilia lining the bronchial epithelium. This fluid is sticky, and traps foreign particles. The fluid is moved to the glottis, where it is expelled from the airways and swallowed<sup>4</sup> or expectorated.

The ciliated epithelial cells of the airways are covered by a two-layered mucous blanket: an upper high-viscosity gel layer and a bottom low-viscosity serous layer termed the periciliary liquid (PCL), in which the cilia beat in a coordinated manner<sup>5</sup>. The gel-mucous blanket transports insoluble particles, cells and particles that have been transported from the nonciliated alveoli to the ciliated airways. In humans the ciliated epithelium extends from the trachea down to the terminal bronchioles. The speed of mucus movement is faster in the trachea than in the small airways and depends on factors that affect cilia movement or amount and quality of mucus. Particles deposited in the nonciliated compartments lower in the lungs move much more slowly, so small differences in solubility can result in significantly different clearance rates.<sup>6</sup>

Respiratory cilia are about 0.2 microns in diameter and 2-7 microns long, with a typical separation between cilia of 2-5 microns.<sup>7</sup> They are composed of projections of the epithelial membrane with cores containing microtubule-based motors<sup>8</sup>. These motors beat in coordinated fashion, moving the PCL and ASL toward the glottis.

The effectiveness of ciliary action depends on the speed, amplitude, time course and form of stroke, length of the cilia, the ratio of ciliated to nonciliated area, and the susceptibility of the cilia to intrinsic and extrinsic agents that modify their rate and quality of motion. The characteristics of the mucous layer are critically important, as the thickness of the mucous layer and its rheological properties may vary widely.<sup>9</sup>

---

<sup>2</sup> Ibid, page 2.

<sup>3</sup> J. Blanchard, H. Füglein and R. Köbrich. *Deposition and Fate of Inhaled Pharmacological Aerosols*. page 2.

<sup>4</sup> Richard Boucher, C. William Davis, Garrett Matthews. *Mucociliary Clearance for Cystic Fibrosis*.  
<http://www.cs.unc.edu/>. 4/29/2004, page 1

<sup>5</sup> Ibid, page 1

<sup>6</sup> J. Blanchard, H. Füglein and R. Köbrich. *Deposition and Fate of Inhaled Pharmacological Aerosols*. page 25

<sup>7</sup> Robert A. Freitas Jr. *Nanomedicine, Volume 1: Basic Capabilities*. 8.2.2 Navigational Bronchography.  
1999, page 1

<sup>8</sup> Richard Boucher, C. William Davis, Garrett Matthews. *Mucociliary Clearance for Cystic Fibrosis*.  
<http://www.cs.unc.edu/>. 4/29/2004, page 1

<sup>9</sup> J. Blanchard, H. Füglein and R. Köbrich. *Deposition and Fate of Inhaled Pharmacological Aerosols*, page 25

It was formerly believed that the PCL was more or less static in the transport of mucus, which is propelled forward by the power stroke of the cilium, but this is not the case. Within the resolution of the confocal microscope, the entire PCL is transported during mucus transport at the same rate as the overlying mucus gel. It appears that the ciliary mixing of the PCL effectively distributes the energy imparted to the PCL by its frictional interactions with mucus.<sup>10</sup> In layman's terms, it was thought that thicker mucus glides along on relatively static PCL, propelled by the power stroke of the cilium, which then bends and rides under the gel on the return stroke. In reality, it appears that the PCL layer moves with the gel, both of them being propelled by the cilium, which are densely spaced and work in unison.

We suggest that the dual layer is not intended for lubrication to cause the mucus gel to "skate" on the PCL, but to prevent its adherence to the epithelial cells to allow effective ciliary mobility and to permit vibrations of the conduit walls. The airways are composed of many branches of varying diameters and lengths, each one with its own resonant frequency and having flexible walls. Passage of air through these many tuned ducts keeps the walls constantly in movement. This movement allows sound waves of all sorts of frequencies to be generated and transmitted in the thorax, something that is readily demonstrated with a stethoscope. A Fast Fourier Transform (FFT) analysis of the sound of pulmonary auscultation would show a broad spectrum of small resonances that varies constantly with time and the listening position.

At every inspiration and expiration, the airway walls flex, causing shear to occur in the interface between the PCL and the airway walls. We believe the acoustic vibrations from rushing air and the lower frequency higher amplitude flexing from breathing help to prevent "sticking" of the gel layer to the top of the cilia, allowing them beat freely in the PCL. It may be as well that the movement of the cilia aids in the segregation of sticky mucus from the PCL in much the same way that a vibrator placed in concrete will surround itself with water and cause the concrete to slump into place.

It is difficult to study the natural secretions of the healthy tracheobronchial tree in man, for only about 100 ml is produced daily and most of this is swallowed.<sup>11</sup>

Mucociliary transport has been studied by monitoring the movement of inert or radiolabeled particles deposited on the tracheal mucus via either a bronchoscope or an inhaled bolus. Tracheal mucous velocity can be estimated from the distance particles move over time. Bronchoscopic techniques give tracheal mucous velocities of 15-21 mm/min, while non-invasive bolus techniques yield lower values of around 4.4 mm/min. The values are characteristic only for the trachea and large central airways. Transport speed in the terminal bronchioles is about 0.1-0.6 mm/min.<sup>12</sup>

Particles in the nonciliated portion of the lungs are cleared by dissolution and/or mechanically by movement toward the ciliated region within alveolar macrophages. Particles may also move because of a surface tension gradient in the mucus due to surfactant that extends from the alveoli to the airways<sup>13</sup> and the capillary forces resulting from the small diameters of those passages. However, these passages are so small that they can be blocked partly or totally by high viscosity mucus.

## ***Cystic fibrosis***

Cystic fibrosis is an autosomal recessive inherited disease of all exocrine glands, caused by a gene mutation on chromosome 7. This mutation causes a defective transmembrane regulator protein (the cystic fibrosis transmembrane conductance regulator, or CFTR), which is an  $\alpha$ -adrenergic gated chloride channel. Normally,

---

<sup>10</sup> Richard Boucher, C. William Davis, Garrett Matthews. *Mucociliary Clearance for Cystic Fibrosis*. <http://www.cs.unc.edu/>. 4/29/2004, page 1

<sup>11</sup> D.J. Lane. *The clinical presentation of chest diseases*. <http://www.attar.4t.com/>. 4/29/2004., page 2

<sup>12</sup> J. Blanchard, H. Füglein and R. Köbrich. *Deposition and Fate of Inhaled Pharmacological Aerosols*, page 25

<sup>13</sup> *Ibid*, page 26

an elevated cAMP in the epithelial cell will open the chloride channel, but this does not happen in cystic fibrosis. As a result, there is less excretion of NaCl to the airways, sweat ducts and pancreatic ducts, along with less excretion of water and increased secretion viscosity. These secretions plug the airways and duct systems.

Patients with cystic fibrosis suffer from pulmonary infection with obstructive lung disease, bronchiolitis and bronchiectasis, and from pancreatic insufficiency. Thus, cystic fibrosis is one of most severe of the many diseases that cause airway obstruction and can profit from better mucus clearance.

## **Coughing**

Usually, the mucociliary escalator functions silently and efficiently to clear the airways. However, at times foreign bodies, thick and/or abundant mucus, dust, and chemical irritants or fumes may prove too much for the mucociliary escalator, and the body reacts by coughing. Sudden and large changes in airway caliber or lung collapse can also stimulate cough receptors<sup>14</sup>, and coughing can be voluntary.

The cough reflex is both a protective and a clearing mechanism. Cough receptors are found in the pharynx, larynx and larger airways. Nerve endings are located within the epithelium throughout much of the respiratory system, being most numerous on the posterior wall of the trachea, at the main carina, and at the branching points of large airways, and less numerous in the more distal smaller airways. No nerve endings have been found beyond the respiratory bronchioles. The most distal sites may be more sensitive in stimulating coughing.<sup>15</sup>

Although coughing is primarily vagal, since cough may be voluntarily initiated, postponed, or suppressed, there may be afferent input from higher centers.<sup>16</sup>

A cough starts with a deep inspiration followed by expiration against a closed glottis. Glottal opening then allows a forceful jet of air to be expelled. The pressure which builds up behind the closed glottis can reach as much as 40 kPa (5.8 psig), which is over twice the pressure that can be developed by blowing into a closed container. The explosive action of the respiratory muscles produces very high laryngeal air velocities and is accompanied by laryngeal and bronchial constriction, mucus secretion, and a transient systemic hypertension<sup>17</sup>

Coughing causes momentary collapse of the tracheal wall when the equal pressure point has moved to a part of the airway that is not supported by cartilage and has the smallest cross sectional area, but the highest kinetic energy.

The peak airway resistance, where flow limitation takes place, occurs in the medium-sized segmental bronchi around the 4<sup>th</sup>-7<sup>th</sup> generation moving peripherally as lung volume decreases. In healthy people the least resistance to airflow is found in the many terminal bronchioles. At low lung volumes the elastic pull in the bronchioles becomes smaller and the airways tend to collapse more easily.

Cough may produce sputum. An effective cough for mucus movement depends on the ability to achieve high gas flows and intrathoracic pressures, enhancing the removal of mucus adhering to the airway wall.<sup>18</sup>

---

<sup>14</sup> D.J. Lane. *The clinical presentation of chest diseases*. <http://www.attar.4t.com/>. 4/29/2004., page 1

<sup>15</sup> Richard S. Irwin, Louis-Philippe Boulet, and others. *Managing cough as a defense mechanism and as a symptom; a consensus report of the American College of Chest Physicians*. Chest. August 1998., page 6

<sup>16</sup> Ibid, page 7

<sup>17</sup> D.J. Lane. *The clinical presentation of chest diseases*. <http://www.attar.4t.com/>. 4/29/2004., page 1

<sup>18</sup> Richard S. Irwin, Louis-Philippe Boulet, and others. *Managing cough as a defense mechanism and as a symptom; a consensus report of the American College of Chest Physicians*. Chest. August 1998., page 1

Dynamic compression during coughing decreases the cross-sectional area of the trachea, increasing gas velocity by as much as 5x and kinetic energy by 25x. Since velocity is proportional to the square of the airway diameter, and kinetic energy is proportional to the square of the velocity, a slight narrowing of the airway passages can greatly increase the kinetic energy of the gas. This kinetic energy enhances the removal of mucus adhering to the airway wall. Normally, dynamic compression begins in the trachea and larger bronchi at high lung volumes and extends to the more peripheral airways as lung volume decreases, ensuring that the whole length of the tracheobronchial tree is coughed. For this to occur, high intrathoracic pressure must be sustained throughout the expiratory effort. Sick or weak patients may not be able to sustain this pressure.

Afferent impulses from coughing may stimulate secretion of mucus, serving as a barrier against irritant chemicals and enhancing clearance of foreign bodies from the airways.<sup>19</sup>

Air velocities during coughing may approach the speed of sound, or approximately 345 m/s. Even as low as 25 m/s, mucus is torn off the airway walls and droplets are suspended within the airway lumen in a pattern called misty flow. At velocities of less than 25 m/s, the mucus-gas interaction is less effective, and the mucus may remain adhering to the airway walls.

Besides misty flow, coughing can create waves of mucus, which may further enhance particle clearance. Since airways behave more like collapsible tubes than rigid pipes, they may vibrate due to coughing, and their walls may flatten, further aiding in loosening mucus and promoting clearance.

Cough effectiveness is directly proportional to the depth of the mucus, and is inversely proportional to mucus tenacity (adhesiveness x cohesiveness).

If mucus is to be transported by cilia, it should be elastic and of low viscosity. To be transported by coughing, mucus should be less elastic and more viscous, yet lie on an underlayer of low viscosity, so that it tears away from the airway wall more easily as a lump. Most mucus shows intermediate levels of viscosity to be able to respond to both mechanisms.

Models of misty flow in tubes suggest that cough may be effective down to the 7<sup>th</sup> to 12<sup>th</sup> airway generations in healthy individuals. When there is excess low-viscosity mucus production, so that the serous layer has a low viscosity close to that of water, the effect of coughing can extend down to the level of the respiratory bronchioles. These experiments, however, deal with a mechanical model and not with the *in vivo* situation in which there is dynamic compression and flapping of the airway walls. It may be that coughing can send shock waves even further down into the airways and aid in their clearance.

Experimentation in PVC channels has shown that wave initiation occurs during coughing at lower linear velocities if the mucus layer is thicker and less viscoelastic. Furthermore, flow disturbances caused by upper airway irregularities, asymmetries and vibrations of airway walls enhance clearance and are essential for effective cough clearance.

The high-velocity expired air during cough may also promote mucus clearance by stimulating the mucociliary apparatus, either by changing secretions of PCL or by increasing ciliary beat frequency. Stress has been known to open potassium channels in vascular endothelial cells, increasing potassium flux out of the cell and leading to hyperpolarization. The goblet cells may respond similarly to shear stress associated with the rapid flows of cough or rapid inhalations. Neural reflexes may be mediated by rapidly adapting receptors in the lung that respond to rapid deflation or inhalation by increasing mucus secretions.<sup>20</sup>

---

<sup>19</sup> Ibid, page 8

<sup>20</sup> Ibid, page 9

Because effective coughing requires the detachment and mobilization of secretions from the epithelial surface, sputum cough clearability is strongly dependent on adhesiveness and cohesiveness. When the water content of mucus is decreased, mucus clearance decreases as well. This is one of the main problems for CF patients.<sup>21</sup>

## ***Mucus Rheology***

The rheology of a material is its capacity to undergo flow and deformation. A true solid responds to a stress with an elastic deformation that is totally recovered after the stress is removed, unless the stress is so high that the material yields. An example of this is a car spring that stores energy, and then releases it. A Newtonian liquid such as water responds to a stress with viscous deformation, flowing continuously for the time that the stress is applied. After the removal of the stress, the flow ends and there is no recovery of the strain.

Viscoelasticity is a time-dependent property in which a material under stress produces both a viscous and an elastic response. A viscoelastic material will exhibit viscous flow under constant stress, but a part of the mechanical energy is conserved and recovered after stress is released. Often associated with polymer solutions, melts and structured suspensions, viscoelastic properties are usually measured as responses to an instantaneously applied or removed constant stress or strain or a dynamic stress or strain. Because they can both store energy and flow, viscoelastic materials tend to dampen vibration, since their stress-strain curve undergoes considerable hysteresis. Sorbothane is an example of a well-known viscoelastic polymer made from very soft polyurethane, and is used to dampen vibration.

A viscoelastic gel (termed a Maxwellian liquid, because its stress-strain curve is not linear) such as mucus initially stores energy, but with continued stress, it will begin to flow like liquid.<sup>22</sup> When the flow stops, it returns to its original state. A well-known example of viscoelastic gel is driplless paint. When it is pulled along by a brush or roller, it spreads well. However, when the stretching stops, it “gels” in place. This behaviour, although desirable in paint, can cause problems in mucus clearing. Since viscoelastic gels move only when applied stress is greater than a threshold level, if they are very viscous they may not reach the threshold value of stress required for flow, and may simply deform without flowing.

Intrabronchial mucus exists in two layers, a low viscosity, high elasticity PCL that we discussed above, and above this a more viscous layer, termed airway surface fluid (ASF). The elasticity of sputum appears to change with the rate of application of stress to it, and may be important to the rate of beating of the bronchial epithelial cilia.

Excessively large quantities of sputum are found in bronchiectasis, particularly where this is widespread, as in cystic fibrosis.<sup>23</sup> Because this sputum is thick and viscous, it does not flow easily. Furthermore, in CF, the PCL liquid layer is thinner, and the thicker ASF tends to impede the movement of the cilia.

ASF is composed of water, carbohydrates, proteins, and lipids. The physical properties of the mucous gel, and interactions between mucus and airflow or mucus and cilia, contribute to airway clearance. Mucus hypersecretion and impaired mucociliary clearance, generally associated with infected mucus and induced inflammation can reduce airway capacity.

The three-dimensional structure that forms the mucous gel is dependent upon several forms of bonding:

1. Intramolecular disulfide bonds, which join glycoprotein subunits in extended macromolecular chains known as mucins;

---

<sup>21</sup> Ibid, page 10

<sup>22</sup> Bruce K. Rubin. *An in vitro comparison of the Mucoactive properties of Guaifenesin, Iodinated Glycerol, surfactant, and Albuterol*. Chest. July, 1999, page 2

<sup>23</sup> D.J. Lane. *The clinical presentation of chest diseases*. <http://www.attar.4t.com/>. 4/29/2004., page 2

2. Entanglements with neighbouring macromolecules, acting as time-dependent crosslinks, that are susceptible to mechanical degradation and can be reduced by high frequency oscillation and other physiotherapy;
3. Weak hydrogen bonds between oligosaccharide side-chains comprising about 80% of the mucin.
4. Ionic interactions between fixed negative charges resulting in a stiff, more extended conformation
5. In an infection, extra networks of high molecular weight DNA and actin filaments released by dying leukocytes, and exopolysaccharides secreted by bacteria.<sup>24</sup>

In the ASL of normal humans, the concentration of mucins in the mucus is about 1% by weight. In cystic fibrosis (CF), an inherited disease characterized by a hyperabsorption of Na<sup>+</sup> and liquid from the ASL, the mucin content increases to as high as 3-4%. This serves to increase viscosity, reduce elasticity, and increase adhesivity, which hinders its transport.<sup>25</sup>

The absolute viscosity of normal mucus is typically ~1kg/m-sec, rising as high as ~500 kg/m-sec in the cystic fibrosis patients. Mucus rheology and mucociliary clearance mechanisms of the respiratory tract have been widely studied, along with the energy dissipation per cilium in the periciliary fluid.<sup>26</sup>

### ***Modification of mucus rheology due to mechanical oscillation***

A paper which has some significance in laying the background for the mucus clearance observed with the Frequencer involved a comparison of the Flutter device (described in a later section) with autogenic drainage.

In a 9-week study, no significant changes in FVC, FEV<sub>1</sub>, or sputum volume were noted, although participants showed a tendency toward improved FVC, up to 200 mL on average (about 6.5% of the baseline value). This may be attributed to a non-specific improvement in pulmonary function or to an overall training effect.

Sputum viscoelasticity was significantly lower (p<0.01) after physiotherapy with the Flutter than with autogenic drainage at two analytical frequencies (1 rad/s and 100 rad/s).

In the *in vitro* Flutter experiment, it was found that the elastic properties of CF sputum samples, as measured by a filancemeter, were affected significantly by application of oscillations generated by the Flutter at 15 and 30 minutes, with a median frequency of Flutter-generated oscillations of 19 Hz.

Changing the viscoelastic properties of the bronchial secretions may be perhaps one of the most important mechanisms of the Flutter, Vest, and Frequencer. However, no *in vivo* evidence has been shown so far to prove this theory. Dasgupta and colleagues were recently able to show in an *in vitro* study that when frequencies similar to those generated by the Flutter device were applied to CF sputum, viscoelasticity was significantly reduced with increasing oscillation time. This was also true for mucous gel simulants; the higher the applied frequency, the greater the reduction in viscoelasticity.

An earlier *in vitro* study showed a frequency-dependent (0, 12, and 22 Hz) decline in sputum rigidity.<sup>27</sup>

---

<sup>24</sup> Malcom King. *Summary of Research Efforts*. 4/29/2004. <http://www.ualberta.ca/~king/>, page 1

<sup>25</sup> Richard Boucher, C. William Davis, Garrett Matthews. *Mucociliary Clearance for Cystic Fibrosis*. <http://www.cs.unc.edu/>. 4/29/2004, page 2

<sup>26</sup> Robert A. Freitas Jr. *Nanomedicine, Volume 1: Basic Capabilities*. 8.2.2 Navigational Bronchography. 1999, page 1

<sup>27</sup> Ernst M. App; Rita Kieselmann; Dietrich Reinhardt; Hermann Lindemann; Bonnie Dasgupta, Malcolm King, Peter Brand. *Sputum Rheology Changes in Cystic Fibrosis Lung Disease Following Two Different Types of Physiotherapy*. *Chest*. July , 1998, page 175

The mechanism or mechanisms that reduce viscoelasticity when activated by mechanical oscillation are unknown. However, the most likely possibilities involve the cooperative unfolding of the physical entanglements between the primary network of mucous glycoproteins and other structural macromolecules, the rupture of crosslinking bonds such as disulfide bridges, and the fragmentation of larger molecules such as DNA or F-actin, which are present as a byproduct of infection and can increase mucous viscoelasticity due to their interactions with glycoproteins. In short, the more we agitate mucus, the less tacky, sticky, and stiff it appears and the more it behaves like water. This is analogous to shaking a bottle of ketchup. When the ketchup is agitated, it becomes less viscous and flows more easily, just like agitated mucus flows more easily than mucus congealed on the airway walls.

Mucus clearance from the airways of CF patients is needed to prevent mucus plugging, mucus impaction, and further deterioration of lung function. This is more critical in CF than in chronic bronchitis since CF patients do not cough as efficiently as patients with chronic bronchitis. Mechanical oscillation of airways may provide the rheological relief needed to improve mucus mobility.<sup>28</sup>

Another possibility not mentioned by the authors of this most intriguing paper is that the cilia beat continuously at 10-20 Hz in the PCL under the ASL. Could it be that this rapid movement provides the stirring needed to not only move the mucus sheet up the mucociliary escalator, but to also prevent thickening in the region between the two layers where vibratory impulses from the cilia can act to break up bonds and reduce viscosity? This is an intriguing avenue that merits further research, for if that is indeed the case, finding a way of increasing cilia beat frequency and/or effectiveness might provide more mucus mobility for CF patients by lowering the viscosity in the top of the PCL and the bottom of the ASL.

## ***Airway Clearance Techniques***

Although hydration, surfactants, and other drugs may be used to improve mucus mobility, Airway Clearance Techniques (ACT) has been used for many years to treat pulmonary problems. We will describe briefly those methods, before going on to the description of the Frequencer. A summary of mechanical airway mucus methods is shown in Table 1.

## **Chest Physical Therapy (CPT)**

Chest Physical Therapy is a means of removing secretions by having an assistant strike the chest repeatedly with a cupped hand in specific places, while the patient is positioned in such a way as to enhance mucus drainage. CPT works by dislodging mucus from the airway walls enough that subsequent coughing can clear the passages. The mechanism for dislodging the mucus appears to be the shock waves that travel through the thoracic cavity and tissues. When they arrive at the airway passages, they act to deform the passage walls and create a net shear stress that loosens the mucus. When the mucus moves as a result of PCT, it may trigger cough receptors. Together with postural drainage, the coughing serves to expectorate the mucus. CPT is often prescribed 2-3x/day for 20 minutes at a time. It is time-consuming for both the patient and caregiver, and is uncomfortable for the patient. Adherence to CPT is low in adolescent and adult patients. However, since CPT has been in use with beneficial effects for roughly 4 decades, since it costs nothing in the way of medical devices, and since it encourages expectoration of sputum, it has become the “gold standard” against which other Airway Clearance Techniques are compared.

## **Positive Expiratory Pressure (PEP)**

Positive Expiratory Pressure is a self-administered means of airway clearance that is done by forcible expiration against a flow resistance, which can take the form of several different types of masks and other medical devices.

---

<sup>28</sup> Ibid, page 176



When forcing against a flow resistance, the internal passages expand due to an increase in pressure. This serves not only to loosen mucus by inducing shearing stresses due to the relative motion between the mucus and airway passages that occurs at each breath, but also to widen airway passages. Once mucus movement begins, coughing is triggered, with resultant expectoration.<sup>29</sup>

A published review found that PEP had similar effects on sputum clearance when compared with other methods. In a 1-year randomized controlled clinical trial of PEP vs. conventional physiotherapy in 40 children with CF, the patients treated with PEP showed improvements in pulmonary function, although pulmonary function declined in patients treated with conventional physiotherapy.<sup>30</sup>

## **Flutter device**

This is a handheld device through which the patient exhales. Inside the device, a steel ball sits on an orifice. Outgoing air is prevented from going past the steel ball until it reaches a pressure sufficient to unseat the ball from the orifice. Once the ball is unseated, the ball returns to its position and the cycle repeats itself. The weight of the ball and the size of the orifice, together with the angular orientation of the ball work in unison to produce an oscillation of 6-25 Hz. When the oscillations of the ball are equal to the resonant frequency of the upper (large) airways, the patient feels a fluttering sensation in the chest and mucus clearance is enhanced in the upper airways.<sup>31</sup> Cost is low, but effectiveness is typically limited to upper airways only, since the vibration can only be stimulated down to the upper end of the blocked passages.

## **Vest (High Frequency Chest Wall Oscillation)**

This is a self-administered vest that the user puts on, and that is designed to fit snugly around the thorax when inflated (different sized vests are needed for different sized users.) The vest is inflated with a rapidly oscillating pressure. This provides external vibration to the chest walls, stimulating cough and promoting airway clearance. The effect is similar to the Flutter, except that the Vest acts by contact with the outside of the chest rather than modulating internal air pressure. Cost of the equipment is very high.

## **Intrapulmonary Percussive Ventilation (IPV)**

Intrapulmonary percussive ventilation is administered by a percussive air pressure delivered to the lungs by a machine. The hammer effect is supposed to affect airways that have retained secretions.

## **Hydroacoustic pulmonary resonance therapy (HAT)**

Like the vest, this method consists of inducing resonance in the chest cavity to loosen secretions by placing the patient in a water bath, and then exciting the bath with underwater sound. Like the vest, this is a whole chest resonance rather than a localized one, although selective use of frequencies can stimulate different resonances. HAT is not portable, and so is limited to home or clinical use.

## **“Natural” Techniques**

Forced Expiration Technique (FET), Autogenic Drainage (AD), and Active Cycle Breathing (ACB) are three techniques designed to open the airways and aid in mucus drainage. The techniques require no external equipment, but can involve dizziness and some discomfort. Because they are learned, they are impractical for young patients.

---

<sup>29</sup> J. Blanchard, H. Füglein and R. Köbrich. *Deposition and Fate of Inhaled Pharmacological Aerosols*, page 2

<sup>30</sup> Aetna. *Clinical Policy Bulletins. Number 0067*. <http://www.aetna.com/cpb/data>. 4/29/2004, page 4

<sup>31</sup> *Ibid*, page 2

## Exercise

Aerobic exercise can benefit people with obstructive lung disease both from the increased pulmonary capacity and from the associated sense of well-being. <sup>32</sup>Anaerobic exercise, such as weight training, can provide the muscular strength needed for effective breathing and coughing.

## The Frequencer

The Frequencer is a digitally controlled electro-acoustical transducer device invented recently by Louis Plante, a CF patient. It is manufactured and marketed by Dymedso. It consists of two parts, a control unit and a power head. The power head transmits sinusoidal mechanical and acoustical vibrations to the airways at various locations at resonant frequencies, providing airway clearance. The Frequencer is easy to use, requiring no special training in breathing techniques, and it works well. Cost of the equipment is much less than the Vest, and it is better adapted to young children.

Operation of the Frequencer is simple:

1. The transducer is applied to the area to be stimulated. The user then adjusts the frequency of the transducer to the point where it causes a sympathetic resonance that can be felt by the patient. This resonant frequency depends on patient size, airway obstruction, airway size, elasticity of passages, etc., but is very easy to determine simply by feeling the resultant movement of mucus and airway. Once the patient has found the suitable resonant frequency, he can adjust the energy input independently of frequency for maximum effectiveness.
2. Within a few seconds, the vibration begins to loosen mucus, provoking coughing, followed by expectoration of sputum.
3. When one application point stops yielding sputum, the patient moves the power head to a second location, readjusts the oscillating frequency to feel maximum movement in chest passages, and begins coughing again. This cycle is repeated for all classic CPT positions. Treatment time is roughly that of classic CPT.
4. The Frequencer can be applied while the patient is sitting up or in a reclining position if needed to encourage mucus flow.

The power head of the Dymedso Frequencer is not a mechanical substitute for clapping. Indeed, use of a mechanical actuator was tried during its development, with disappointing results. Mechanical actuators, like large massagers are not very effective in inducing coughing and airway clearance.

Instead, the power head in the Frequencer provides both mechanical and acoustical oscillation. The forcing frequency is typically between 25Hz and 40Hz, but can go higher if needed, and is specific to each patient and physiotherapy location.

The electro-acoustical transducer operates in two regimes of acoustic loading:

- 1) When pressed against the chest, the transducer diaphragm is damped on both sides, providing a classical 4<sup>th</sup> order bandpass response in the front. The transducer works in the high-pass region of the tuned circuit.
- 2) When working in free air, away from the chest, as it would be between positions, the diaphragm is loaded by a rear chamber that is resistively loaded to avoid exceeding mechanical limits.

---

<sup>32</sup> Ibid, page 3

The mechanical impulse is applied to a rigid circular perimeter surrounding an acoustical compression chamber, while the acoustical wave is applied at lower pressure, but spread over the entire surface contained within the acoustical compression chamber. The impulses are opposite in phase, and are transmitted differently through the tissues of the chest.

The control unit houses a digital frequency generator and a highly efficient Class D power amplifier, and has data logging capabilities to aid the physician in measuring patient adherence to treatment regimes.

Unlike Flutter and HFCWO, the Frequencer acts selectively on different areas, just as does CPT, but with none of the discomfort associated with CPT. It should therefore theoretically provide better clearing of smaller passages than Flutter devices and HFCWO, while achieving similar treatment compliance, and is much more suitable for very young patients. This remains to be proven in large-scale clinical trials, but preliminary smaller-scale clinical trials conducted in collaboration with the CHUS in Sherbrooke, Quebec, have been encouraging, producing similar results to CPT, the current “gold standard”.

## ***Mechanical principles behind the Frequencer’s effectiveness in clearing mucus from airways***

Although simple in concept and operation, the Frequencer is a unique device that breaks new ground in airway clearance, while building on well-established concepts. We believe the Frequencer’s effectiveness is due to several things including:

1. Reduction of mucus viscosity through repetitive vibrations, as outlined in the paper quoted above.
2. Mechanical principles such as:
  - Local use of resonant energy that causes shearing at the mucus/airway interface.
  - A combination of strong (mechanical) and weak (acoustical) coupling to the curved chest wall that transmits vibrations to both deep and shallow tissues.
  - Peristaltic action due to longitudinal waves
  - Acoustic streaming and related phenomena

The mathematics behind these different mechanisms is well proven, and is described in the referenced literature. However, there is no closed form solution to the third order partial differential equation that is the basis of much of that math, termed the Navier-Stokes equation, although it has been known for over 100 years. Even modern computer-based techniques, such as Finite Element Analysis (FEA), become of little value when modeling nonlinear fluids, double layer fluids, flexible walls, air/liquid interfaces, etc., due to simplifying assumptions and unknown boundary conditions. There is no way at the present time to provide absolute answers to the magnitude and importance of the various fluid transport phenomena associated with the Frequencer, except to relate its behavior to earlier studies involving fluid flow phenomena. To keep the discussion simple, the authors of this paper have chosen to use a minimum of mathematics. A summary of mucus transport and mobility mechanisms in operation with the Frequencer is shown in Table 2.

## **Local application of resonant energy**

Clearly the Frequencer does not act in the same way as classical CPT, where blows of the cupped hand provide violent shock waves that loosen mucus from the airways. The maximum long-term power input to the transducer head is about 50WRMS, and most of that is dissipated as heat through a liquid cooling system in the magnetic gap surrounding the linear motor. The sum of the acoustical and mechanical impulses from the Frequencer are over 2 orders of magnitude less than the energy from blows of the hand to the chest during classic CPT, as will be described below in the section comparing safety of the two methods.

There is no denying, however, that the Frequencer works quickly to loosen mucus and provoke coughing. This effect is highly frequency dependent. In fact, for each location on the chest, the Frequencer's operation can be tuned to within 1 Hz of optimum. This suggests resonant behavior, and provides an explanation for the ability of the Frequencer to dislodge mucus with such low energy input.

Resonance is a mechanical phenomenon that occurs when energy stored equals energy released. The resonant frequency can be described mathematically as:

$$F_0 = 2\pi\sqrt{k/m}, \text{ where:}$$

$F_0$ =Resonant frequency

$k$ =stiffness of the resonant system

$m$  = mass of the system

Since the frequency is adjusted digitally, the Frequencer can "zero in" easily on the peak of the frequency that causes resonance at any given point, transferring a maximum of energy to the area to be stimulated. This area will move sympathetically to the transducer at the resonant frequency with much less energy input than the "brute force" of classic CPT. Since thick or solidified mucus does not share the same mass or stiffness as the passage walls, it will not move in unison with them when they resonate. This sets up shear forces between the walls and the mucus that dislodge the mucus and induce coughing. Once dislodged, the mucus will move by coughing and huffing to larger and larger passages, where it can be coughed up and expectorated.

Sine waves were chosen for the Frequencer, since by definition they have the zero harmonic content. Other wave shapes such as square and triangular waves have a high harmonic content, and are less effective at exciting the resonant frequencies of the airways for a given input power.

The chest wall oscillation set up by the Frequencer differs from the Flutter, HAT, and HFCWO, since those devices act to stimulate a single "flutter" frequency, from about 5-20 Hz, corresponding to the primary resonance frequency of the air in the pulmonary cavity. At this primary frequency, air in the cavity resonates, much as does the air in an organ pipe. However, the chest cavity is not a single tuned cavity, but a multiplicity of cavities interconnected together. Methods that excite the primary flutter frequency cannot provide a sharply tuned (high Q) resonance directed to specific areas of the lungs. They thus produce considerably less movement of airway walls and mucus in a given target location than does the Frequencer, for any given power input.

Like in the pipe organ analogy, where smaller, shorter pipes play higher sounds, the resonant frequency of smaller passages and those clogged with mucus is necessarily higher than the primary chest resonance, since their diameter and length is smaller, and their stiffness is higher. Flutter, HAT, and HFCWO devices do not provide much vibrational energy to these hard-to-excite areas, since they excite mostly the primary chest resonance in the upper airways.

In contrast, the Frequencer acts on the area immediately under the transducer. Although the resonant frequency that induces coughing with the Frequencer varies from place to place on the body and from patient to patient, it is in the range of 25Hz-40Hz for many patients, indicative that the Frequencer is not causing the chest cavity to resonate as a whole, as do systems that excite only the primary resonant frequency. Instead, the Frequencer is exciting a mass/compliance system with a higher resonant frequency (higher ratio of spring constant/mass). Furthermore, this frequency varies from location to location on the chest, from day to day, and from person to person. This is indicative that the Frequencer works on individual areas of the lungs that resonate sympathetically with it, getting results from stiffer (higher resonance) areas of the chest, and the small, clogged passages in branches that other devices don't excite as efficiently. Once mucus is moved out of these branches to the main passages, it can be coughed up. Since the lower sections of the lung are most responsible for

air/blood interchange, and since they contain the smallest, non-ciliated passages, they require a clearing mechanism that can work efficiently on specific areas, freeing mucus to be coughed out. The Frequencer targets these hard-to-clear areas neatly, breaking new ground in airway clearance.

The Frequencer does not expel mucus from the lungs, any more than do other mechanical devices. All mechanical treatment methods serve to loosen mucus, to stimulate coughing, and to encourage expectoration. The Frequencer provides so much loosening of mucus that patients have been known to cough up large bronchial casts of dried mucus. Furthermore, the loosening and expectoration of phlegm continues for several minutes after the Frequencer is removed. This may be due to the large amount of mucus dislodged by the Frequencer and/or due to stimulus of secretions from epithelial cells.

We know by observation that the Frequencer works best at resonance, and has little effect above or below it. It provides much sharper tuning (high Q) at resonance than other mechanical devices, both because it acts locally rather than on the whole chest, and because it uses a combination of acoustic *and* mechanical inputs.

At resonance, a minimum of energy causes a maximum of movement of airways, causing a maximum of shear forces between them and mucus. An exact mathematical analysis of mucus fluid flow is for all practical purposes impossible, not only to the complexity of the Navier-Stokes and associated equations, but also due to things such as varying mucus rheology, varying patient physiology, varying thickness of PCL and ASF, size of airways, etc. from place to place, varying position of airways with respect to gravity, etc.

Several other fluid flow mechanisms than mucus thinning and shear forces have been investigated in the literature, and may be operating with the Frequencer. Some are specific to acoustic waves, while others require both acoustic and mechanical excitation. These are described below.

## **Peristaltic flow due to longitudinal waves**

In flexible tubes excited by longitudinal waves (the Frequencer produces both longitudinal and transverse waves in the airways, depending on the orientation of the Frequencer with respect to individual passages), studies have shown enhancement of Maxwellian fluid flow in a tube subject to an oscillatory pressure gradient.<sup>33</sup>

Extreme non-Newtonian fluids (where stress is not linear with strain) may flow in the direction opposite to that of the wave traveling on the tube wall. This is an effect similar to acoustic streaming, in which an acoustic wave propagating in a tube induces a mean flow in the direction of propagation of the acoustic wave.<sup>34</sup>

Since peristaltic flow is a well-established phenomenon in flexible tubes excited by longitudinal waves and carrying fluids with rheology similar to that of mucus, it is a highly likely possibility for the Frequencer, HAT and HFCWO. It is doubtful that the Flutter can set up rhythmic oscillations for a long enough period to create sustained peristaltic flow.

## **Acoustic Streaming and similar phenomena**

### Classic acoustical streaming

Acoustic streaming was described by Lord Rayleigh as the generation of a net flow in a specific direction by pure oscillatory vibration, which in itself has no net motion. What he described was a mechanism where vibrations applied to a fluid boundary will cause the fluid to move in a given direction, even through the

---

<sup>33</sup> David Tsiklauri and Igor Beresnev. *Non-Newtonian effects in the peristaltic flow of a Maxwell fluid*. arXiv.physics/0107076v1 31 July 2001., page 4

<sup>34</sup> Ibid, page 5

vibration itself does stays in one place. For acoustical streaming to occur, the fluid must have a time-dependent variable viscosity, and the driving frequency must be near the resonant frequency of the fluid.

Schlichting went on to develop a now classical theory of the nonlinear analysis of streaming in incompressible oscillatory boundary layers near curved walls. When an oscillatory flow occurs near rigid walls, attenuation is strong and the streaming may play a major role in transport processes.<sup>35</sup>

In acoustic streaming, fluid in close proximity to the vibrating boundary must vibrate rotationally to satisfy the no-slip condition on the tube wall, while fluid away from the boundary vibrates irrotationally as the acoustic wave passes. This deviation from inviscid, irrotational behaviour provides a driving force known as the Reynolds stress. This stress has a quadratic, non-vanishing time-average tangential component to the boundary that drives flow in the boundary layer.<sup>36</sup>

#### Combination of acoustical streaming and a vibrating fluid boundary

A subsequent study has shown that when a vibrating membrane, such as a loudspeaker, generates acoustic waves independently from oscillation motion of a fluid boundary, a change can be provoked in the oscillating flow that generates steady streaming in the Stokes boundary layer, *which is totally absent without the sound wave*. The steady streaming persists even beyond the boundary layer. The authors of this study speculate that the largest effect would occur when the two waves have the same frequency.<sup>37</sup> This is exactly what the Frequencer does, i.e.:

- The rim surrounding the compression chamber provides mechanical energy that vibrates airway passages.
- The acoustic coupling provides an acoustic wave that encourages steady streaming of fluids in the boundary layer and even beyond.

#### Acoustic streaming from action of sound on a fluid surface

Another type of acoustic streaming, much weaker than that described above, has been researched by Russian scientists. They showed that acoustic streaming could occur when sound waves act on the surface of a liquid, rather than on the liquid/solid boundary or at an interface between liquids of different viscosities. The most intense streaming appears when waves are incident on the surface of 45 degrees.<sup>38</sup>

#### Mixing of viscous fluids by waves that produce streaming

Waves produce circulatory streaming motions which can be used to mix viscous fluids. At frequencies and modal shapes determined by eigenfrequencies and eigenmodes of specific structural elements, natural vibrations will occur. To excite these eigenmodes, only a small amount of energy is required at resonant frequencies, and this energy need only operate on a single point of the vibrating surface. A simple and effective method of mixing highly viscous fluids is to let walls vibrate as small amplitude standing waves.<sup>39</sup> This mixing may occur in human airways between the less viscous boundary layer PCL and the thicker ASL, reducing the viscosity of the lower region of the ASL that reduces ciliary mobility. Further research would be required to establish whether this mechanism is significant in mucus clearance.

---

<sup>35</sup> Eduardo Ramos, Sergio Cuevas, and Guadalupe Huelsz. *Interaction of Stokes boundary layer flow with a sound wave*. Physics of Fluids. Volume 13, Number 12. December 2001., page 3709

<sup>36</sup> David Tsiklauri and Igor Beresnev. *Non-Newtonian effects in the peristaltic flow of a Maxwell fluid*. arXiv.physics/0107076v1 31 July 2001., page 6.

<sup>37</sup> Eduardo Ramos, Sergio Cuevas, and Guadalupe Huelsz. *Interaction of Stokes boundary layer flow with a sound wave*. Physics of Fluids. Volume 13, Number 12. December 2001., page 3713

<sup>38</sup> V.A. Mourga. *Acoustic Streaming in a Sound Field near a Free Boundary*. Acoustical Physics. Volume 48, No. 3. 2003., page 342

<sup>39</sup> Fredrik Carlsson, Mihir Sen and Lennart Löfdahl. *Analytical studies of flow effects due to vibrating walls*. Under consideration for publication in Journal of Fluid Mechanics, 2002, page 3

### Farady instability in fluids causing an onset of surface waves

For vibration frequencies close to the inverse relaxation time of non-Newtonian fluids, surface waves respond harmonically (at resonance), rather than sub harmonically (below resonance), as is the case with Newtonian fluids.. Theoretical modelling has shown this to be the case, and the result has been confirmed experimentally using a mixture of 2% polyisobutylene in primol.<sup>40</sup> A large static viscosity and a small relaxation time are favourable for the observation of the harmonic response and surface waves. This is exactly the condition that we find with the mucus on the ASL. The effect, although analogous to acoustic streaming (both require viscoelasticity and resonance), is not the same. Acoustic streaming acts on the boundary layer, while Faraday instability is a bulk property acting on the fluid and generating surface waves.

## **Beneficial coupling**

In order for the Frequencer to provide sufficient amplitude of vibration in the airways with a minimum of energy, it must provide a coupling mechanism that is:

- 1) Efficient, so that a small amount of energy produces the desired oscillations. This is necessary not only to avoid a very bulky unit, but in order to ensure the patient's safety and comfort. Nobody likes to be hit or shaken, especially if they are small or weak. The Frequencer does neither.
- 2) Useful at different depths throughout the chest.

A very interesting study was done at the Université de Paris on the mechanics associated with bullet-proof vests. Although it dealt with the most part with high-energy single incidence shock waves, one of the areas of research investigated the effects of strong and weak coupling with transmission of vibration and shock through the thoracic cage to the lungs. They found that the depth of penetration of P-waves (axial waves) into the lungs is dependent on the degree of coupling, and that S-waves (surface waves) have very little effect on the lungs, since they don't travel well through the rib cage.<sup>41</sup> The Frequencer is primarily a P-wave generator, since its motion is perpendicular to the thorax.

The study further investigated the depth that mechanical and acoustical waves travel into the chest cavity. It found that mechanical waves cause strong surface effects, but diminish rapidly with distance travelled into the chest, while acoustical waves are weaker on the surface, but diminish little with distance, so that at distances deep within the chest cavity, both effects have similar strength.

The Frequencer causes P-waves that couple in two ways to the chest cavity:

- 1) Strong mechanical coupling around the compression chamber and
- 2) Weak acoustical coupling within the chamber

The Frequencer's unique combination of mechanical and acoustic oscillation induces vibrations through an entire range of depths. The strong mechanical coupling is much stronger than the acoustic coupling on the surface of the chest, diminishing with depth of penetration, while the acoustic coupling is weaker at the surface, but diminishes less with depth. A simple mechanical vibrator does not exhibit these two coupling mechanisms, and in our testing did not produce the desired effects. The French paper, as well as the notion of the combined effects of acoustical waves and mechanical vibrations described earlier, provides clues as to the Frequencer's remarkable effectiveness.

---

<sup>40</sup> H.W. Müller and W. Zimmermann. January 15, 1999. Europhysics Letter. **45** (2). *Faraday Instability in a Linear Viscoelastic fluid*, page 169

<sup>41</sup> *Transmission d'une onde à l'interface paroi thoracique-poumon*, page 98

Another interesting result from that study was their investigation of the effect of chest curvature on concentration of energy coming from external shock waves. This effect is not unique to the Frequencer, but is also applicable to HFCWO, HAT and CPT, although not to the Flutter. The study showed that with curvature radii of <23 cm, vibrations on the chest wall are amplified by chest curvature. If the radii were >23 cm, they are diminished.<sup>42</sup>

A final finding in the study that is relevant to the Frequencer is that events under 100  $\mu$ s in length are like those of a drum-head, where the lungs and thoracic cavity “boing” in response to single rapid effects (the term “boing” is ours, intended to give the reader a feel for the phenomenon). Those over 100  $\mu$ s in length are characterized by true wavelike behaviour. Since the Frequencer operates from about 20 Hz to 80 Hz, the period of each wave is 12.5 to 50 ms, or 125-500 times as long as the 100  $\mu$ s threshold. The elastodynamic impulse response of the rib cage is therefore much less important in understanding the Frequencer than its response to sustained wave action. This is in keeping with observed behaviour.

### ***Development of the Frequencer***

The Frequencer’s inventor, Louis Plante, was a CF patient in his 20’s who, being hospitalized and sick with a high fever, refused CPT. Refusal of CPT is one of the main problems affecting CF patients’ longevity, as if the lungs are not cleared regularly, respiratory insufficiency onset occurs more rapidly. As he lay on his hospital bed, Mr. Plante recalled a childhood memory of a time when he had accompanied his mother to a press conference and had sat in front of a large loudspeaker. The loud, low, amplified voice of the male orator shook his chest enough that Louis had a coughing fit, with subsequent expectoration of a large quantity of mucus.

A qualified electronics technician, Louis decided to pursue the idea of applying vibrations to the chest as a substitute for CPT when he left the hospital. He began with mechanical stimulation, and quickly abandoned the idea as it didn’t work. He then applied a subwoofer to his chest, although it was impractically large and heavy, and realized that acoustical stimulation was more effective than mechanical. From then on, he worked to refine his idea, supported in his efforts by friends and the medical staff who had treated him from childhood. With the basics of a mechanical/acoustical transducer and control system worked out, Luis set up a development team to engineer, patent, test, and market the device for CF patients and others who could benefit from it. Throughout the process, he used his own body as a test bed, sidestepping need for lengthy testing protocols on other sick patients for each generation of device and thereby hastening development time.

Mr. Plante noted a large increase in sputum volume (more than 40x in his case) compared to CPT done by a trained person. Medical personnel questioned at times whether there was some particularity in Mr. Plante’s physical makeup and/or some other factor that would explain his success. The question was, “Would other patients benefit from the device, or did it have some sort of training or Placebo effect on Mr. Plante that caused him to cough so effectively?” The only way to answer this was to move on to a pilot study.

### ***Pilot study comparing the Frequencer to PCT***

An open, controlled pilot study comparing postural drainage with PCT (clapping) and the Frequencer was done on 20 mild to moderately affected CF patients with no prior experience using the Frequencer.

PCT was done by experienced people in positions favoring postural drainage, while the Frequencer was applied to people in the sitting position. Since the people had no prior experience with the Frequencer, they were not as experienced in Louis in providing feedback as to when the Frequencer was causing resonance and loosening of sputum. Instead, the person applying the Frequencer relied on the amount of vibration of the chest wall to determine the proper frequency.

---

<sup>42</sup> Ibid, page 105



The protocol involved treating 10 people with PCT and 10 with the Frequencer for 15 minute periods, and then collecting and measuring comparative sputum volumes over the next 5 minutes. After several days, the people receiving PCT began receiving treatments with the Frequencer, and vice versa.

Although patients did not use the Frequencer by themselves or for enough treatment sessions to develop the ability to tune the frequency of the Frequencer to their bodies, and although they used it in a seated position that was less favorable than PCT with postural drainage, results of the test were extremely encouraging. Average sputum quantities generated by the Frequencer were equal to or greater than those generated by CPT, and patients experienced much less discomfort.<sup>43</sup>

### ***In vitro trials with the Frequencer***

Dymedso conducted trials in the summer of 2004 to demonstrate the reduction of mucus viscosity due to vibration in a similar manner to tests done with the Flutter device and discussed previously. The setup was quite simple. Mucus was vibrated for a given time at specified amplitude, and then allowed to flow through a capillary tube under constant pressure. Stickier and higher viscosity fluids take a longer time to flow through an orifice than less adherent, thinner fluids. Thus, lower flow times for a given amount of mucus indicate increased mucus mobility.

Five tests were done in each of several situations, including:

1. Test on mucus, used as a control.
2. Mucus vibrated on a rubber membrane placed over the Frequencer's compression chamber at 40 Hz for 1 minute at half power.
3. Mucus vibrated on the Frequencer transducer's membrane, with no rubber membrane, at 40 Hz for 1 minute at half power.
4. Mucus shaken mechanically for a minute.

The results are shown below in graphical form as Figure 1.

Observations:

1. Unaltered mucus flow time had a standard deviation of 0.835 seconds, so that 99.7% of measurements would occur between 30.1 and 35.1 seconds.
2. In all cases, agitated mucus flowed more freely than unaltered mucus.
3. When mucus was agitated mechanically, its viscosity changed less than when it was vibrated with the Frequencer.
4. Agitation on the rubber membrane was less effective and more variable than direct agitation with the Frequencer, probably due to regions of standing waves on the rubber membrane. Although the rubber membrane has nothing in common with the chest, the intent was to see if the higher bending occurring on the rubber membrane had more effect than the acoustical stirring of lower amplitude with direct contact.
5. Mucus vibrated directly by the Frequencer flowed an average of 25% faster than unaltered mucus, and more than in all other cases.

---

<sup>43</sup> Centre Hospitalier de l'Université de Sherbrooke. *Étude comparative d'efficacité du Frequencer par rapport au drainage postural dans la mobilisation des sécrétions bronchiques chez de patients porteur de fibrose kystique*. 2003.

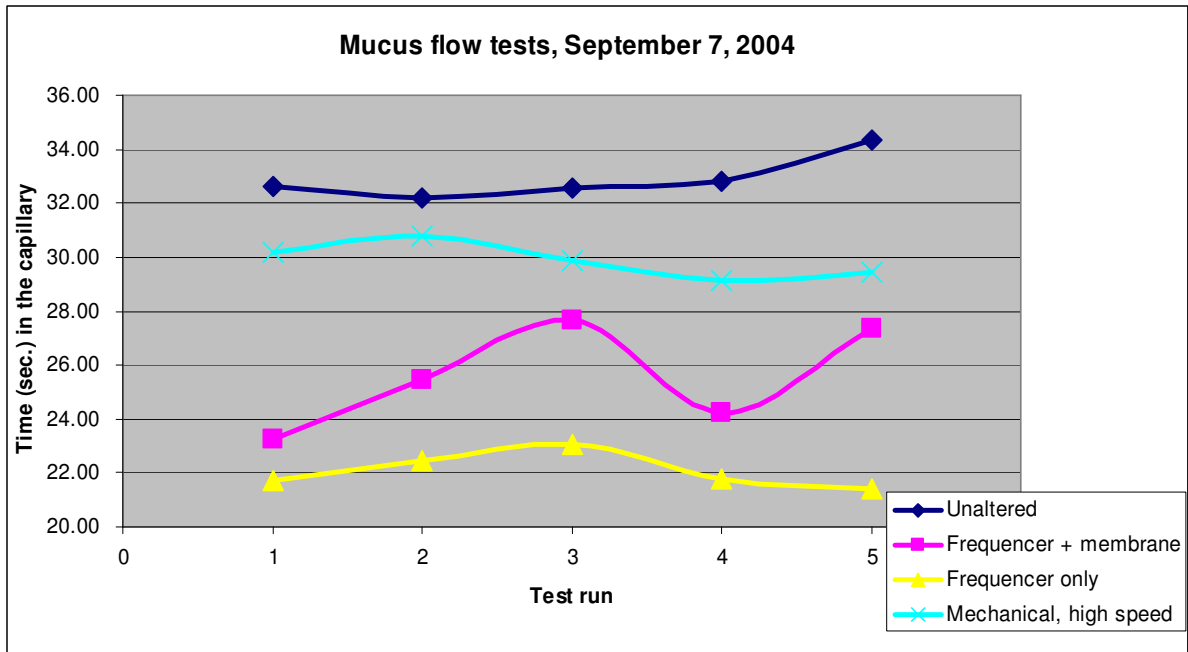


Figure 1 - Mucus flow times through a capillary tube under constant pressure using various agitation methods, Dymedso, September 7, 2004.

## ***Safety Considerations when using the Frequencer***

### **Sound Pressure Level**

When operating in free air at 50W of power, the Frequencer generates about 78dB of sound at 30 Hz. This sound level is frequency dependent, rising to over 100dB if the Frequencer is operated at frequencies over 200 Hz. Since frequencies over 80 Hz are useless for operation, and since Fletcher-Munson curves demonstrate very low hearing sensitivity in the bass range, the Frequencer is not a potential source of hearing damage, nor is it uncomfortable to listen to.

The acoustic pressure when pressed against the chest cavity is much greater than that in free air, due to the improved coupling, but this increase in efficiency is not heard outside the compression chamber.

### **Stray magnetic fields**

Stray magnetic fields from the transducer are minimal, due to the unique enclosed structure of the neodymium magnet in the transducer's linear motor. Use of the Frequencer on patients with implanted electrical devices should be safe, but this must be verified by the manufacture of the implanted device.

### **Electrical shock**

The highest voltage applied to the terminals of the transducer is 20 VAC at full power. Although the Frequencer is not designed to be used in wet environments, and its control unit must be connected to a suitably grounded outlet, there does not appear to be any danger of lethal electrical shock from the transducer.

## **Mechanical force compared to other mechanical methods of mucus clearance**

### **Frequencer vs. HFCWO device, Flutter, HAT and PEP**

The Frequencer is pressed directly against the area to be treated. Although the transducer's weight is negligible, a force of about 4 lbs. is required to seal the interface between the transducer and the skin. This provides a local pressure around the rim of the transducer of about 1 psi, allowing efficient transfer of energy to the body with minimal effort. (A HFCWO device, with its area of about 400 sq. inches for an average vest, would have to compress the thorax with 400 lbs. of force to provide a similar energy transfer efficiency.) We have not noted any discomfort or bruising with the Frequencer, and there does not appear to be any reason why it could not be used on very young or frail patients.

The Frequencer provides peak air pressure variations of up to +/- 66 cm of H<sub>2</sub>O in the area under the compression chamber. This compares with peak air pressure variations of 34-53 cm of H<sub>2</sub>O for the Vest HFCWO device, but with much less effective coupling.

In comparison to the Flutter, the Frequencer and HFCWO devices provide much longer-term stimulation (more cycles at higher frequencies) than could be provided by breathing against an oscillating ball.

The Frequencer, like HFCWO, does not directly open airway passages due to PEP effects, as does the Flutter. However, since it does not require special breathing techniques, can be used on smaller patients than HFCWO devices, and is not uncomfortable, it may become the PT treatment of choice for young children.

### **Frequencer vs. PCT (clapping)**

To evaluate whether the Frequencer is as safe for clearing airway obstruction as PCT, the current "gold standard", we evaluated equivalence as follows, assuming documented forces for PCT and maximally high power to the Frequencer:

- 1) Peak pressure on the skin from the Frequencer is 1 psi on the rim. This pressure is practically constant, and very low, resulting from the 4 lbs of pressure required to seal the rim. This static loading will have no effect on all but the weakest patients.
- 2) Dynamic force from PCT has been measured to be 58.10 +/- 15.32 Newtons, at a rate of 6.6 Hz +/- 1Hz<sup>44</sup>. To compare this with the Frequencer, we can perform the following calculations:
  - a. Electrical power input: 50WRMS maximum.
  - b. Transducer efficiency, with an Fs of 66Hz, a Vas of 2.78 liters and a Qes of 0.5, is calculated from
    - Efficiency of a transducer in free air =  $9.64 \times 10^{-10} \times Fs^3 \times Vas/Qes$ , where
      - Fs = resonant frequency
      - Vas = volume of air with equal compliance to that of the membrane
      - Qes = electrical Q of the transducer
    - Efficiency =  $9.64 \times 10^{-10} \times 66^3 \times 2.78/0.58$ , = 0.00266<sup>45</sup>
  - c. Acoustical power = Electrical power x efficiency, so
    - Acoustical power = 0.00266 x 50W = 0.133 W. All of the remaining energy is dissipated as heat. Acoustical transducers of small diameters are typically very inefficient, and one acoustical watt is a very large number.
  - d. Dynamic force in free air can be calculated from efficiency as follows: Using the proper units:
    - 0.133W = 0.133 J/sec = 0.133 N/m/sec.

---

<sup>44</sup> Blazey SM, Jenkins SC and Smith RA. *Rate and force of application of manual chest percussion by physiotherapists*. Australian Journal of Physiotherapy 44: 257-264

<sup>45</sup> Dickason, Vance. *The Loudspeaker Design Cookbook, 3<sup>rd</sup> edition*. Audio Amateur Publications. 1998

- The Xmax (excursion limit) is 3mm each way, so the transducer moves 4 x 3 or 12mm in each cycle. At 30 Hz, this means the transducer moves 0.36m/sec.
  - The average force on the membrane therefore is 0.133/0.36 or 0.37 Newtons. This is 58.1/0.37, or 157 times less than clapping.
  - The maximum force of a sine wave is 1/0.637 x the average force, or 0.58 N. This is two orders of magnitude ( $10^2$ ) less than PCT.
- e. When the Frequencer is pressed to the chest, the free air calculations above no longer apply. In a closed chamber, efficiency increases considerably over that of free air. If coupling were perfect, all of the force moving the diaphragm would be transmitted to the chest. The mechanical force to do this can be determined from the equation  $F=ma$ , where F = force in Newtons, m = mass in kilograms, and a = acceleration in  $m/sec^2$ :
- At 30 Hz, the diaphragm accelerates to maximum speed twice in each cycle. The maximum speed is twice the average, or 0.72m/sec, and acceleration takes place from 0 to that speed in  $\frac{1}{4}$  of a cycle, or 1/120 second. The rate of acceleration is therefore  $0.72 * 120$ , or  $86.4 m/sec^2$ .
  - The mass of the diaphragm is 7.4g. Adding the amount of air carried by the diaphragm, the total moving mass is approximately 8 grams.
  - $F=ma$ , so  $F = 8 \times 86.4/1000 = 6.9N$ . In reality, since there is a “springiness” in the front volume, the force is less than this upper limit (we will not do the math here), but is nearer to the 6.9N maximum than the 0.58N of free air.
  - Coupling efficiency will depend on how well the Frequencer is pushed against the chest, how much fatty tissue is on the chest, etc., as well as on the front volume of the Frequencer. A good estimate would be around 5 N of peak force, or 3N of average force. This is approximately 6% of the force resulting from PCT.
  - Thus, if clapping is safe, the Frequencer must be much safer. The only reason such a small force can have any effect at all is due to the previously mentioned amplification at resonance, effects on mucus viscosity, and streaming effects. PCT is a “brute force” method, relying on impact to dislodge mucus, while the Frequencer acts through gentler, metered, and targeted mechanical and acoustical vibrations to achieve results.

<b>Airway clearance technique</b>	<b>Chest Physiotherapy</b>	<b>Positive Expiratory Pressure Techniques</b>	<b>Flutter</b>	<b>HAT</b>	<b>HFCWO</b>	<b>Frequencer</b>
<b>Probable mechanism</b>						
Gravity causes mucus to flow	<b>x</b>					<b>x</b> <b>(if done in reclining positions)</b>
Opening of airways by increasing expiratory pressure		<b>x</b>	<b>x</b>			
Shock waves travelling through the thorax cause mucus to loosen from airway walls	<b>x</b>					
Resonant flexure exciting the primary thoracic resonance in the upper airways			<b>x</b>	<b>x</b>	<b>x</b>	
Targeting of individual areas of the lungs	<b>x</b>			<b>Limited</b>		<b>x</b>
Resonant flexure that occurs locally, rather than exciting only the primary thoracic resonance						<b>x</b>
Modification of mucus rheology with mechanical oscillation			<b>x</b>	<b>x</b>	<b>x</b>	<b>x</b>
Peristaltic flow in tubes due to longitudinal waves.						<b>x</b>
Classical acoustical streaming in a boundary layer.						<b>x</b>
Acoustical streaming in a boundary layer adjacent to a mechanically vibrating surface						<b>x</b>
Acoustical streaming from acoustical waves acting on the fluid surface						<b>x</b>
Mixing of viscous fluids by waves in conditions that promote streaming						<b>x</b>
Faraday instability that causes surface waves of Maxwellian fluids						<b>x</b>
Beneficial coupling						<b>x</b>

**Table 1 – Comparison of the Frequencer to other mechanical airway clearance methods**

<b>Mucus transport or mobility mechanism</b>	<b>Description</b>	<b>Evidences for this behaviour</b>
Resonant flexure that occurs locally, rather than exciting only the primary thoracic resonance	Large waves at resonant cause shearing between mucus and airways and between layers of mucus.	<p>Frequencer activity is highly frequency dependent, and yields good results with very low energy input. This is typical of resonant behaviour. Research from France indicates that the lungs transmit vibratory impulses very well in the timeframe in which the Frequencer operates. Non-sinusoidal waves do not produce desired effects.</p> <p>Evidence that Frequencer resonance is local comes from a resonant frequency that is nearly an octave higher than the primary thoracic resonance, and varies from location to location of power head application.</p> <p>Evidence of the effectiveness of the shear forces in separating adhering mucus from airways comes from loosening and coughing up of strongly adhering bronchial casts that had not been loosened previously by CPT.</p>
Modification of mucus rheology with mechanical oscillation	Mucus becomes less viscous over time with continued application of mechanical oscillation	Observed in tests with Flutter device. Further research needed to prove this does occur with Frequencer, but there is no reason to believe this is not so.
Peristaltic flow in tubes due to longitudinal waves.	Longitudinal waves in tubes cause peristaltic flow	Observed in tests with Maxwellian fluids in flexible tubes in referenced literature.
Classical acoustical streaming in a boundary layer.	Acoustic waves axial to a surface cause a net sideways movement due to time-dependent viscosity of fluid, especially when excited at resonance.	Behaviour described by Rayleigh, observed commonly in non-Newtonian fluids in an acoustic field. Much work, involving lots of higher mathematics, has built on his theories.
Acoustical streaming in a boundary layer adjacent to a mechanically vibrating surface	A stronger variant of classical streaming that provides a maximum of effect when the boundary layer is excited by an acoustic field at the same frequency as the mechanical vibration.	Mechanical application of vibration at the same frequency as the Frequencer to the thoracic cavity, even at much higher amplitudes, does not provide the immediate mucus production and stimulate coughing. Acoustic stimulation (sitting in front of a high-powered loudspeaker), can provoke coughing, but only at much higher energy levels and sound pressures than those generated by the Frequencer.
Acoustical streaming from acoustical waves acting on the fluid surface	A weak variant of classical acoustical streaming, where the sound wave is incident on the surface of the viscoelastic liquid	The conjunction of the two methods, using both mechanical and acoustical stimulation at the same frequencies, causes the Frequencer to work well with a minimum of size and energy input to the body.
Mixing of viscous fluids by waves in conditions that promote streaming	Waves generated by streaming at a resonant frequency cause mixing of the boundary layer and layers above it.	This may be part of the observed lowering of mucus viscosity observed with the Flutter device. A good research project.
Faraday instability that causes surface waves of Maxwellian fluids	Although akin to acoustic streaming, this mechanism is a bulk mechanism, affecting not only the boundary layer, but the liquid above it.	Most effective at resonance in a liquid with a large static viscosity and a small relaxation time. This phenomenon could explain why thick, viscous ASL is easily loosened with the Frequencer.
Beneficial coupling	Mechanical energy is very effective at the surface, less in deep tissues. Acoustical energy is more constant with depth.	The Frequencer provides both sorts of energy through two distinct means of coupling to the thoracic cavity, allowing it to be effective on a wide range of depths.

**Table 2 – Summary description of mucus transport and mobility mechanisms operating when using the Frequencer**