Comparison of High-Frequency Chest Wall Oscillation With Differing Waveforms for Airway Clearance in Cystic Fibrosis

Robert R. Kempainen, Cynthia B. Williams, Ann Hazelwood, Bruce K. Rubin and Carlos E. Milla

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Background: High-frequency chest wall oscillation (HFCWO) is commonly used by cystic fibrosis (CF) patients for airway clearance. The primary objective of this study was to determine whether the use of a newer HFCWO device that generates oscillations with a triangular waveform results in greater sputum production than a commonly used device that generates oscillations with a sine waveform.

Methods: This was a controlled, randomized, double-blind, crossover study. Fifteen clinically stable, adult CF patients participated. Patients performed airway clearance with each device once and at matched oscillation frequencies and pressures. All sputum produced during each session was collected. Patients completed pulmonary function tests before and after each session, and rated the comfort of the two devices.

Results: Mean sputum wet and dry weight produced during sine waveform and triangular waveform HFCWO sessions did not differ (p = 0.11 and p = 0.2, respectively). Mean changes in FEV₁ and FVC following HFCWO therapy were also comparable (p = 0.21 and p = 0.56, respectively). However, there was a significant reduction in air trapping by residual volume/total lung capacity ratio following triangular waveform HFCWO (p = 0.01). In addition, in vitro cough transportability was 10.6% greater following therapy with the triangular waveform device (p = 0.05). Patients perceived the two devices as equally comfortable (p = 0.8).

Conclusions: Single-session sputum production is comparable with sine and triangular waveform HFCWO devices. Longer term comparisons are needed to determine whether sustained use of the devices results in clinically important differences in outcomes. (CHEST 2007; 132:1227–1232)

Registered at: clinicaltrials.gov (NCT 00308958).

Key words: airway clearance techniques; bronchial drainage; cystic fibrosis; high-frequency chest wall oscillation

Abbreviations: ACT = airway clearance technique; CF = cystic fibrosis; dN₂ = slope of phase III of the nitrogen washout curve; HFCWO = high-frequency chest wall oscillation; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity

Most of the morbidity and mortality experienced by patients with cystic fibrosis (CF) is due to pulmonary manifestations of the disease. Individuals with CF are prone to chronic airway infection and inflammation that results in progressive loss of pulmonary function. This process is rooted in the relative absence of mucin in the CF airway and dehydration of the pus-like airway secretions, resulting in impaired mucociliary clearance. Therapies to enhance the clearance of airway secretions are central to the management of CF lung disease. Airway clearance techniques (ACTs) facilitate the expectoration of tenacious secretions that otherwise accumulate in the airways. However, there is no consensus on which ACT is most efficacious. Metaanalyses of studies of ACTs in CF patients concluded that higher-quality studies are needed to clearly identify the most effective forms of therapy.
One widely used ACT, high-frequency chest wall oscillation (HFCWO), consists of an air-pulse generator connected to an inflatable vest that fits over the torso. Air pulses are transmitted to the vest at high frequency, creating oscillatory chest wall compressions. Currently, the most widely prescribed HFCWO device generates oscillations with a sine waveform. Recently, a new device was developed that generates oscillations with a triangular waveform. This modification of the waveform is postulated to introduce improvements in the mechanical shear forces generated in the airways to dislodge the secretions. Limited evidence suggests that this modification results in greater sputum production.

We conducted a controlled, randomized, double-blind, cross-over study to compare the efficacy, assessed by sputum production, of these two HFCWO devices in CF patients with mild-to-moderate lung disease. Secondary outcomes included pulmonary function tests (PFTs), sputum rheology and cough transportability, and patient perceptions of comfort and efficacy.

**Materials and Methods**

The Institutional Review Board at the University of Minnesota approved this study, and the trial was registered with ClinicalTrials.gov (NCT00308958). The sine and triangular waveform devices were lent free of charge by the manufacturers (VEST 104; Hill-Rom; St. Paul, MN; and InCourage System; RespirTech; St. Paul, MN, respectively). These companies did not provide any form of financial support or participate in any study activities.

**Subjects**

Patients were at least 18 years old and seen consistently at the Minnesota Cystic Fibrosis Center. All patients had a confirmed CF diagnosis according to Cystic Fibrosis Foundation criteria, performed HFCWO at least daily with a sine waveform device, had regular sputum production, and had baseline FEV₁ and FVC > 40% of predicted. Exclusion criteria included current pulmonary exacerbation or in the preceding 2 months, hemoptysis in the preceding month, chronic pain managed with narcotics, and prior use of the triangular waveform device. Patients were enrolled over a 4-month period.

**Study Procedures**

This was a controlled, randomized, double-blind, cross-over study. Figure 1 illustrates the study design and procedures. Following enrollment, patients were instructed to perform their last routine airway clearance session the evening prior to each study visit. The following morning, patients performed PFTs and were then randomly assigned to a session using the triangular or sine waveform device. All sputum produced during the session, and for 10 min following the session, was collected. An aliquot of sputum collected at the end of the session was immediately frozen and saved for biophysical analysis. Patients then repeated PFTs and completed an eight-item questionnaire that rated the study HFCWO session against their baseline home sessions using a 5-point Likert-type scale. After completion of the study visit, patients had a 2-day washout period during which they continued...
Table 1—HFCWO Settings Utilized for the Study*

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Sine Waveform</th>
<th>Triangular Waveform, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>8, 9, 10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>18, 19, 20</td>
<td>6</td>
<td>70</td>
</tr>
</tbody>
</table>

*Both devices use different arbitrary pressure units, and the settings shown reflect this difference. Pressures were matched by inserting a pressure transducer into the upper posterior aspect of the vest while the devices were run on a manikin and recording the setting for the triangular waveform device that resulted in exactly the same pressure reading for a given setting with the sine waveform device.

Table 1—HFCWO Settings Utilized for the Study

HFCWO Settings and Implementation

Vests were optimally sized and adjusted before randomization. The HFCWO pressures and frequencies used are summarized in Table 1. Patients were instructed to cough vigorously three times with the vest deflated prior to changing to the next combination of pressure and frequency. These settings were selected based on previous experience and studies assessing airflow and volume of air displaced at the mouth as previously described (referred to hereafter as tuning).11

Sputum Weights

All sputum produced during the HFCWO session was collected in a preweighed specimen container and immediately sealed. Specimens were centrifuged at 27,000g for 15 min at 4°C, and the supernatant was completely removed to eliminate saliva. The container with the sputum pellet was then weighed, and this weight was recorded as the “wet weight.” The specimen was then left open in an oven with the temperature set at 65°C for 3 days to allow for complete desiccation. The container was reweighed, and this weight was recorded as the sputum “dry weight.”

PFTs

Spirometry and plethysmographic lung volumes were performed according to American Thoracic Society/European Respiratory Society standards.10,13 To assess ventilation inhomogeneity, patients underwent single-breath nitrogen washout to determine the slope of phase III of the washout curve (dN2). For this test, patients performed a slow maximal inspiratory capacity maneuver in which 100% oxygen was inhaled and nitrogen concentration was continuously monitored during a slow full exhalation. Expiratory nitrogen concentration was plotted against volume, and the dN2 was calculated by computer analysis of the best-fit line through the phase III portion of the curve.14 All measurements were performed with a plethysmograph (Medgraphics Elite DX; Medical Graphics Corporation; St Paul, MN).

Viscoelasticity (Rheology)

Samples were studied with a rheometer (AR1000; TA Instruments; New Castle, DE) to assess the dynamic frequency range of stress strain of a 20-μL sputum sample over driving frequencies of 1 to 100 rad/s. The storage modulus G' and the elasticity G'' of the specimen were determined from these curves after nondestructive creep transformation.15,16

In vitro Cough Transportability

A simulated cough machine was used to measure the airflow-dependent clearability of sputum. A model Plexiglas trachea, rectangular in cross section (1.2 × 2 cm) was connected to a 6.4-L tank containing air pressurized to 11 pounds per square inch, giving a flow of approximately 11 L/s. A solenoid-controlled air release through a flow constrictive element used to mimic the airflow pattern of a natural cough. A sample, 40 μL in volume and 0.5 mm in depth, was placed in a thin line across the base of the Plexiglas trachea. The bulk transport of the sample was measured in millimeters after three cough maneuvers, and the results were averaged.17

Statistical Analysis

Descriptive data are reported as frequencies or means with SDs as appropriate. The order of HFCWO device assignment was incorporated into the formal analysis to assess for confounding due to period or carryover effects. Data analysis was performed by repeated-measures analysis of variance following the method proposed by Grizzle19 and implemented using software (PROC GLM, SAS v 9.0; SAS Institute; Cary, NC). Statistical significance was set a priori at 0.1 for carryover effects and at 0.05 for differences between treatment groups. Based on our sample size calculations, enrollment of 15 patients provided an 80% chance of detecting a ≥ 3.5-g difference in the sputum wet weights and at a significance level of 0.05.

Results

Fifteen patients were randomized and completed the study protocol. Table 2 summarizes the characteristics of these 15 patients. No patients experienced an adverse event.

No carryover effects were noted for any of the outcomes of interest (p > 0.2), which allowed for performing comparisons without need for adjustments. For our primary outcome, patients produced a mean sputum wet weight of 7.1 ± 6.4 g with use of triangular waveform HFCWO vs 5.1 ± 5.0 g with the sine waveform device. This difference was not statistically significant (p = 0.11). Findings were similar for sputum dry weights (mean 0.26 ± 0.42 g triangular waveform vs 0.17 ± 0.17 g sine waveform, p = 0.2).
Table 2—Baseline Characteristics of the 15 Participants*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>31.1 ± 10.0</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>7/8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3 ± 6.7</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>Δ F508 homozygote</td>
<td>10/15</td>
</tr>
<tr>
<td>Δ F508 heterozygote</td>
<td>5/15</td>
</tr>
<tr>
<td>Pulmonary function†</td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>72 ± 21</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>90 ± 20</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>112 ± 14</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>33.8 ± 10.7</td>
</tr>
<tr>
<td>Sputum microbiology</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>10/15</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>4/15</td>
</tr>
<tr>
<td>Other Gram-negative organisms</td>
<td>5/15</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No.
†Based on Knutson standard.

Table 3 summarizes the changes in spirometry and lung volumes following use of each HFCWO device. The FEV₁, FVC, and forced expiratory flow, midexpiratory range did not change significantly after HFCWO, and there was no significant difference between devices (p > 0.2 for all). With regards to lung volumes, residual volume (RV)/total lung capacity (TLC) increased after sine-wave therapy while the expiratory reserve volume decreased. In contrast, RV/TLC fell after triangular-wave HFCWO, but the expiratory reserve volume increased. These changes were statistically significant between the two devices (p < 0.05 for all). The dN₂ decreased slightly following sine wave form HFCWO and increased after triangular waveform, but this difference did not reach statistical significance (p = 0.09).

Table 4 summarizes the results of the rheologic and cough transportability studies performed. Eleven patients produced sputum suitable for analysis. Overall, the samples obtained with either device had a comparable proportion of solids, which suggests similar quality of the sputum samples. There were no significant differences between devices for elasticity, viscosity, and mechanical impedance G* (all p > 0.1). However, the cough transportability of sputum produced after HFCWO with the triangular waveform device was significantly greater (25.9 cm vs 23.4 cm, p = 0.05).

As a group, patients did not perceive therapy with the two devices differently. Specifically, patients’ rating of overall comfort of therapy with each device was equivalent and was comparable to their baseline sessions (p = 0.8). Ease of cough during therapy was perceived as slightly easier than during typical home sessions, but ratings did not differ between devices (p = 0.9).

**Discussion**

The current comparison of two HFCWO devices in individuals with CF is noteworthy for documenting comparable short-term efficacy, providing a model for performing methodologically rigorous short-term comparisons of ACTs, and for offering explicit guidance on the implementation of airway clearance with HFCWO. Previous studies found superior⁷,¹⁹–²¹ or at least comparable,²²–²⁴ efficacy of HFCWO compared to conventional chest physiotherapy consisting of manual percussion and postural drainage. It also appears that patients prefer airway clearance modalities that can be performed independently.¹⁹,²⁴

Unlike a previous comparison of the two devices,⁸ we did not observe a significant difference in short-term sputum production. A number of reasons could account for this. The initial study was of longer duration (2 weeks) and selected HFCWO frequencies delivered to the vest by each device in

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*ELV, L 0.005 ± 0.037 0.031 ± 0.042 .01

*EF₂₅₋₇₅ = forced expiratory flow, midexpiratory phase; ERV = expiratory reserve volume.*
order to isolate the effect of the two waveforms. However, previous work using a manikin model suggested the frequencies selected for the current study were higher than optimal for the triangular waveform device. How this might have influenced our results is unclear because there are no data to indicate the potential impact of different frequencies on relevant clinical measures, including sputum production. Lastly, the triangular waveform device allows the vest to deflate at regular intervals without disconnecting the hoses, a feature not available with the sine waveform device. Deflation potentially allows for more effective cough and thereby may have contributed to the greater sputum weight produced with use of the triangular waveform device in the earlier study because this was not emphasized during the use of the sine waveform device.

In addition, we did not find any significant differences in spirometry, patient comfort, and most rheologic measurements. We did find significant but small changes in lung volumes. HFCWO is known to decrease end-expiratory lung volumes, and this was observed to a modest degree following HFCWO with the sine waveform device. The reduction in RV and RV/TLC following triangular waveform HFCWO is consistent with reduced air trapping, although small in magnitude. Regardless, the significant changes noted suggest these observations are related to differences between the devices and merit further investigation. Changes in dN2 also suggest the devices differ in their effect on distribution of ventilation, although the difference did not reach statistical significance. The trend toward increased heterogeneity in alveolar ventilation following triangular waveform HFCWO may reflect increased mobilization of peripheral airway secretions.

The 10% greater in vitro cough transportability of sputum following HFCWO with the triangular waveform device suggests greater polymer disruption in these samples. Sputum tenacity (the product of adhesive work and cohesivity) is the biophysical property of sputum most strongly related to cough transportability. HFCWO can disrupt the DNA/F-actin polymer cofilaments characteristic of the pus-like sputum in the CF airway. Consistent with the Bueche theory of polymers, previous work has shown that depolymerizing the DNA/F-actin network will decrease the cohesivity and tenacity of CF sputa. Given the nonsignificant trend toward decreases in sputum elasticity and viscosity, cough clearability may have improved by disentangling and perhaps irreversibly fracturing the DNA/F-actin bundles that constitute the major polymer fibers in CF sputa.

In contrast to previous trials of overtly different ACTs, blinding was performed in the current comparison of two HFCWO devices. To our knowledge, this is the first blinded, randomized study of its kind. Of note, we did not formally assess the effectiveness of the blinding process, although limited, unsolicited feedback from subjects suggests it was successful. Other features of our trial often absent in previous studies of ACT in CF include explicit inclusion criteria, concealed allocation, adequate washout period, standardized study interventions, and comprehensive outcomes assessment.

The protocol followed for the use of HFCWO in this study is based on previous research and extensive clinical experience at a center with favorable outcomes. As such, it is of potential interest to clinicians seeking specific guidance on use of this ACT modality. Vest deflation between changes in frequencies may improve cough effectiveness and avoid the potentially deleterious effects of reduced end-expiratory lung volumes associated with HFCWO therapy. Some investigators individualize HFCWO frequencies based on tuning, but it is unclear whether this process enhances efficacy. In addition, serial tuning to accommodate changes in patient habitus and respiratory status may not be feasible at many centers. Previous studies typically specify HFCWO frequencies but make no mention of the pressures applied. Our anecdotal experience suggests higher pressures, such as those utilized in the present study, are more effective than lower pressures for a given frequency.

For clinicians and patients who prefer HFCWO for ACT, deciding between the currently available sine and triangular waveform devices is hindered by a lack of information on their relative advantages and disadvantages. More research is needed to assess important long-term outcomes such as frequency of respiratory exacerbations, overall decline in PFT results, and impact on quality of life and exercise tolerance.

In summary, patients in this controlled, blinded, randomized, short-term crossover study produced comparable amounts of sputum using sine waveform and triangular waveform HFCWO. However, modest differences in secondary outcomes suggest the two devices may exert different physiologic effects on airways and secretions. Longer-term comparisons of the two devices are needed to determine if these differences can translate into clinically important outcomes. The current study provides a model for performing short-term studies of ACTs and demonstrates the feasibility of conducting rigorous, unbiased comparisons.

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