PROCEEDINGS REPORT*

Mechanical airway clearance using the Frequencer electro-acoustical transducer in cystic fibrosis*

André M. Cantin[1], **Marc Bacon**[2], **Yves Berthiaume**[3]

[1]Respiratory Division, Department of Medicine, Centre Hospitalier Universitaire de Sherbrooke; [2]Fabgroups Technologies Inc., St.Laurent, Quebec; [3]Respiratory Division and Research Centre, Department of Medicine, Centre Hospitalier de l'Université de Montréal

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Abstract

Purpose. Clearance of mucus from airways is the cornerstone of therapy for lung disease in patients with cystic fibrosis (CF). This paper describes the operation of the Frequencer, a novel respiratory physiotherapy device comprised of an electro-acoustical transducer. We hypothesized that the Frequencer would be a safe and effective therapy to help clear secretions from the airways of subjects with CF.
Methods. To verify this hypothesis, 22 individuals with CF were recruited to this study comparing sputum production during conventional chest physiotherapy (CCPT) and Frequencer therapy using a crossover design. The sputum weight was the main outcome measure.
Results. Sputum weight was found to be a reproducible measure of the efficacy of chest physiotherapy in individual patients. The Frequencer induced airway clearance in patients with CF that was equivalent to that of CCPT. Furthermore, treatment of a 4% mucin preparation ex vivo with the Frequencer significantly reduced the viscosity of the mucin solution as determined in a capillary rheometer.
Conclusions. These results indicate the Frequencer is safe and as effective as CCPT in inducing airway clearance in patients with CF.

Bronchial mucus exists in two layers, a low viscosity periciliary liquid (PCL), and above this a more viscous mucus layer,[1,2] The elasticity of mucus appears to change with the rate of application of stress to it, and may be important to the rate of beating of bronchial epithelial cilia. Excessively large quantities of secretions are present in the airways of patients with bronchiectasis particularly in those with cystic fibrosis (CF).[3]. Furthermore, in CF the PCL layer is thinner, and the thicker mucus layer tends to impede the movement of the cilia.[4]. In normal humans, the concentration of mucins in the mucus may be as high as 1% by weight.[5] In CF, the mucin concentration of mucus increases due to excessive transepithelial water absorption. This serves to increase viscosity, reduce elasticity, and increase adhesiveness, which hinders its transport.[6]. The absolute viscosity of normal mucus is typically 1 Poiseuille, rising as high as 500 Poiseuilles in CF patients.[7].

FIGURE 1. Illustration of the Frequencer. The power head to the left is controlled by an amplifier unit to right, which allows one to adjust both the power and the frequency of the output signal. The results of the study reported in the current manuscript were obtained using a prototype of the illustrated apparatus.

Mucus is a viscoelastic gel termed a Maxwellian liquid because its stress-strain curve is not linear.[8]. Upon application of stress, mucus initially stores energy but with continued stress it will begin to flow like liquid. When the flow stops, it returns to its original state. A well-known example of a viscoelastic gel is dripless paint. When the paint is pulled along on a surface 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. Viscoelastic gels move only when applied stress is greater than a threshold level. If the threshold value of stress required for the flow of very viscous gels is not reached, then the gel will simply deform without flowing. Since airway secretions in patients with CF are particularly viscous, mechanisms applying continued stress are needed to induce airway clearance.[9-15] Acoustic percussion has been suggested as a potential modality that may help induce airway clearance.1[6]

The Frequencer is a digitally controlled electro-acoustical transducer device invented recently by Louis Plante, a CF patient. It is manufactured by Dymedso. It consists of a control unit and a power head (Figure 1). The power head transmits sinusoidal mechanical and acoustical vibrations to the airways at various locations in the chest. The Frequencer's transducer is applied to the area of the thorax to be stimulated. The power head in the Frequencer provides both mechanical and acoustical stimulation at an adjustable forcing frequency that is typically between 25Hz and 40Hz. The user adjusts the frequency of the transducer such that it causes a sympathetic resonance felt by the patient within the thorax. In most CF patients, the Frequencer induces coughing, followed by expectoration of sputum. This treatment is repeated at all conventional chest physiotherapy (CCPT) positions for approximately the same time as CCPT. 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 said chamber. The impulses are opposite in phase, and are transmitted differently through the tissues of the chest to both surface and deep locations. The control unit houses a digital frequency generator and a highly efficient amplifier.

This novel device imparts a continuous stress to airway mucus through the generation of acoustical waves. We hypothesized that the Frequencer would be as effective as CCPT in helping to clear mucus from the airways of patients with CF. The results of this study were obtained with a prototype of the Frequencer rather than with the illustrated model.

METHODS

Study population. Twenty-two subjects with a diagnosis of CF were enrolled into this study after providing written informed consent. The study was approved by the ethics review board of the Centre Hospitalier Universitaire de Sherbrooke. Patients with an established diagnosis of cystic fibrosis [17] and an FEV1 ≥ 35% of predicted were included in the study. The characteristics of the study population are presented in Table 1. Patients with evidence of respiratory exacerbation within the two weeks preceding the study, or with a history of more than two episodes of severe hemoptysis, defined as > 10 ml of blood, were excluded. No change in antibiotic or other respiratory treatment regime was instituted during the study period.

Validation of sputum weight. The major outcome parameter of this study was sputum weight, which has been suggested to be an appropriate physiotherapy outcome measure in CF patients.[18] In order to validate sputum weight as a reproducible outcome measure in CF patients, eight CF patients underwent two 20 min CCPT sessions at one week intervals. The amount of sputum produced during each therapy and in the 5 minutes following therapy was determined by weight.

TABLE 1. Characteristics of the study population.

Male/Female	11/11
Age (yr)	27.5 ± 1.4
Height (cm)	162.2 ± 2.0
Weight (kg)	54.9 ± 2.0
BMI (kg/m^2)	20.8 ± 0.4
FEV_1 (% predicted)	57.8 ± 3.9
Chronic inhaled antibiotic therapy (n)	15
Chronic azithromycin therapy (n)	7
Pulmozyme aerosol therapy (n)	2

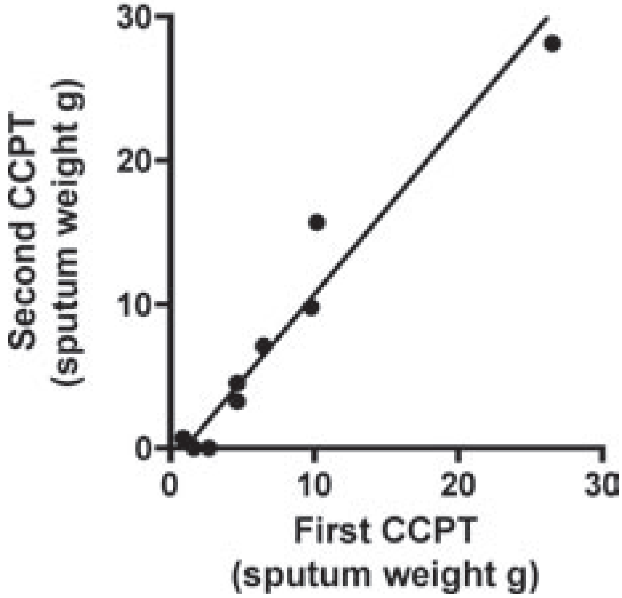

FIGURE 2. Comparison of the reproducibility of sputum weight as a measure of conventional chest physiotherapy efficacy (CCPT). Each patient with cystic fibrosis underwent a first CCPT treatment (abscissa) during which sputum was collected and weighed. One week later the same patients underwent a second CCPT treatment (ordinate) and the results are plotted as a function of the sputum weight from the first CCPT.

Study design. All patients underwent CCPT for 20 min with clapping and postural drainage. Sputum was collected during CCPT and during the 5 min following this therapy. All collected sputum was weighed. The Frequencer therapy was applied for a total time of 20 min, with applications of 5 min to the anterior and posterior areas of each hemi-thorax. All Frequencer treatments were done with the patient sitting, and no attempt was made to combine the Frequencer with postural drainage. As with CCPT, sputum was collected during the 20 min of treatment and the 5 min following the end of treatment and weighed. The CCPT and Frequencer therapies were separated by 12 – 24 h in each patient, with 11 receiving the CCPT first, and 11 the Frequencer therapy first.

Effect of the Frequencer on mucin rheology in vitro. To determine whether the mechanical vibrations generated by the Frequencer were sufficient to alter mucin rheology, mucin (Sigma-Aldrich, St. Louis, MO) was prepared at a concentration of 40 mg/ml in phosphate buffered saline, pH 7.4. The mucin solution was then divided into three fractions each placed in 1.5 ml polypropylene tubes. The first fraction did not undergo further treatment. The second was exposed to mechanical agitation applied with a vortex stirrer (Vortex-Genie II, Fisher Scientific, Nepean, Ontario, Canada) set at force 4 for 5 sec. The third fraction was placed on a membrane at the Frequencer's power head and the frequency was set to 40 Hz with 50% maximum power output for 5 sec. All three samples were then tested in a capillary rheometer comprised of a 10 µl borosilicate glass micropipette (catalog no.: 21-164-2C, Fisher Scientific). A mucin sample of 5 µl was loaded into the capillary and subjected to a pressure of 0.5 cm H_2O. Results are expressed as the flow rates of the mucin solutions. Each test was repeated eight times.

Statistical analysis. Data are expressed as the mean ± sem unless otherwise indicated, and the null hypothesis was tested with a paired t-test. Deming linear regression analysis was used to assess the correlation between sputum weights obtained by CCPT at different times in the same CF patients, and between sputum weights obtained with either CCPT or the Frequencer. Calculation of the power of the study to detect a smallest average difference of 35% CCPT sputum weight with a significance level (alpha) of 0.05 (two-tailed) was done using Statmate-2 software from GraphPad. The rheology data were analyzed by one-way ANOVA with a Bonferonni post-hoc test. A value of $P < 0.05$ was considered significant.

RESULTS

The principal outcome measure for this study was the weight of sputum produced during airway clear-

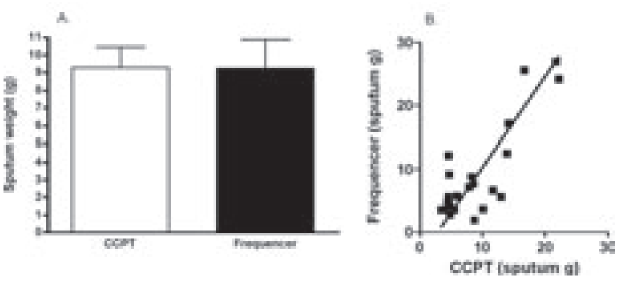

FIGURE 3. Effect of CCPT versus Frequencer therapy on sputum production as determined in 22 patients with cystic fibrosis. All patients underwent both forms of chest physiotherapy for 20 minutes and sputum was collected and weighed during this therapy and during 5 minutes following therapy. Between 18 and 24 hours separated the two therapies. Results are expressed in panel A as the mean ± sem (n = 22, $P = 0.97$) and in panel B with the results of the Frequencer are expressed as a function of those obtained with CCPT. The solid line represents the best fit line created by Deming model II linear regression. The slope is significantly different from 0 ($P < 0.0001$).

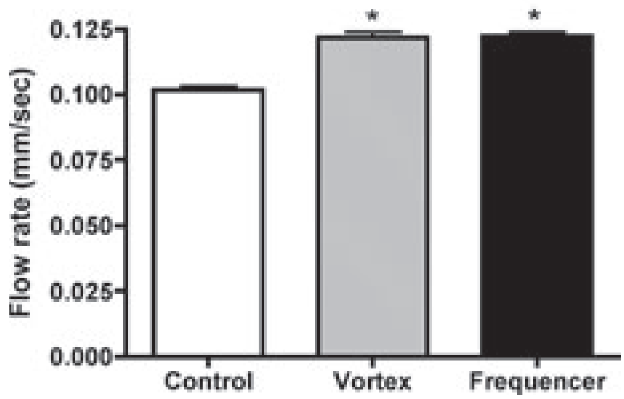

FIGURE 4. In vitro rheological properties of 40 mg/ml mucin solution without (control) and with 5 second treatment using either a vortex stirrer (vortex) or the Frequencer at 40 Hz and 50% maximal power. Results are expressed as the mean ± sem of the flow rate of 5 µl mucin solution through a glass capillary under a constant pressure of 0.5 cm H_2O (n = 8, *$P < 0.001$ vs control).

ance techniques. The weights of sputum samples produced by each patient during different sessions of CCPT were remarkably similar, (Figure 2) indicating that this measure is reproducible within an interval of one week. Each subject produced similar amounts of sputum during the two CCPT sessions. The median and interquartile range of sputum weight was 4.70 g [2.15 -10.00] for week 1 and 4.60 g [0.35 -12.75] for week 2. The Deming linear regression analysis indicated a slope of 1.182 ± 0.1024 (95% confidence interval 0.94 -1.42) and a correlation coefficient r = 0,98, $P < 0.01$.

As shown in figure 3A, the amount of sputum produced during CCPT was similar to that produced with the Frequencer (CCPT = 9.27 ± 1.20 g *vs* Frequencer = 9.24 ± 1.62 g, $P = 0.97$, n = 22). The mean of the differences in sputum weights between the two forms of therapy was 0.032 g with a 95% confidence interval of -1.85 g to 1.91 g. The Frequencer therapy data plotted as a function of CCPT (Figure 3B) demonstrates a slope of 1.43 ± 0.21 with a 95% confidence interval of 0.99 – 1.87 and a deviation from 0 ($P < 0.0001$). The study had a 95 % power to detect a smallest average difference between pairs of 3.26 g, which corresponds to 35% of the CCPT sputum weight, with a significance level (alpha) of 0.05 (two-tailed).

The application of the Frequencer to a simulated mucus preparation of 40 mg/ml mucin resulted in a significant acceleration of the flow of the mucin solution as measured by a capillary rheometer. The Frequencer-treated mucin preparations reached flow rates similar to those treated with a vortex mixer (Figure 4; control = 1.02 ± 0.01 mm/sec, vortex = 1.22 ± 0.02 mm/sec, Frequencer = 1.22 ± 0.02 mm/sec, $P < 0.001$ each vs. control; $P > 0.05$ vortex vs Frequencer, n = 8).

DISCUSSION

We present evidence that the mechanical and/or acoustical vibrations generated by an amplified low-frequency audio signal at the chest wall can be used to induce sputum production in patients with CF. The Frequencer is a transducer in which an electromechanical process moves a cone to produce sound waves at a power and frequency determined by the user. The study population as a whole did not show any differences in efficacy between CCPT and the Frequencer. However differences in efficacy between these forms of chest physiotherapy were observed in some individuals as is illustrated in figure 3B. Interestingly, it may be possible to predict the efficacy of the different forms of physiotherapy in an individual patient. We found that the weight of sputum produced by the same CF patient was remarkably similar within a 1week interval, suggesting that the measurement of sputum weight to compare the efficacy of physiotherapy techniques may be a reasonable approach to choose the best form of physiotherapy for an individual patient.

Therapy with the Frequencer was well tolerated, and in contrast to CCPT, all the Frequencer treatments were done in the sitting position, thus simplifying the therapy. The Frequencer has the potential to provide therapeutic autonomy since the energy is delivered to the chest wall by a device and not by an individual. Since the power and frequency are set prior to therapy, caregivers including parents and spouses do not need to worry about whether the intensity of their therapy is sufficient or excessive. Furthermore, the Frequencer can deliver treatments to specific areas of the chest identified as requiring more intense airway clearance efforts by auscultation and/or by thoracic imaging.

No adverse events were observed with the use of the Frequencer. Several aspects of the Frequencer indicate that it is a safe device. First, the sound pressure level was measured at 56 – 78 dB in free air at a frequency range of 25 - 70 Hz at maximal power, which is well below the threshold for hearing damage in the bass range.[19] Second, stray magnetic fields are minimal, due to the neodymium motor structure. Third, the unit is isolated from electrical shock, and the transducer operates at 20VAC or less. Finally, the constant force applied to the body is about 16 Newtons (N) in order to produce an acoustic seal, yet the Frequencer can provide peak pressures of about twice that of the high frequency chest wall oscillation (HFCWO) device. CCPT (clapping), the current "gold standard" of chest physiotherapy has been measured to deliver 58.10 +/- 15.32 N, at a rate of 6.6 Hz +/-1Hz.[20] The dynamic force applied by the Frequencer's mechanical and acoustical vibrations is between 0.4N and approximately 3N, depending on the degree of coupling between the apparatus and the body. Thus, if clapping is safe, the Frequencer must be much safer. CCPT 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.

The mechanisms by which the Frequencer helps to mobilize respiratory secretions are not fully known. However, our in vitro data indicating a more rapid flow rate of a mucin solution after treatment with the Frequencer suggests that the changes in airway secretion viscoelasticity may be one of the mechanisms. These observations are consistent with a study of the Flutter, another physiotherapy device that imparts oscillations to the airway secretions. In a 9-week study, oscillations of CF airways using the Flutter device at frequencies of 22 Hz and less resulted in significantly lower viscoelasticity of sputum in comparison with autogenic drainage.[21] In addition to the reduction of mucus viscosity through repetitive vibrations as described above, other potential mechanisms of action of the Frequencer include shearing at the mucus/airway interface induced by resonant energy targeted to specific locations in the lungs, a combination of mechanical and acoustical coupling from the chest wall that transmits vibrations to small and large airways, peristaltic action due to longitudinal waves, and acoustic streaming and related phenomena. More work is needed to define the mechanisms by which the Frequencer induces airway clearance.

Several options for chest physiotherapy are available to CF patients and their caregivers. A recent analysis of chest physiotherapy publications in the Cochrane database of systematic reviews indicated that while there is no evidence of differences in pulmonary function outcomes between the available techniques and CCPT, participants preferred self-administered airway clearance techniques.[22] Among these techniques were the following: autogenic drainage requiring no device, the PEP-mask device based on positive expiratory airway pressure that favors airway opening and mucus displacement, as well as the Flutter and Acapella which are hand-held devices that use positive pressure and vibration to dislodge airway mucus. Each of these techniques provides autonomy and is relatively inexpensive, but each also requires patient understanding and collaboration, thus limiting usage in young children. Mechanical percussive devices provide more autonomy than CCPT, but can also be associated with discomfort during treatment. More recently, chest physiotherapy applied with a vest that rapidly inflates and deflates to provide HFCWO has gained popularity. Although HFCWO devices provide patient autonomy, they are not recommended for use in infants. In contrast, because the Frequencer does not compress the entire chest wall it may provide an interesting alternative for infants needing airway clearance therapy.

The simplest explanation for the lack of a difference in the efficacy of CCPT and the Frequencer in the current study is that the study may have been under-powered. The study was calculated to have a

95 % power to detect with a significance level of 0.05 a smallest average difference between CCPT and Frequencer of 3.26 g, which corresponds to 35% of the CCPT sputum weight. More patients would need to be studied to detect a smaller difference and it remains possible that the Frequencer may be superior or inferior to CCPT. However, , our results are consistent with the concept that both therapies provide equivalent efficacy. The ease of use of the Frequencer and its potential to be used without the aid of a caregiver, provide significant advantages over CCPT.

In addition to being under-powered to detect small differences in sputum production, our study has other limitations. First, the study did not compare the efficacy of the Frequencer with that of other physiotherapy devices and techniques. Second, we cannot predict from this study whether use of the Frequencer will be associated with a significant improvement in clinically meaningful parameters such as quality of life, the number of respiratory exacerbations, and pulmonary function tests. Third, the study was performed using a prototype of the current Frequencer. Since the current model illustrated in figure 1 has an improved power head with a cooling system and a more potent amplifier, better results may be obtained with the current model.

In summary, we have reported a novel physiotherapy device based on the generation of acoustic and mechanical energy that can be delivered to all areas of the chest of patients with disease causing excessive airway mucus production. The device is comfortable, easy to use and safe. Most importantly, it allows the patient autonomy in the delivery of this essential form of therapy. The results presented in this study suggest that the Frequencer is at least as effective as CCPT in facilitating the expectoration of sputum. Further studies will be needed to determine and compare the clinical efficacy of this new form of respiratory physiotherapy delivered alone or in combination with other therapeutic modalities for airway mucus clearance.

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Address correspondence to:

André M. Cantin, M.D.
Respiratory Division, Department of Medicine
Centre Hospitalier Universitaire de Sherbrooke
3001 12ième Avenue Nord, Sherbrooke, Quebec, J1H 5N4
E. mail: Andre.Cantin@USherbrooke.ca

