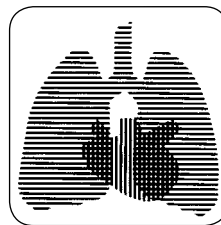


Assessing Efficacy of High-Frequency Chest Wall Oscillation in Patients With Familial Dysautonomia*

Philip Giarraffa, MPH; Kenneth I. Berger, MD, FCCP; Alice A. Chaikin, RN; Felicia B. Axelrod, MD; Cynthia Davey, MS; and Brian Becker, MEd, RRT



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Assessing Efficacy of High-Frequency Chest Wall Oscillation in Patients With Familial Dysautonomia*

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Study objective: To determine the benefits of daily use of high-frequency chest wall oscillation (HFCWO) in familial dysautonomia (FD) patients with lung disease.

Design: Pulmonary function tests, chest radiographs, and blood tests were performed on entry to the study. A retrospective chart review of 12 months prior to entry provided baseline data regarding respiratory illnesses, medications, doctor visits, hospitalizations, and absenteeism. Daily logs provided prospective data on these parameters as well as HFCWO usage. Evaluations were performed at 1, 3, 6, 9, and 12 months for pulse oximetry, spirometry, and log review. At the exit evaluation, blood tests and chest radiographs were repeated.

Patients: Fifteen FD patients with history of lung disease requiring daily inhalation therapy (7 female and 8 male; age range, 11 to 33 years) were enrolled in a 1-year clinical trial of HFCWO therapy. Two subjects withdrew after 3 months and 6 months, respectively. Each individual served as his/her own control.

Results: Oxygen saturation improved by 1 month (median, 97.5%; interquartile range [IQR], 96 to 98%; vs median, 94%; IQR, 89 to 96%) and was sustained at exit evaluation (median, 98%; IQR, 98 to 98%) [$p = 0.004$]. Median FVC and peak expiratory flow rate (PEFR) were the pulmonary function measures with sustained improvement from baseline to exit ($p = 0.02$ and $p = 0.03$, respectively). When retrospective and prospective data were compared, all measured health outcomes improved significantly, including pneumonias ($p = 0.0156$), hospitalizations ($p = 0.0161$), antibiotic courses ($p = 0.0005$), antibiotic days ($p = 0.0002$), doctor visits ($p = 0.0005$), and absenteeism ($p = 0.0002$).

Conclusion: In this limited study of FD patients, HFCWO effected significant improvements in all measured health outcomes and oxygen saturation; FVC and PEFR were the pulmonary function measures demonstrating sustained improvement. (CHEST 2005; 128:3377-3381)

Key words: antibiotic use; aspiration; familial dysautonomia; gastroesophageal reflux; hospitalizations; mucus; pneumonia; pulmonary function; secretions

Abbreviations: ATS = American Thoracic Society; FD = familial dysautonomia; GER = gastroesophageal reflux; HFCWO = high-frequency chest wall oscillation; IQR = interquartile range; PEFR = peak expiratory flow rate

Familial dysautonomia (FD), also known as the Riley-Day syndrome, is a genetic disorder that is commonly associated with pulmonary disease.¹⁻³ It is primarily a neurologic disorder that affects sensory and autonomic function and is clinically manifested as uncoordinated swallowing, esophageal dysmotility, and depressed cough and gag reflexes.¹ The major cause of recurrent lung disease is aspiration as

a result of either misdirected swallows or gastroesophageal reflux (GER).²⁻⁴ The recurrent lung insults contribute to FD being considered a life-threatening disorder with high morbidity and mortality.^{5,6}

Most of the damage to the lung occurs during infancy and early childhood when oral coordination is especially poor and the percentage of liquid in the diet is high.¹⁻⁴ Even if the FD patient is treated with

*From the Dysautonomia Center (Mr. Giarraffa, Drs. Berger and Axelrod, and Ms. Chaikin), New York University Medical Center, New York University School of Medicine, New York, NY; Division of Biostatistics (Ms. Davey), University of Minnesota School of Public Health, St. Paul, MN; and Clinical Research (Mr. Becker), Hill-Rom Inc., St. Paul, MN.

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Correspondence to: Brian Becker, MEd, RRT, Clinical Research Manager, Hill-Rom, Inc., 1020 West County Rd, F, St. Paul, MN 55126; e-mail: brian.becker@hill-rom.com

fundoplication and gastrostomy, lung damage can continue, as there is the continued risk of aspiration of saliva.² These children are also hypotonic, have poorly coordinated breathing, and often have spine curvature (85% have structural spinal curvature by 10 years of age).^{1,4} As a result, they have a decreased ability to effectively clear secretions and are at increased risk for chronic lung disease associated with atelectasis, and eventually bronchiectasis.^{1,2,4}

The FD patient's cough is often ineffective secondary to hypotonia and restrictive lung disease. Consequently, chest physiotherapy and nasotracheal suctioning have been used to compensate for inability to expectorate.³ Chest physiotherapy, consisting of postural drainage and inhalation of bronchodilators, is helpful as part of short-term and long-term care³ but has some limitations in the FD population. Postural drainage requires Trendelenberg positioning, which is poorly tolerated in the individual affected with FD due to cardiovascular lability characterized by postural hypotension without compensatory tachycardia, as well as supine hypertension.^{1,2,4,7,8} Furthermore, in individuals without fundoplication, or whose fundoplication is not fully functional, the head-down position can exacerbate GER, leading to esophagitis and risk of aspiration. Thus, traditional chest physiotherapy methods have inherent complications and often result in poor compliance.

High-frequency chest wall oscillation (HFCWO) therapy is delivered by an inflatable vest connected via hoses to an air-pulse generator.^{9,10} HFCWO occurs as the vest inflates and deflates rapidly. HFCWO generates increased airflow velocities that create repetitive cough-like shear forces and decrease the viscosity of secretions.⁹⁻¹² The action of the vest creates a vibration on the chest wall that mobilizes mucous within the airway passages of the lung.^{12,13} The mobilized mucous can then be coughed up, thus clearing the airways. Theoretically, improved pulmonary function and shortened illness time should result.¹⁴⁻¹⁷

Our objective was to determine if daily use of HFCWO would benefit patients with FD whose neurologic disorder predisposed them to chronic lung problems and difficulty clearing secretions due to respiratory muscle weakness, weak cough, and compromised thoracic space due to scoliosis. A number of alternative airway clearance therapies are now available. We were particularly interested in assessing the effectiveness of HFCWO therapy because it is an alternative that does not require patient coordination. Additionally, we have previously tried the therapy on a few of our patients and have observed that these patients seemed to have success with the therapy. We therefore hypothesized that

HFCWO use would reduce the frequency of lower respiratory problems and associated medical interventions and hospitalizations, and might improve lung function.

MATERIALS AND METHODS

Patient Selection

Fifteen FD patients with a history of recurrent lung disease for whom chest physiotherapy, *ie*, daily inhalations with bronchodilators and percussion, had been prescribed were enrolled into the clinical trial (7 female and 8 male patients; range, 11 to 33 years). Each individual served as his/her own control. Study subjects were permitted to continue usual medications to treat other aspects of their disorder. All patients were being followed up at the Dysautonomia Treatment and Evaluation Center at New York University Medical Center and met established clinical diagnostic criteria for FD: they were of Ashkenazi Jewish extraction, lacked lingual fungiform papillae, did not have an axon flare after intradermal histamine injection, had decreased or absent deep tendon reflexes, and lacked overflow tears.¹ All patients were homozygous for the common FD IKAP gene mutation.¹⁸ The protocol was approved by the Institutional Review Board of New York University Medical Center. Informed consent was obtained prior to the study. For subjects < 21 years of age, signatures were obtained from both the participant and a parent.

Procedure

On entry into the study, baseline data were obtained that included historical data regarding frequency of respiratory problems (number of pneumonias and hospitalizations) in the past year as well as current inhalation regimen. All patients underwent height and weight measurements, pulse oximetry, chest radiography, and blood tests that included CBC count with differential and erythrocyte sedimentation rate, and a comprehensive metabolic screen.

Pulmonary function measures were obtained using an office-based spirometry system (KoKo; Pulmonary Data Services Instrumentation; Louisville, CO). This spirometry system can test pulmonary function in the office and utilizes a computer screen to facilitate compliance. A variety of incentive programs are available to improve patient cooperation and effort. The KoKo system meets the American Thoracic Society (ATS) recommendations. Appropriate calibrations of the spirometer were performed. Pulmonary function testing was administered to achieve the best performance on individual measures. The effort performed by patients with neuromuscular disease is by definition submaximal, and weakness often results in data that is not reproducible. Furthermore, the poor coordination in FD confounds these measurements. Due to the nature of FD, although effort was maximal, it did not always meet ATS criteria for reproducibility. For this study, as in the clinical setting, it is necessary to use best performance as indicative of the level of function. In this group of patients, the best performance was considered a valid measure, consistent with ATS guidelines.¹⁹ Each patient served as his or her own control, and there was also individual patient reproducibility.

The pulmonary function measures obtained initially and then at each follow-up visit included FVC, FEV₁, FEV₁/FVC, forced expiratory flow rate at 50% of vital capacity, peak expiratory flow rate (PEFR), slow vital capacity, and expiratory reserve volume. In our study, pulmonary function measures were not readminis-

tered to assess for response to bronchodilators. These neurologically impaired children tend to fatigue with repeated testing and accuracy declines. In addition, patients are sympathetically denervated, and use of certain bronchodilators can trigger marked hypertension, tachycardia, and in some cases dysautonomic crisis. Thus, we believed that pulmonary function test results would be easiest to compare if we eliminated these confounding variables.

After completion of the baseline studies, the patient was fitted with an inflatable vest and taught how to use the HFCWO apparatus (The Vest airway clearance system; Hill-Rom, Inc.; St. Paul, MN). The patient was then tried on various settings to determine tolerance and effectiveness, *ie*, stimulation of cough. Pressure dial settings varied from 3 to 5, and frequency was between 10 Hz and 15 Hz with durations from 20 to 30 min per session. The patient was then instructed to use The Vest treatment twice daily at prescribed settings for 1 year.

Scheduled longitudinal evaluations were performed over a 1-year period, at 1, 3, 6, 9, and 12 months. At each scheduled evaluation session, the log regarding treatment schedules (HFCWO and inhalation), infection frequency, use of antibiotics, and use of respiratory medication was reviewed, and the subject underwent pulse oximetry and pulmonary function tests. At the 12-month exit evaluation, weight and height measurements, blood tests, chest radiography, and pulse oximetry were repeated.

Statistical Analysis

Data were analyzed using the Wilcoxon signed-rank test (SAS Software Version 8, 1999; SAS Institute; Cary NC), which was deemed appropriate for our small sample sizes with nonnormally distributed data. A positive signed-rank statistic indicates that more than half the subjects experienced change in a positive direction; *p* values ≤ 0.05 identified statistically significant differences. Summary statistics for data analyzed by the Wilcoxon signed-rank test are reported as median and interquartile range (IQR).

RESULTS

Patient Demographics

Patient demographics are shown in Table 1. The mean age \pm SD of the 15 patients was 19.5 ± 7.5 years. All patients had fundoplication with gastrostomy performed prior to the study at an average age of 8.7 ± 10 years (range, 0.6 to 28.4 years). Only 1 of

the 15 patients was permitted to drink oral fluids other than water because of the risk of aspiration. Eight of the 15 patients had scoliosis, 4 patients had spine fusion prior to the study, and 2 patients had fusion during the study but continued HFCWO treatment through the recuperative period. Two patients (one male and one female) withdrew from the study because they did not like the sensation of the therapy and did not like adhering to the routine of daily HFCWO treatment. Therefore, 13 patients completed the study.

Pulmonary Function Outcomes

Chest radiographs were reviewed and compared in an unblinded manner by one of the investigators (F.B.A.). At initiation of the study, all patients had radiographs that showed bilaterally increased interstitial markings. Two patients also had atelectasis in the left lower lobe. There were no significant changes in the radiographs at the end of the study.

Oximetry

Oximetry data exhibited statistically significant improvement with HFCWO treatment. Median oxygen saturation in all 15 patients at baseline was 94% (IQR, 89 to 96%) and increased at 1 month (14 patients) and 3 months (15 patients) to 97.5% (IQR, 96 to 98%) and 98% (IQR, 98 to 98%), respectively. Oxygen saturation data were available for 9 of the 13 patients completing the study. Median oxygen saturation at 12 months was 98% (IQR, 98 to 98%). Comparison of baseline and 12-month oxygen saturations on those patients revealed significant improvement (*p* = 0.004) as evaluated by the Wilcoxon signed-rank test.

Pulmonary Function Measures

Subjects exhibited a wide range of pulmonary function prior to enrollment in the study. At baseline, the median FVC for 15 patients was 1.47 L (IQR, 1.27 to 1.92 L), median FEV₁ was 1.15 L (IQR, 0.81 to 1.28 L), and median FEV₁/FVC was 0.72 (IQR, 0.66 to 0.88). Poor coordination of breathing yielded inconsistent and unreliable results for measures such as slow vital capacity and expiratory reserve volume.

Improvements in FVC, FEV₁, percentage of predicted FVC, and PEFR for the group were appreciated by the 6-month evaluation and were maintained through the 9-month evaluation for FVC and PEFR. When analysis was done for only those 13 subjects with 12-month data, FVC and PEFR exhibited statistically significant improvements (*p* = 0.02 and *p* = 0.03, respectively) [Fig 1, Table 2]. Positive

Table 1—Population Demographics and Medical Histories

Parameters	Mean \pm SD	Patients, No.	%
Age, yr	19.5 \pm 7.5	15	
Gender			
Male		8	53
Female		7	47
Age at fundoplication, yr	8.7 \pm 10.0	15	
Age at gastrostomy tube, yr	7.6 \pm 9.5	15	
Placement			
Sleep apnea		11	73
Scoliosis		8	53
Spinal fusion		4	27
GER		14	93

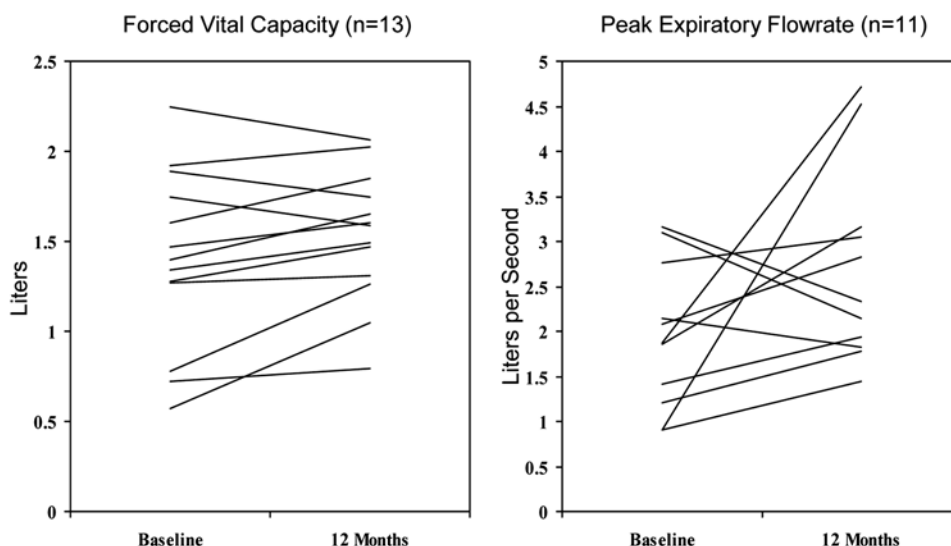


FIGURE 1. Comparison of baseline and 12-month data for FVC and PEFr.

signed-rank statistics that did not reach statistical significance were obtained for FEV₁ and percentage of predicted FVC (Table 2).

Health Outcome Measures

Data from the year prior to entry as compared to data from the year during HFCWO treatment were analyzed using Wilcoxon signed-rank tests. For the 13 patients who completed the study, there were significant improvements in all health outcome measures (Table 3). No significant changes were noted in laboratory data that might be considered measures of chronic infection, such as WBC count, erythrocyte sedimentation rate, or lactate dehydrogenase. The number of subjects receiving medication (albuterol, cromolyn, montelukast, prednisone, fluticasone, or ipratropium) at 12 months decreased from baseline for each medication, but these changes were not statistically significant.

Table 2—Percentage Change in Pulmonary Function Measures From Baseline to 12 mo*

Parameters	Patients With Increase, %	Patients, No.	p Value†
FVC	77	13	0.022
FVC % predicted	62	13	NS
FEV ₁	62	13	NS
FEV ₁ /FVC	46	13	NS
FEF ₅₀	38	13	NS
PEFR	73	11	0.032

*FEF₅₀ = forced expiratory flow at 50% of vital capacity.

†Wilcoxon signed-rank test.

DISCUSSION

FD is a complicated neurologic disorder with multiple impedances to optimal respiratory function. Interstitial damage from repeated aspiration and restrictive disease imposed by spinal curvature reduce pulmonary function measures. These problems are further complicated by chemoreceptor insensitivity, so that hypoxia leads to rapid decompensation.^{20,21} Therefore, it is imperative to have an effective means to clear the bronchi of mucus.

Because the FD patient's cough is often ineffective and traditional chest physiotherapy cannot always be employed due to GI or cardiovascular problems, HFCWO therapy offers some immediate advantages. HFCWO treatment can be administered in the upright position and does not require patient cooperation or coordination. Furthermore, the individual patient can administer it, which is an attractive option for the adolescent patient. HFCWO is able to maintain a consistent, effective, and safe chest ther-

Table 3—Health Measure Outcomes After 1 yr of HFCWO Usage in 13 Patients*

Health Measure Outcomes	Prestudy Year	Study Year	p Value†
Doctor visits per year	11 (9 to 12)	5 (4 to 8)	0.0005
Days absent	32 (30 to 60)	9 (8 to 20)	0.0002
Antibiotic courses	8 (6 to 13)	4 (2 to 6)	0.0005
Days receiving antibiotics	85 (50 to 106)	34 (20 to 47)	0.0002
Pneumonia episodes	3 (2 to 3)	1 (0 to 2)	0.0156
Hospitalizations	1 (1 to 2)	0	0.0161

*Data are presented as median (IQR).

†Wilcoxon signed-rank test.

apy irrespective of respiratory muscle weakness, weak cough, patient position, or compromised thoracic space (scoliosis). In pediatric patients with other chronic respiratory problems such as cystic fibrosis, HFCWO has been shown to increase mucus mobilization, improve pulmonary function, and reduce costs for insurance payers and hospitals.^{14–17}

In this 1-year study, we noted a dramatic improvement in all measured health outcomes. Specifically, our FD patients were better able to tolerate intercurrent infections as demonstrated by a statistically significant decrease in doctor visits, antibiotic use, job/school absences, and number of hospitalizations (Table 3), which led to a positive impact on overall quality of life and health-care costs. Pulmonary function measures exhibited statistically significant improvements in FVC and PEFr, and positive signed-rank statistics for percentage of predicted FVC and FEV₁ (Table 2). It is possible that the lack of sustained improvement in all pulmonary functions was a reflection of decreased compliance over time or that the patients had irreversible changes or that poor coordination of breathing made this an unreliable parameter to assess efficacy.

In assessing the implications of the results of this study, it should be remembered that this was an unblinded trial. A number of the outcome parameters were also dependent on patient recall. Additionally, the fact that patients were enrolled in a formal trial could have influenced the results. Nevertheless, overall results were positive and suggest that HFCWO may be a valuable tool in the care of these patients.

CONCLUSION

In this small, nonrandomized study of FD patients, HFCWO effected significant improvements in all measured health outcomes, including pneumonias, hospitalizations, antibiotic courses, antibiotic days, doctor visits, and absenteeism. Oxygen saturation values improved as well. FVC values demonstrated sustained improvement. Although no specific quality-of-life measure was included in this study, objective evidence of increased function such as increased attendance at school and fewer hospitalizations suggests improvement in quality of life. The decrease in antibiotic use and in the number of hospitalizations also suggests that study participants experienced health-care cost reductions as a result of HFCWO therapy. Although the sample size is insufficient to permit broad generalization, results suggest that HFCWO is beneficial for patients with FD.

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