Comparison of Settings Used for High-Frequency Chest-Wall Compression in Cystic Fibrosis

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BACKGROUND: Cystic fibrosis (CF) patients commonly use a high-frequency chest-wall compression (HFCWC) device for airway clearance that generates oscillatory flow with a sine-wave configuration. Typical HFCWC settings combine a lower Vest inflation pressure setting (eg, 5 on the Vest's arbitrary 1–10 scale for the setting that controls the background pressure of the inflatable vest) with mid-range frequency (14–16 Hz) (lower-pressure/mid-frequency HFCWC). OBJECTIVE: To determine whether HFCWC with higher pressure settings (6–10 on the Hill-Rom Vest's arbitrary 1–10 scale) combined with variable mid-frequencies (8, 9, and 10 Hz, plus 18, 19, and 20 Hz) (higher-pressure/variable-frequency HFCWC) results in greater sputum expectoration than lower-pressure/mid-frequency HFCWC. METHODS: This was a controlled randomized crossover study. Sixteen clinically stable, adult CF patients participated. Patients performed airway clearance with HFCWC, once each with lower-pressure/mid-frequency HFCWC and higher-pressure/variable-frequency HFCWC, on separate occasions. All sputum produced during each session was collected. Patients completed pulmonary function tests before and after each session. RESULTS: Median sputum wet weight was greater with higher-pressure/variable-frequency HFCWC than with lower-pressure/mid-frequency HFCWC (6.4 g, range 0.49–22.0 g, versus 4.8 g, range 0.24–15.0 g, $P = .02$). Dry sputum weight differences did not reach statistical significance (higher-pressure/variable-frequency HFCWC 0.20 g, range 0.009–0.62 g, lower-pressure/mid-frequency HFCWC 0.12 g, range 0.0001–1.0 g, $P = .23$). Higher-pressure/variable-frequency HFCWC and lower-pressure/mid-frequency HFCWC resulted in similar increases in FEV_1 (70 mL vs 90 mL, $P = .21$) and forced vital capacity (80 mL vs 80 mL, $P = .94$). Post-therapy sputum viscoelastic properties did not differ. Patients perceived the 2 regimens as equally comfortable and effective ($P = .35$ and $P = .35$, respectively). CONCLUSIONS: In adult CF patients, single-session higher-pressure/variable-frequency HFCWC resulted in greater sputum expectoration by wet weight, but not other differences, compared to the commonly used lower-pressure/mid-frequency settings. Longer-term comparisons are needed in a larger, more diverse population to determine whether sustained use of the higher-pressure/variable-frequency settings results in clinically important differences in outcomes. (Clinicaltrials.gov registration NCT00685035). *Key words: high-frequency chest wall compression; HFCWC; cystic fibrosis; airway-clearance techniques; bronchial drainage.* [Respir Care 2010;55(6):695–701. © 2010 Daedalus Enterprises]

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Introduction

Progressive loss of lung function is characteristic of cystic fibrosis (CF) lung disease.[1] Airway-clearance techniques facilitate the expectoration of tenacious secretions that otherwise accumulate in the airways.[2] However, higher-quality studies are needed to clearly identify the most effective forms of airway clearance therapy for CF patients.[3,4]

High-frequency chest-wall compression (HFCWC) is a commonly used airway-clearance technique with efficacy similar,[5-7] if not superior,[8-11] to conventional manual percussion and postural drainage. It consists of an air-pulse generator connected to an inflatable vest that fits over the torso. Air pulses are transmitted to the vest, creating chest-wall compressions that enhance tracheal mucus clearance.[8] As with other airway-clearance techniques, vigorous coughing is needed to maximize the effectiveness of HFCWC. HFCWC devices generate air pulses with a sinusoidal or triangular waveform.[12,13] Adjustments in device inflation pressure and frequency of compressions produce differences in the volume of displaced air, as well as flow of air, measured at the mouth of the patient.[8] Hence, selection of settings may be an important determinant of HFCWC efficacy.

It is unclear which pressures and frequencies provide optimal airway clearance. Previous studies of sine-waveform HFCWC that used higher inflation pressure settings (6–10 on the Vest's arbitrary 1–10 scale for the setting that controls the background pressure of the inflatable vest) reported the largest volume of air displacement with low (7–10 Hz) frequencies, and the highest air flow with high frequencies (18–20 Hz).[12,13] However, this combination of higher pressure and variable frequency (higher-pressure/variable-frequency HFCWC) is used by few CF patients. Rather, it appears the vast majority of United States CF centers use lower inflation pressure (4–6 on the Vest's arbitrary 1–10 scale) and one mid-frequency (10–14 Hz, lower-pressure/mid-frequency HFCWC) (personal communication, 2010, Brian Becker, Hill-Rom).

We conducted a controlled randomized crossover study to compare the efficacy, assessed by sputum production, of sine-wave higher-pressure/variable-frequency HFCWC versus lower-pressure/mid-frequency settings HFCWC in patients with mild to moderate CF lung disease. Secondary outcomes included pulmonary function tests (PFTs), sputum viscoelastic properties, and subject perceptions of comfort and efficacy.

Methods

The institutional review board of the University of Minnesota approved this study. Hill-Rom provided support for this research but did not participate in the study's design,

conduct, data analysis, data interpretation, or writing of the manuscript.

Subjects

Subjects were at least 18 years old and seen consistently at the Minnesota CF Center. All had been diagnosed according to Cystic Fibrosis Foundation criteria,[14] had chronic daily sputum production, had baseline FEV_1 and forced vital capacity (FVC) greater than 40% of predicted, and had less than 10% variation in FEV_1 and FVC over the preceding 3 months. All subjects had used HFCWC at least daily for at least 1 year prior to study entry. Six subjects reported using the higher-pressure/variable-frequency settings at baseline, and none recalled using lower-pressure/mid-frequency HFCWC. The remainder were unsure of their baseline settings, or used an HFCWC device that generates triangular compressions. Exclusion criteria included: hospitalization or use of intravenous antibiotics for pulmonary exacerbation within the preceding 2 months, single episode of hemoptysis > 60 mL in the preceding month, and chronic pain managed with narcotics. Enrollment was completed over a 4-month period.

Study Procedures

This was a controlled randomized crossover study. Figure 1 illustrates the study design. Following enrollment, subjects performed their last routine airway-clearance session the evening before each study visit. The following morning, subjects performed PFTs and were then randomly assigned to a session using higher-pressure/variable-frequency HFCWC (the Vest, Hill-Rom, St Paul, Minnesota) or lower-pressure/mid-frequency HFCWC (Table 1). Subjects used their usual nebulized medications during the session. All sputum expectorated during the session was used to determine sputum weight. Additional sputum was collected for 15 min immediately following the session and immediately frozen and saved for biophysical analyses. Subjects then repeated PFTs and completed a 7-item questionnaire that rated the comfort and efficacy of the session using a 5-point scale. Subjects continued their baseline regimen during the subsequent 2-day wash-out period. At the second visit, subjects repeated a protocol identical to the first visit except they used the alternative HFCWC settings.

Masking

Device settings were obscured from the subject's view by placing the air-pulse generator behind a curtain. Only
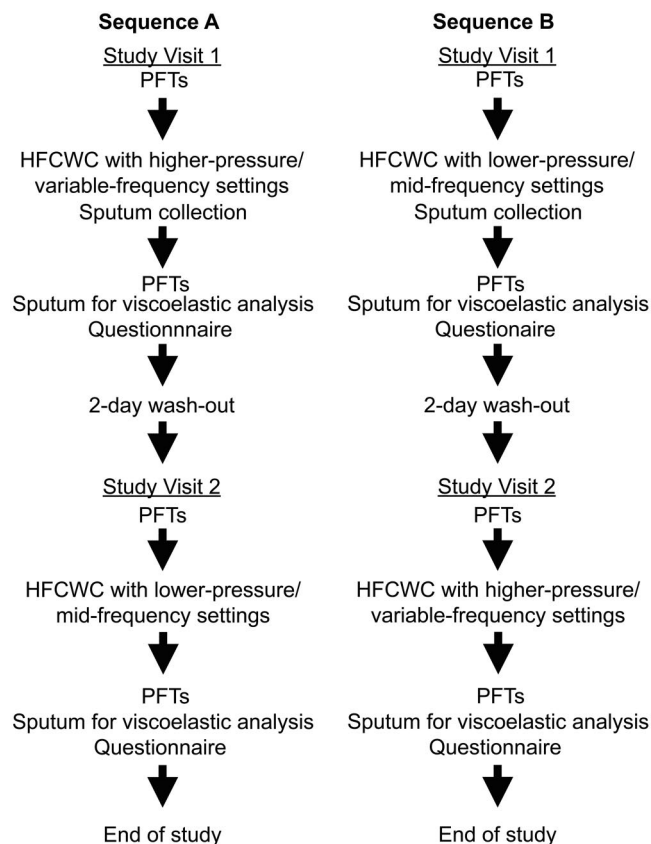
Fig. 1. Schematic of study design and procedures. Patients were randomly assigned to one of 2 possible sequences: perform high-frequency chest-wall compression (HFCWC) with the higher-pressure/variable-frequency settings first and then with lower-pressure/mid-frequency after wash-out; or perform HFCWC with the lower-pressure/mid-frequency settings first and then with the higher-pressure/variable-frequency settings after wash-out. Eight patients were randomized to sequence A, and 8 to sequence B. All subjects completed their assigned sequence.

the respiratory therapists (AH, CW) were aware of treatment assignment for a given study day. The subject was instructed to deflate the vest and forcefully cough 3 times every 5 min, regardless of the regimen being used. Treatment allocations were concealed until after completion of data analysis. Following each session, subjects indicated

whether they thought they had received their baseline settings, different settings, or were unsure.

High-Frequency Chest-Wall Compression Settings and Implementation

The HFCWC vests were optimally sized and adjusted before randomization. Table 1 summarizes the study HFCWC pressures and frequencies. The higher-pressure/variable-frequency settings were derived from previous studies,[12,13] and the lower-pressure/mid-frequency settings from data provided by Hill-Rom. Of 120 United States CF centers that use Hill-Rom HFCWC devices, all but 4 (97%) use a pressure setting of 5 or 6 (on the Vest's arbitrary 1–10 pressure-setting scale) and frequencies of 10–14 Hz (personal communication, 2010, Brian Becker, Hill-Rom). Patients who use the SmartVest HFCWC system (Electromed, New Prague, Minnesota) at more than 100 United States CF centers routinely spend 10 min each at frequencies of 10, 12, and 14 Hz (personal communication, 2010, Chet Sievert, Electromed). All sessions were 30 min duration.

Table 1. HFCWC Settings Used for the Study

	Vest Pressure Setting*	Frequency (Hz)
Higher-pressure/variable-frequency HFCWC†	10	8, 9, 10
	6	18, 19, 20
Lower-pressure/mid-frequency HFCWC†	5	12

* These numbers are not pressures, but a device setting. The Vest uses an arbitrary 1–10 scale for setting the background pressure of the inflatable vest, and the 1–10 scale does not correlate to specific pressure units.
† In the higher-pressure/variable-frequency high-frequency chest-wall compression (HFCWC) sessions the subject spent 5 min at each combination of pressure and frequency, for a total session of 30 min. In the lower-pressure/mid-frequency sessions the subject spent all 30 min at a frequency of 12 Hz and a setting of 5 on the Vest's arbitrary 1–10 pressure scale.

Sputum Weight

All sputum expectorated during the HFCWC session was collected in a pre-weighed specimen container and immediately sealed. Specimens were centrifuged at 21,150 g for 15 min at 4°C, and the supernatant was completely removed to eliminate saliva. The sputum "wet weight" was calculated after re-weighing the container with the sputum pellet. The container was then left open in an oven with the temperature set at 65°C for a minimum of 3 days to allow for complete desiccation. The sputum "dry weight" was calculated after re-weighing the container.

Pulmonary Function Tests

Spirometry and plethysmographic lung-volume measurements were performed according to American Thoracic Society/European Respiratory Society standards.[15,16] To assess ventilation homogeneity, patients underwent single-breath nitrogen wash-out to determine the slope of phase III of the wash-out curve. For this test the patient slowly inhaled 100% oxygen to maximum inspiratory capacity, and the nitrogen concentration was continuously monitored during slow full exhalation. The expiratory nitrogen concentration was plotted against volume, and the slope of phase III of the nitrogen wash-out curve was calculated via computer analysis of the best-fit line through the phase III portion of the curve.[17] These measurements were performed with a plethysmograph (Elite DX, Medical Graphics, St Paul, Minnesota).

Viscoelasticity

Samples were studied with a rheometer (AR1000, TA Instruments, New Castle, Delaware) to assess the dynamic frequency range of stress-strain of a 20 μL sputum sample over driving frequencies of 1–100 rad/s. Shear storage modulus (G′) and shear loss modulus (G″) were determined from these curves after nondestructive creep transformation.[18,19] G′ (or dynamic elasticity) measures stored energy and is a property of ideal solids. G″ is directly proportional to viscosity (viscosity $\times$ frequency) and is a property of ideal liquids. Mechanical impedance (G*) is a measure of resistance to deformation and is the vectorial sum of G′ and G″.

Statistical Analysis

Four subjects (25%) were unable to perform a valid nitrogen wash-out curve, and these results were excluded from the analysis. One dry sputum weight was deemed an outlier, as the dry weight/wet weight ratio was > 0.5, which was 25.5 standard deviations greater than the other 31 study samples. All decisions to exclude data were made before unblinding and before statistical analysis. Descriptive data are reported as frequencies, medians (range), or mean $\pm$ SD, as appropriate. Pre-session versus post-session outcomes with non-normal distributions were compared using a Wilcoxon matched-pairs signed-rank test. Those with normal distributions were compared using paired t tests. Paired dichotomous data were assessed using a McNemar's test. Primary analysis of the crossover data were performed following the method proposed by Grizzle,[20] using parametric analysis for normally distributed data and non-parametric analysis for non-normal data. Both period and carry-over effects were assessed. There was no indication that these effects were significant in any of the measurements assessed (P all $\geq$ 0.20), therefore data were collapsed over periods and treatment effects were assessed using paired comparisons. Analysis was performed using statistics software (SPSS version 17, SPSS, Chicago, Illinois). All results were considered significant at $P < .05$. In a previous study with similar design,[21] the standard deviation for the difference in the mean sputum wet weight between treatment arms was 4.6 g. Assuming the same standard deviation for the current study, enrollment of 16 subjects provided an 80% chance of detecting a $\geq$ 3.5-g difference in the sputum wet weights at a significance level of .05.

Table 2. Baseline Characteristics of the 16 Participants*

Demographics	
Age (mean $\pm$ SD y)	33.3 $\pm$ 7.3
Male/female (n)	6/10
Body mass index (mean $\pm$ SD kg/m^2)	23.3 $\pm$ 3.3
CFTR Genotype (no. patients)	
Δ F508 homozygote	12
Δ F508 heterozygote	4
Sputum Microbiology (no. patients)	
Pseudomonas aeruginosa	11
Staphylococcus aureus	4
Other Gram-negative organisms	2
Pulmonary Function†	
FEV$_1$ (mean $\pm$ SD % predicted)	68 $\pm$ 15
FVC (mean $\pm$ SD % predicted)	82 $\pm$ 15
TLC (mean $\pm$ SD % predicted)	103 $\pm$ 14
RV/TLC (mean $\pm$ SD %)	152 $\pm$ 35
Nebulized Medications Used in Study (no. patients)	
β_2 agonist	16
N-acetylcysteine	13
Cromolyn	5
Dornase alfa	3
Ipratropium bromide	3
Tobramycin	2
Colistin	2
Budesonide	2
7% saline	1

* Based on the standards in the National Health and Nutrition Examination Survey.
CFTR = cystic fibrosis transmembrane regulator
FVC = forced vital capacity
TLC = total lung capacity
RV = residual volume

Table 3. Changes in Pulmonary Function Following HFCWC Session

Changes in PFTs (pre vs post HFCWC)	Higher-Pressure/ Variable-Frequency HFCWC	Lower-Pressure/ Mid-Frequency HFCWC	P
FEV_1 (mean ± SD mL)	70 ± 90	90 ± 120	.21*
FVC (mean ± SD mL)	80 ± 160	80 ± 230	.94*
Residual volume (median and range mL)	−10 (−1,200 to 170)	0 (−810 to 530)	.75†
Total lung capacity (median and range mL)	−70 (−410 to 530)	−30 (−410 to 370)	.57†
RV/TLC (%, range %)†	0 (−13 to 3)	0 (−10 to 11)	.87†
Expiratory reserve volume (median and range mL)	10 (−320 to 1,300)	−60 (−540 to 120)	.32†
Slope of phase III of nitrogen wash-out curve	0.17 (−0.89 to 1.1)	0.23 (−1.8 to 1.6)	.64†

* Via paired-samples *t* test.
† Via Wilcoxon matched-pairs signed-rank test.
HFCWC = high-frequency chest-wall compression
FVC = forced vital capacity
RV = residual volume
TLC = total lung capacity

Table 4. Viscoelasticity of Sputum Obtained at the End of the HFCWC Session*

	Higher-Pressure/ Variable-Frequency HFCWC median (range)	Lower-Pressure/ Mid-Frequency HFCWC median (range)	P*
G′ (storage modulus)			
At 1 rad/s	4.43 (0–162)	4.61 (0–119)	.88
At 100 rad/s	107.3 (11.2–1,352)	130.7 (34–24,850)	.64
G″ (loss modulus)			
At 1 rad/s	10.7 (0.4–205)	7.4 (0.93–144)	.88
At 100 rad/s	1,224 (383–11,270)	862 (0–7,603)	.43
G* (mechanical impedance)	11.6 (0.4–205)	7.9 (0.93–187)	> .99
Percent solids	3.8 (1.8–10.9)	4.9 (1.1–10.7)	.56

* Via Wilcoxon matched-pairs signed-rank test.
HFCWC = high-frequency chest-wall compression

Results

Characteristics of the 16 subjects who completed the study protocol are summarized in Table 2. Technical problems precluded one subject from completing day 1 of the protocol; that subject completed the entire protocol 2 weeks later. No carryover effects were noted for any of the outcomes of interest ($P > .2$), which allowed for performing comparisons without adjustments. Use of the higher-pressure/variable-frequency settings resulted in significantly greater median sputum wet weight expectoration (6.4 g, range 0.49–22.0 g, versus 4.8 g, range 0.24–15.0 g for lower-pressure/mid-frequency HFCWC, $P = .02$). Median sputum dry weight was greater with the higher-pressure/variable-frequency settings, but the difference was not statistically significant (0.20 g, range 0.009–0.62 g, versus 12 g, range 0.0001–1.0 g, $P = .23$). Inclusion of the single outlier dry weight did not significantly alter the result ($P = .30$).

Use of higher-pressure/variable-frequency HFCWC and lower-pressure/mid-frequency HFCWC produced similar, modest gains in pre-therapy versus post-therapy spirometry. Airway clearance had a minimal effect on lung volumes, regardless of HFCWC settings (Table 3). The slope of phase III of the nitrogen wash-out curve increased following HFCWC, suggesting increased heterogeneity in ventilation, but the effect of the different settings was similar.

Twelve subjects (75%) produced sputum suitable for measurement of viscoelastic properties, and these properties did not differ following higher-pressure/variable-frequency and lower-pressure/mid-frequency HFCWC (Table 4). The similar proportion of solids suggests equal quality of the sputum samples.

As a group, the subjects did not perceive the comfort or effectiveness of therapy with the 2 settings differently (Fig. 2). No subjects experienced pain, nausea, heartburn, or arm numbness. Two (12%) noted dyspnea with use of the higher-pressure/variable-frequency settings, compared to none with the lower-pressure/mid-frequency settings ($P = .50$ via McNemar's test). Only 6 subjects recalled using the higher-pressure/variable-frequency settings at
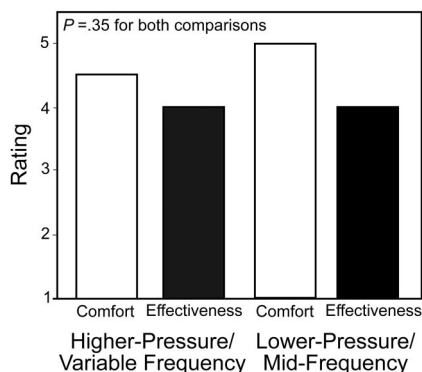
Fig. 2. Subjects' perceptions of comfort and effectiveness of high-frequency chest-wall compression (HFCWC) session using the higher-pressure/variable-frequency and the lower-pressure/mid-frequency settings. Subjects used a 5-point scale to rate comfort (1 = very uncomfortable, 5 = very comfortable) and effectiveness (1 = minimally effective, 5 = maximally effective) of each airway-clearance session.

baseline, and none recalled using lower-pressure/mid-frequency, which limited the assessment of blinding effectiveness. However, of the 6 baseline users of higher-pressure/variable-frequency HFCWC, only 2 consistently differentiated when they received higher-pressure/variable-frequency rather than an alternative to their baseline.

Discussion

This study is noteworthy for finding greater sputum expectoration, based on sputum wet weight, with a protocol using higher pressures and variable frequency. This protocol uses settings that differ significantly from those in use by most CF centers. The difference in dry sputum weight was not statistically significant. Secondary end points, including sputum viscoelasticity and changes in PFTs, did not differ. Subjects' perceptions of comfort and efficacy were also comparable. However, baseline use of the higher-pressure/variable-frequency settings among some of the subjects may, in part, account for the good tolerance observed in the current study. In our center's experience, some patients unfamiliar with the higher-pressure/variable-frequency settings better tolerated a step-wise escalation of pressure and frequency.

These results are consistent with previous HFCWC studies, in which air flow and volume of displaced air were measured at the mouth of subjects at various frequencies, using a sine-wave device similar to the one employed in our study.[12,13] In a study of 100 CF out-patients, Milla et al found that lower frequencies produced the greatest volume of displaced air, while higher frequencies generated the highest flow.[13] Fifteen frequencies between 6 Hz and 20 Hz were tested. Subsequent adoption of the higher-pressure/variable-frequency settings was based on allowing equal

time for larger volumes and higher flows, although the relative importance of the two is unknown. In contrast, a study performed by the manufacturer of The Vest (Hill-Rom, St Paul, Minnesota) found the highest HFCWC-induced flow at a frequency of 12 Hz, leading to widespread use of 10–14 Hz. However, that study included only 10 normal subjects and tested only 3 frequencies: 5, 12, and 20 Hz (personal communication, 2010, Brian Becker, Hill-Rom).

Pressure settings have received little emphasis in studies of HFCWC.[21,22] Zucker et al studied a sine-wave HFCWC in 10 normal subjects and found that higher background pressure and higher frequency generated higher esophageal pulse pressure and airway flow.[22] Insufficient HFCWC pressure might decrease secretion mobilization, independent of the frequency setting. Therefore, it is important that trials involving HFCWC devices attempt to determine the most effective pressure setting in order to accurately assess the efficacy of the devices.

As with most short-term comparisons of airway-clearance techniques, this study did not demonstrate significant treatment-related differences in spirometry.[4,21,23] This cumulative experience suggests that short-term changes in spirometry may be insensitive for detecting differences in airway-clearance modalities. HFCWC is known to decrease end-expiratory lung volume,[24] but lung volume changed minimally in our study. Deflation of the vest with subsequent deep breathing and cough every 5 min while performing therapy may account for the preservation of post-therapy lung volumes. The higher-pressure/variable-frequency and the lower-pressure/mid-frequency settings increased the slope of phase III of the nitrogen wash-out curve to a similar degree, although the lack of valid maneuvers in 25% of subjects limited our ability to detect a difference. An increased slope of phase III of the nitrogen wash-out curve reflects greater heterogeneity in ventilation, possibly due to increased mobilization of peripheral airway secretions, and was previously noted following use of a triangular-wave HFCWC device, but not a sine-wave HFCWC device.[21]

Post-therapy sputum viscoelasticity was also similar following the 2 regimens. This is consistent with a previous study and suggests that the beneficial effects of oscillatory flow in the airways may be independent of changes in sputum viscoelasticity.[21]

Strengths of the study design often absent in previous investigations of airway-clearance techniques included masking, explicit inclusion criteria, concealed allocation, adequate wash-out period, standardized study interventions, and comprehensive outcomes assessment.[3,4] However, we were unable to fully assess the effectiveness of the blinding process. The study has other important limitations. Sputum weight varied more than anticipated, and, as a result, the study was underpowered to detect differences in

the primary outcomes. In addition, use of sputum weight as an outcome can be problematic due to variable ability of subjects to expectorate secretions, potential contamination with saliva, variability in secretion production, and difficulty differentiating increased mucus production from increased clearance.[25] The crossover design, short study duration, consistent adherence to study protocol, and exclusion of clinically unstable subjects reduced the likelihood that these factors interfered with the accuracy of our measurements. Nonetheless, whether increased sputum weight is a good surrogate marker for long-term outcomes remains unknown.

The generalizability of the results is limited by our exclusion of patients with FEV_1 less than 40% of predicted. Also, the baseline inhaled medication regimen of our subjects entailed greater use of inhaled N-acetylcysteine and cromolyn, and less dornase alfa and hypertonic saline, compared to most other United States CF centers. Another concern is that the 2 regimens may have a complementary effect on airway clearance, in which case the subjects' greater baseline use of the higher-pressure/variable-frequency settings could have falsely reduced the efficacy of the higher-pressure/variable-frequency regimen. Use of the lower-pressure/mid-frequency settings is uncommon at our center, which precluded balanced recruitment in terms of baseline HFCWC regimen.

Conclusions

In summary, the current study indicates a possible advantage to using the higher-pressure/variable-frequency settings for HFCWC in CF patients. The study offers a rigorous, unbiased comparison of the 2 regimens using the same device, but further investigation is needed to assess important long-term outcomes such as frequency of respiratory exacerbations, overall decline in PFT results, and quality of life. Our results also indicate that pressure settings may be an important determinant of HFCWC efficacy, and merit close attention during future comparisons of airway-clearance techniques.

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