Effect of High-Frequency Chest Wall Oscillation on the Central and Peripheral Distribution of Aerosolized Diethylene Triamine Penta-acetic Acid as Compared to Standard Chest Physiotherapy in Cystic Fibrosis

Steven W. Stites, MD, FCCP; Gayln V. Perry, MD; Tom Peddicord, PharmD; Glen Cox, MD; Chris McMillan, CNMT; and Brian Becker, MEd, RRT

Background and objectives: High-frequency chest wall oscillation (HFCWO) has been shown to be as effective as standard chest physiotherapy (SCPT) for removal of pulmonary secretions as well as increasing FEV₁ in cystic fibrosis (CF) patients. Patients using HFCWO often administer aerosolized medications simultaneously, reducing time required for daily care. While peripheral pulmonary distribution of tracer in normal subjects has been shown to be unaffected by HFCWO, this has not been studied in CF patients. We evaluated distribution of aerosolized ⁹⁹ᵐTc diethylene triamine penta-acetic acid (DTPA) administered simultaneously with HFCWO and compared this with DTPA aerosolized after SCPT.

Study design: Ten CF patients, ages 22 to 38 years, with moderate-to-severe obstructive disease were studied in a crossover design after documentation of stable lung function. ¹³³Xe was administered to delineate total lung volume. DTPA was aerosolized (Pari LC Plus nebulizer and Pulmo-Aide compressor; Pari Respiratory Equipment Inc.; Richmond, VA) to delineate airway deposition. The central to peripheral deposition ratio (C/P ratio) of each lung was analyzed in each study group. Central regions were represented by the inner one third of the ¹³³Xe scan as demonstrated in previous research models.

Results: The mean C/P ratio (± SD) for both lungs was 1.45 ± 0.31 with HFCWO and 1.46 ± 0.28 following SCPT (p = not significant [NS]). Right lung mean C/P ratio was 1.74 ± 0.43 with HFCWO and 1.85 ± 0.63 after SCPT (p = NS). Left lung mean C/P ratio was 1.25 ± 0.29 with HFCWO and 1.21 ± 0.35 after SCPT (p = NS). There was no correlation between C/P ratio and FEV₁ or FVC.

Conclusions: Use of HFCWO in combination with aerosolized DTPA did not result in increased central deposition as compared with aerosolized DTPA administered after SCPT. Further study is required to determine if combining HFCWO with aerosolized medications can be modified to improve peripheral deposition.

Key words: aerosol; airway clearance; central to peripheral deposition ratio; chest physiotherapy; cystic fibrosis; high-frequency chest wall oscillation; pulmonary; ¹³³Xe

Abbreviations: ACT = airway clearance therapy; CF = cystic fibrosis; DTPA = diethylene triamine penta-acetic acid; C/P ratio = central to peripheral deposition ratio; HFCWO = high-frequency chest wall oscillation; NS = not significant; ROI = region of interest; RRT = respiratory therapist; SCPT = standard chest physiotherapy

Cystic fibrosis (CF), a disease of chronic bronchial infection, airway obstruction, and thick viscid mucous secretions, requires aggressive pulmonary hygiene as well as other therapies to help slow progressive loss of lung function. Daily health maintenance consists of airway clearance therapy (ACT), antibiotics, dornase alfa, and bronchodilators, and can be very time consuming for CF patients. More
than 50% of patients at our institution reported spending >1 h/d administering ACT and aerosolized medications. Nearly all patients admitted non-compliance with ACT, with the most frequent reason cited for missing treatments being “too busy.”

Standard chest physiotherapy (SCPT), also called percussion and postural drainage, refers to the use of a number of positions and utilization of gravity to drain secretions from the lungs. Positioning is commonly combined with percussion or vibration over the area of the lung being drained. SCPT has been part of the standard care regimen in CF patients for >50 years. A number of studies\(^1,2\) support the effectiveness of this therapy; however, it is typically quite time consuming, requiring the use of a number of positions to achieve effective therapy.

Newer techniques may improve compliance by providing more convenient ways of administering ACT. Products such as oscillatory positive expiratory pressure devices (eg, the flutter valve) are more portable. High-frequency chest wall oscillation (HFCWO) allows for self-administration of therapy, providing patients more independence by removing the need for a caregiver to administer ACT. These newer modalities have been shown to be as effective as traditional chest percussion.\(^3\)

HFCWO, marketed in the United States as The Vest airway clearance system (Hill-Rom; Charleston, SC), consists of an inflatable vest and an air-pulse generator. This system is a mechanical high-frequency chest wall oscillator capable of superimposing oscillatory airflow over a patient’s inspiratory and expiratory efforts. During HFCWO, pressure pulses within the vest oscillate the thoracic wall and generate transient increases in airflow within the lung. The result is high oscillatory volumes at the mouth and high peak expiratory flow rates similar to that seen during a cough. These cough-like shear forces have been shown to alter the consistency of secretions.\(^4–6\)

Furthermore, there is evidence that HFCWO removes secretions by generating differences between expiratory and inspiratory flow and velocity.\(^7,8\) Several studies\(^9–12\) have suggested that HFCWO is as effective as SCPT. In addition to the airway clearance effect, HFCWO has been shown to enhance nitrogen washout, suggesting that alveolar ventilation may be increased during HFCWO as well.\(^13\)

More than 50 patients in our Adult Cystic Fibrosis Center use HFCWO as their primary means of ACT. Of these patients, we found that 50% began administering their aerosolized medications during vest treatments in order to simplify their regimen and save time. The majority of patients not using HFCWO use SCPT delivered by a home caregiver as their primary ACT. Patients using this therapy require sequential administration of airway clearance followed by certain aerosolized medications. Surveyed HFCWO patients reported that combining this therapy with aerosolized medications resulted in a 25 to 50% reduction in daily treatment time. Recognition of this practice in our patients raised concerns about the effect of HFCWO on pulmonary distribution of aerosolized medications.

Distribution of aerosols can be influenced by numerous factors, such as particle diameter and inertia, airway geometry, respiratory rate, and delivery system, thus impacting the overall effectiveness of drug delivery to the periphery of the lung. In CF patients with obstructive lung disease, bronchiectasis and mucus impaction result in flow limitation. This increases local turbulence and significantly increases central deposition.\(^14\) HFCWO increases inspiratory and expiratory flow rates and may exacerbate central deposition, leading to decreased clinical efficacy of aerosolized medications. In addition, the circumferential nature of the vest worn with HFCWO may limit inspiration and also add to central deposition. While one initial investigation\(^15\) found no effect of HFCWO on peripheral deposition in normal subjects, this has not been tested in patients with CF or other obstructive diseases. With patients frequently combining the use of aerosols with HFCWO, we sought to investigate whether there was a significant effect on distribution of aerosolized medications.

**Materials and Methods**

**Patient Selection**

Ten patients (3 female and 7 male) with CF were studied in a randomized crossover design following informed consent approved by the Human Subjects Committee and Radiation Safety Committee at the University of Kansas Medical Center. The history of a positive sweat chloride test result and the presence of sinopulmonary disease confirmed the diagnosis of CF. Patients...
were included if they did not have symptoms of an exacerbation and had spirometry testing within 15% of their stable baseline. Exclusion criteria included hospitalization during the previous month, hemoptysis > 30 mL during the previous month, hemoptysis requiring embolization within the previous 2 months, or an FEV₁ decline of > 15% from baseline.

**Study Design**

This pilot study utilized a crossover, within-subject comparison design. Subjects were randomized to avoid “order effect” using a predetermined block randomization scheme in groups of three, three, and four subjects. A washout period of at least 72 h but not more than 10 days was included between treatments.¹⁶

**Determination of Drug Deposition**

The protocol for determination of aerosol deposition was based on previous studies conducted by Smaldone and Messina¹⁴ and Ilowite et al.⁻¹⁷ In order to determine pulmonary distribution of aerosol, lung size and volume must first be established to use as a standard to compare the distribution of aerosol particles.¹³³Xe is an inert gas governed by flow properties similar to oxygen and carbon dioxide. Because of its radioactive nature, and because it distributes freely throughout the lung,¹³³Xe is commonly used to determine the alveolar volume.

In our study, patients underwent a standard equilibrium¹³³Xe scan at functional residual capacity to demonstrate total alveolar volume.¹³³Xe was administered by standard protocol via a specialized delivery system as a 10-mCi dose utilizing a low-energy, all-purpose collimator with 20% windows on Siemens specialized delivery system as a 10-mCi dose utilizing a low-energy, all-purpose collimator with 20% windows on Siemens.

Immediately following¹³³Xe administration, 4 mL or approximately 40 mCi of ⁹⁹m-Tc diethylene triamine penta-acetic acid (DTPA) was nebulized. Aerosolization of DTPA yields particle sizes of 1 to 5 μm, similar to nebulized medications, and is commonly used as a radiolabeled aerosol for determining regional pulmonary distribution.¹⁸⁻²⁰ DTPA was nebulized (Pari LC Plus; Pari Respiratory Equipment; Richmond, VA) for 15 min. All nebulizations were performed with the compressor (Pulmo-Aide; DeVilbiss Health Care; Somerset, PA) to eliminate droplet size variability. This system generates aerosol particles with a mass-mean aerodynamic diameter of < 5 μm with an operating pressure of 12 to 18 pounds per square inch and flow of 5 to 7 L/min. The nebulizer, generator, and collection system was designed to eliminate positive pressure and to simulate, as closely as possible, clinical administration of aerosolized medications used at home. Patients used a nose clip and a large mouthpiece, and were instructed on standard aerosol technique using slow, deep inhalations and normal exhalations. Esophageal and gastric deposition was minimized during DTPA administration by discouraging swallowing and rinsing immediately after the procedure. All images were obtained in the sitting position to reach a pixel count of one million by a large-field-of-view gamma camera fitted with a low-energy, all-purpose collimator.

**Patient Protocol**

All patients underwent spirometry measurement by registered respiratory therapists (RRTs) using standards approved by the American Thoracic Society¹¹ immediately before undergoing the study protocol. In a randomized crossover fashion, patients were selected to receive either SCPT immediately prior to¹³¹Xe and DTPA or to undergo HFCWO during¹³¹Xe and DTPA administration. The study days were separated by at least 72 h to ensure adequate decay time for DTPA, and no more than 10 days to ensure stable pulmonary function. An RRT experienced in treating CF patients completed the SCPT arm of the study using a chest percussion protocol designed for CF patients at the University of Kansas Medical Center. The protocol utilized a clapping technique in a number of different positions, including sitting, lying flat, and lying in a head-down position on the right and left sides with the therapist clapping different areas of the chest wall. The total SCPT therapy took approximately 30 min to complete. HFCWO was administered by an RRT with specific training in its operation using a frequency setting of 13 Hz and a pressure setting of 6. Each HFCWO therapy was delivered for a total of 20 min.

**Data Analysis Protocol**

Data were collected for patients undergoing the¹³³Xe scan and DTPA nebulization as described above. The radiologist interpreting scans was blinded to the treatment used prior to or during aerosol administration. The distribution of radiolabeled aerosol was determined as the central to peripheral ratio (C/P ratio) using techniques established by prior investigators.¹⁴,²² This requires measurement of total lung volume by outlining regions of interest (ROIs) around the¹³³Xe equilibrium lung images utilizing pixel counts. The inner one-third and peripheral two-thirds regions were assigned based on the total pixel counts from the¹³³Xe scan. The inner one third of the image is considered the central region. Images obtained after nebulization of aerosolized DTPA were transposed onto the¹³³Xe images. An ROI was drawn around the stomach to identify gastric radioactivity. Figure 1 shows a representative study. The amount of this activity compared to overall counts was small; however, the stomach images were removed before the data were analyzed. The C/P ratio of each lung determined by the pixel counts in those regions was obtained. Differences in regional volume were corrected by dividing C/P aerosol deposition ratio by the C/P ratio for¹³¹Xe gas distribution. A C/P ratio < 1 demonstrates more peripheral deposition, whereas a C/P ratio > 1 indicates more central deposition.

Spirometry and C/P ratios after SCPT were compared with the data found during concomitant HFCWO by a paired Student t test (p < 0.05 considered significant). C/P ratios in both groups were also correlated with severity of airway obstruction using linear regression.¹⁶

**RESULTS**

Ten patients (7 men and 3 women) met the criteria for inclusion and exclusion, and all were able to complete both arms of the study. Mean age of the patients was 27 ± 6.2 years (± SD), with a range of 18 to 48 years. No significant difference was found in FEV₁ or FVC obtained prior to the nuclear studies in the respective treatment groups. Baseline characteristics are documented in Table 1.

The mean C/P ratios comparing both lungs showed no statistical difference whether aerosol administration occurred during HFCWO (1.45 ± 0.32) or after SCPT (1.46 ± 0.28). In addition, no difference was found in the C/P ratios between the SCPT and HFCWO groups involving the right and left lungs (Table 2).
The effect of lung function on aerosol distribution was evaluated in each group by comparing FEV₁ and FVC percentage of predicted with the C/P ratio using linear regression. We were unable to document an increase in central deposition in patients with worse spirometry results. Correlation coefficients appear in Table 3.

**DISCUSSION**

We evaluated the effect of HFCWO on aerosol distribution by comparing the result of concomitant administration of therapy with deposition after SCPT using patients as their own control. We used a protocol that maintained the standard practices at our center for patients receiving ACT and aerosolized medications at home, including the nebulizer, compressor, and breathing techniques commonly recommended.

We were unable to detect any decremental effect of combined HFCWO and aerosol treatment in the C/P ratio. In addition, no significant correlation was found between the C/P ratio and the level of lung function in the HFCWO group.

Virtually all CF patients require daily aerosolized medications during the course of their disease. Maximizing the administration of these medications and ensuring appropriate delivery of antibiotics to the site of infection are the goals of aerosol therapy. Many factors influence whether an aerosolized particle deposits centrally or peripherally, including particle size, inspiratory flow rate, and lung volume. More specifically, in patients with CF, bronchospasm, abnormal secretions, and airway collapse contribute significantly to the impaction of airway particles centrally.

We were concerned that HFCWO, by its restrictive effect on the chest wall, may limit inspiration, a

<p>| Table 1—Baseline Characteristics of Study Group* |</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>27 ± 6.2 (18–48)</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>7/3</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.7 ± 0.45 (0.92–2.33)</td>
</tr>
<tr>
<td>FEV₁, % predicted†</td>
<td>47 ± 13 (25–69)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.66 ± 0.785 (1.32–3.94)</td>
</tr>
<tr>
<td>FVC, % predicted†</td>
<td>60 ± 16 (30–83)</td>
</tr>
<tr>
<td>FEF₂₅–₇₅</td>
<td>1.008 ± 0.43 (0.49–1.9)</td>
</tr>
<tr>
<td>Maximum FEF</td>
<td>5.57 ± 1.73 (2.58–9.08)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD (range) or No. FEF₂₅–₇₅ = forced expiratory flow at 25 to 75% of FVC; FEFmax = maximum forced expiratory flow.

†Calculated based on predicted values of Crapo et al.₂₆

| Table 2—Mean C/P Ratios in HFCWO and SCPT Groups* |
| Variables | Following SCPT | Concurrently With HFCWO | p Value |
| Both lungs | 1.46 ± 0.28 | 1.45 ± 0.32 | NS |
| Right lung | 1.85 ± 0.63 | 1.74 ± 0.43 | NS |
| Left lung | 1.21 ± 0.35 | 1.25 ± 0.29 | NS |

*Data are presented as mean ± SD.
major factor determining aerosol deposition. Super-imposed oscillatory airflow, compressive pulses, and high peak expiratory airflow also may affect distribution of aerosolized medication. These effects may be exaggerated in patients with more severe airway disease or hyperinflation. In our study, the difference in aerosol deposition was not significant (NS) between the two groups, suggesting that concurrent administration of HFCWO and aerosol therapy does not significantly alter the deposition of the aerosol particles. Although our sample size was small, based on these results we would not expect to see either a decrease in the effectiveness of aerosolized medications or an increase in untoward side effects when these medications are used in conjunction with HFCWO therapy.

We further expected to find an inverse correlation between lung function and peripheral deposition. Studies\(^1\)\(^{17}\)\(^{23}\)\(^{24}\) have demonstrated that as FEV\(_1\) decreases, central deposition increases. Bronchoconstriction results in smaller airway diameter and airway collapse on exhalation, and both result in enhanced central deposition. In a study evaluating the deposition of aerosolized gentamicin in 13 patients with CF, Ilowite et al\(^17\) found a relatively strong correlation between FEV\(_1\) percentage of predicted and C/P ratio. However, the range of lung function was quite broad, with FEV\(_1\) from 16 to 172% of predicted and four patients with FEV\(_1\) > 100% of predicted. Mean FEV\(_1\) was 73.8 ± 45.1% of predicted. Eliminating patients with FEV\(_1\) > 80% of predicted would have yielded a significantly less conclusive correlation between level of FEV\(_1\) and C/P ratio. Similar results were found in an evaluation of the factors related to aerosol deposition of recombinant human deoxyribonuclease in 15 CF patients, but again the range of FEV\(_1\) was broad, from 63.7 to 135% of predicted and mean of 86.9%\(^2\)\(^{24}\).

When comparing the severity of obstruction (FEV\(_1\) percentage of predicted, FVC percentage of predicted, FEV\(_1\)/FVC) with the mean C/P ratio, we could not demonstrate the expected inverse correlation between these two variables. This, in part, may be because the range of lung function for our population was somewhat narrower. Our population contained patients with more severe disease not uncommon in adults with CF (Table 1). Hence, in this population, differences in lung function may not play as great a role in determining drug deposition. Investigations with larger numbers of patients in different subgroups of obstruction are necessary to analyze this further.

Aerosolized medications are becoming an increasingly important component of the treatment regimen for CF patients. To reduce chronic Pseudomonas colonization, aerosolized aminoglycosides are commonly administered to CF patients, thus providing high concentrations of antibiotics to the lungs without concomitant systemic toxicity. Currently, an aminoglycoside formulated specifically for inhalation therapy (TOBI; Chiron Corporation; Seattle WA) is approved for endobronchial suppressive therapy.\(^2\)\(^{17}\) Ilowite et al\(^17\) showed that increased sputum concentration of the administered aerosolized aminoglycoside correlated with enhanced central deposition, reflecting poor peripheral deposition. A relatively small percentage of the nebulized medication was actually delivered to the lung. Results further suggested that the amount delivered is highly variable and is dependent on many factors, including the breathing pattern.\(^17\) This underscores the importance of understanding the effects of delivery systems and therapy combinations on aerosol deposition. As the treatment of CF, as well as other diseases, becomes more dependent on the appropriate administration of aerosolized medications, further studies are necessary to distinguish which modalities enhance or hinder their delivery.

CF patients will continue to depend on airway clearance techniques and aerosol medications for management of pulmonary complications. HFCWO is an effective form of chest physiotherapy that allows CF patients more independence, and when combined with administration of aerosol therapy simplifies their lives. In order to improve the quality of life by increasing independence and decreasing treatment time, many CF patients in our center self-initiated combining HFCWO with their aerosolized medications.

The sample size for our study was small; however, our results offer preliminary reassurance to care providers and their patients that combining these treatment modalities can be done safely without concern for diminished deposition to the peripheral airways. Further study is necessary to better understand these interventions, to identify combinations and newer protocols that may enhance delivery of aerosolized medications to the peripheral airways, and to determine whether distribution is affected by additional factors, including severity of obstruction.

<table>
<thead>
<tr>
<th>Groups</th>
<th>FEV(_1) % Predicted</th>
<th>FVC % Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCPT</td>
<td>0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>HFCWO</td>
<td>0.33</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 3—Correlation (r) of C/P Ratio and Each Treatment Group With Level of Obstruction as Determined by FEV\(_1\) and FVC

\(r\) determined by FEV\(_1\) and FVC

1. Ilowite et al.
References