ORIGINAL ARTICLE

Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis

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ABSTRACT

Background Positive expiratory pressure (PEP) is the most commonly used method of airway clearance (AC) in Canada for patients with cystic fibrosis (CF) whereas, in some countries, high frequency chest wall oscillation (HFCWO) is the preferred form of AC. There have been no long-term studies comparing the efficacy of HFCWO and PEP in the CF population.

Objectives To determine the long-term efficacy of HFCWO compared with PEP mask therapy in the treatment of CF as measured by the number of pulmonary exacerbations (PEs).

Methods A randomised controlled study was performed in 12 CF centres in Canada. After a 2-month washout period, subjects were randomised to perform either HFCWO or PEP mask therapy for 1 year.

Results 107 subjects were enrolled in the study; 51 were randomised to PEP and 56 to HFCWO. There were 19 dropouts within the study period, of which 16 occurred prior to or at the time of randomisation. There were significant differences between the groups in the mean number of PEs (1.14 for PEP vs 2.0 for HFCWO) and time to first PE (220 days for PEP vs 115 days for HFCWO, p=0.02). There was no significant difference in lung function, health-related quality of life scores or patient satisfaction scores between the two groups. PEP mask therapy required a shorter treatment time.

Conclusions The results of this study favour PEP and do not support the use of HFCWO as the primary form of AC in patients with CF.

Clinical Trial Registration number NCT00817180.

Key messages

What is the key question?

- Is high frequency chest wall oscillation (HFCWO) as effective as positive expiratory pressure (PEP) in maintaining health in patients with cystic fibrosis as measured by the number of pulmonary exacerbations (PEs)?

What is the bottom line?

- The number of PEs was significantly higher in patients performing HFCWO compared with those performing PEP.

Why read on?

- This article explains the background, methodology and outcome of a long-term trial studying the effectiveness of HFCWO compared with PEP.

INTRODUCTION

Cystic fibrosis (CF) is a lethal genetic disease caused by abnormalities in cystic fibrosis transmembrane conductance regulator protein function. Depletion of airway surface liquid, dehydrated mucus, chronic inflammation and infection contribute to accumulation of secretions and progressive airway damage.[1 2] Promoting airway clearance (AC) using mucolytics together with airway clearance techniques (ACTs) form the basis for pulmonary therapy in CF care.[3] Guidelines from the British Thoracic Society support with level 1+ evidence the teaching of an ACT to patients with CF to increase mucus transport in the short term (grade A).[4]

The International Physiotherapy Group for Cystic Fibrosis (IPG/CF) has adopted a number of ACTs which are supported by randomised controlled studies as acceptable methods of AC.[5] These include the active cycle of breathing technique, positive expiratory pressure (PEP), oscillating PEP, autogenic drainage and postural drainage and percussion (PD&P). A survey of Canadian CF centres in 2007 revealed that PEP was the ACT of choice for the majority of patients over the age of 7.[6] This was based on the results of comparative trials conducted in Canada, demonstrating equivalence or superiority of PEP therapy compared with PD&P.[7 8]

In the late 1980s another ACT called high frequency chest wall oscillation (HFCWO) was developed. HFCWO involves the use of an inflatable vest/jacket that covers the chest and is attached to an air pulse-generating compressor which rapidly inflates and deflates the vest, producing oscillations to the chest wall of 5–25 Hz. It is proposed that HFCWO enhances mucociliary transport by creating a cough-like expiratory flow bias that shears mucus from the airway walls by enhancing ciliary beat frequency[9] and by altering the rheological properties of mucus.[10] In a Cochrane review on oscillating devices for people with CF, the authors concluded that there was no clear evidence that oscillation was a more or less effective intervention overall than other forms of AC and that more adequately powered long-term randomised

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controlled trials were necessary.[11] One other aspect when considering which ACT to use is cost. The cost of a PEP device with a mask ranges from £40 to £60 whereas the cost of a HFCWO device is approximately £7000. This places a huge economic burden on the family of a patient with CF.

At the onset of this study there were no published long-term randomised controlled studies comparing HFCWO with any other AC technique including PEP. The primary objective of the present study was to determine the efficacy of HFCWO compared with PEP in maintaining respiratory health in patients with CF over a period of 1 year as measured by the number of pulmonary exacerbations (PEs). Secondary outcome measures included time to first PE, changes in lung function between groups and over time and health-related quality of life questionnaires.

METHODS

Study design

This was a 1-year prospective multicentre randomised controlled trial of HFCWO versus PEP as ACTs in the treatment of children and adults with CF. As 73% of participants were performing PEP on enrollment and to avoid any potential bias from using PEP, we included a 2-month washout period between visit 1 and visit 2. During this time participants performed an IPG/CF recommended ACT[5] other than HFCWO or PEP. Subjects were randomised to perform either PEP or HFCWO, but were not informed which ACT they had been assigned until visit 2 which followed the washout period. At visit 2, participants were instructed in their assigned ACT and commenced the 1-year study period using this technique. Although participants were not blinded as to the arm of the study to which they were randomised, physicians and respiratory therapists performing the respiratory assessments and lung function tests, respectively, were unaware of the treatment assignment. Assessments were performed at 3-monthly intervals during the regular visits of the participants to the CF centre, with visit 2 occurring at the commencement of the 1-year study period and visit 6 occurring at the end of 12 months.

Study participants

Eligible participants were CF patients over the age of 6 years with a confirmed diagnosis of CF who were clinically stable and met the inclusion/exclusion criteria (see online supplement).

The study took place between October 2008 and April 2012 in 12 CF Canada accredited CF centres across Canada (eight paediatric and four adult centres). Enrollment was completed by December 2010. The study was approved by the research ethics boards at each centre and written informed written consent/assent was obtained from each participant or their parents as appropriate.

Protocol

The principal investigators and research coordinators from each participating CF centre met for a 2-day training session prior to commencing the study. Both PEP and HFCWO techniques were reviewed along with practical training. RespirTech (St Paul, Minnesota, USA) representatives provided the training for HFCWO and supplied pre-programmed devices for the study. The PEP masks and devices were supplied by Smith Medical (Norwell, Massachusetts, USA). Neither company was involved in the design of the study nor did they provide any remuneration for the study.

At visit 2, after the 2-month washout period, study participants were instructed to perform the ACT assigned twice daily for a period of 1 year. Participants who were normally prescribed once daily AC prior to enrollment in the study were permitted to continue this frequency during the study. A Data Safety Monitoring Board (DSMB) was instituted as mandated by Good Clinical Practice Guidelines. The study was registered at Clinical Trials.gov (identifier NCT00817180).

PEP mask technique

PEP was performed using a TheraPEP system with a mask. Participants were instructed to perform 15 breaths through the PEP mask followed by 2–3 huffs. This was repeated for six cycles (for further details see online supplement).

High frequency chest wall oscillation (HFCWO)

The HFCWO device used in this study was the inCourage System (RespirTech) as the triangular wave form produced by this system is thought to increase airflow velocity more than other devices.[12] For the purposes of this study, the 30 min pre-programmed ramped Quick Start Program was used. Six 5-min cycles were performed, with the participant performing 2–3 huffs between cycles (for further details see online supplement).

Outcome measures

The primary outcome measure was the number of PEs requiring the use of an oral, inhaled or intravenous antibiotic. This definition was the same as that used by Saiman *et al* in the azithromycin study,[13] and was based on the Early Pseudomonas Infection Control (EPIC) study with the exception that the duration of symptoms must have been longer than 3 days instead of 5 days (see online supplement).[14] When a subject was prescribed an antibiotic, the prescribing physician completed an antibiotic utilisation form which included the signs and symptoms on which the PE was based.

Secondary outcomes measures included time to first PE; number of courses of intravenous antibiotics; changes in lung function; and health-related quality of life questionnaires. Lung function was measured using standardised equipment according to the American Thoracic Society guidelines.[15] The prebronchodilator forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$) were reported as absolute change and as a change in percent predicted from baseline using the National Health and Nutrition Examination Survey (NHANES) III scales.[16]

Quality of life was evaluated using the Cystic Fibrosis Questionnaire V.2.[17 18] A satisfaction questionnaire using a visual analogue scale of 1–5 was used to evaluate differences in satisfaction between treatment modalities. This measured the comfort, independence and flexibility in performing the treatments.

The above assessments were performed at 3-monthly intervals. In addition, participants received a monthly telephone call from study coordinators to check on adverse events and to encourage good adherence. They also kept a daily diary reporting any adverse events and checking off when they had performed their daily AC.

Statistics

As there was no standardised definition for PEs in patients with CF, we based our preliminary sample size calculations on Fuchs' criteria as used in the hypertonic saline trial by Elkins *et al*.[19] In that study the mean number of PEs per participant over a 1-year period in the control group was 2.74 compared with 1.37 in the treatment group (difference 1.42). Thus, we based our study size on the mean number of exacerbations in the control group being 2.80 per year. To be able to detect a difference of 50% between the PEP and HFCWO groups, we would require 70 participants in each group (SD estimated to be 2.89). This statistical calculation has a power of 80% and $\alpha=0.05$ to detect a change from the control group. We calculated we would need to enroll 170 participants (85 in each group), which would

allow for a 10% dropout in each group. This was later modified (see Results section).

Participants were randomised into two groups by an independent statistician using a computer generated randomisation table. As we were studying both children and adults and as a positive *Pseudomonas* status has been associated with a greater decline in lung function,[20] we matched the subjects for age, sex and *Pseudomonas* status. The statistician also attempted to block patients within each centre to control for any treatment differences between centres. Statistical analysis was performed using SPSS V.18 according to the intention-to-treat principle. The primary outcome of number of PEs was analysed using the Mann–Whitney non-parametric test. A cross-tabulation was also performed using the Pearson χ^2 test for all categorical data. Time to first PE was analysed using Kaplan–Meier survival analysis including a log rank test. Multivariate analysis was used to analyse the lung function data with repeated measures of ANOVA used to compare within-group differences between visits and between interventions. Satisfaction questionnaires were also analysed using the Mann–Whitney non-parametric test. A p value of <0.05 was considered significant.

RESULTS

Participants

Study enrollment was stopped in December 2010 once 107 patients were enrolled after discussion with the DSMB. This decision was based on the following considerations: (1) failure to recruit the expected number of subjects in the proposed time frame; and (2) the initial statistical calculations were based on the Fuchs' criteria[21] for PEs rather than the modified EPIC trial definition[14] that served as the predefined primary outcome measure in this study, so the initial sample size calculation was considered rather conservative. The DSMB performed an interim analysis in October 2011 after two-thirds of the participants had completed the study due to an imbalance in the reported incidence of serious adverse events for PEs between the two groups and proposed that the study be completed with the current sample size.

Fifty-one subjects were randomised to the PEP arm of the study and 56 to the HFCWO arm. Both groups were clinically comparable at enrollment (table 1). At visit 2, when subjects were to commence their prescribed arm of the study, there were eight dropouts from each arm of the study. Thus, at visit 2, 43 participants commenced on the PEP arm and 48 on the HFCWO arm. The study results were analysed on the intention-to-treat premise based on these participants. Between visit 2 and visit 6 at the end of the study there was one further dropout in the PEP group and two in the HFCWO group. Thus, 42 subjects in the PEP arm and 46 in the HFCWO arm completed the study (figure 1).

Table 1 Patient demographics and baseline characteristics

	PEP	HFCWO
Number of subjects	51	56
Median age (years)	12 (range 6–41)	11 (range 6–47)
Age 6–11 years	25	31
Age 12–17 years	18	14
Age 18–47 years	8	11
Female/male	25/26	25/31
Pseudomonas positive/negative	17/34	19/37
FVC percent predicted	100.7±13.8	94.3±14.8
FEV_1 percent predicted	92.9±17.2	85.8±18.0
$FEF_{25–75}$ percent predicted	79.7±31.6	73.8±32.5
Body mass index	18.43±3.37	18.62±4.55
Delta F508 homozygous	47%	43%
Regular use of inhaled bronchodilator	88%	88%
Regular use of hypertonic saline	12%	13%
Regular use of rhDNase	25%	30%
Regular use of inhaled steroids	55%	48%
Regular use of an inhaled antibiotic	24%	20%
Regular use of azithromycin	19%	14%
Number of patients performing ACT once daily	12	12

Data for body mass index, FVC, FEV_1 and $FEF_{25–75}$ are represented as mean±SD.
ACT, airway clearance technique; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HFCWO, high frequency chest wall oscillation; PEP, positive expiratory pressure.

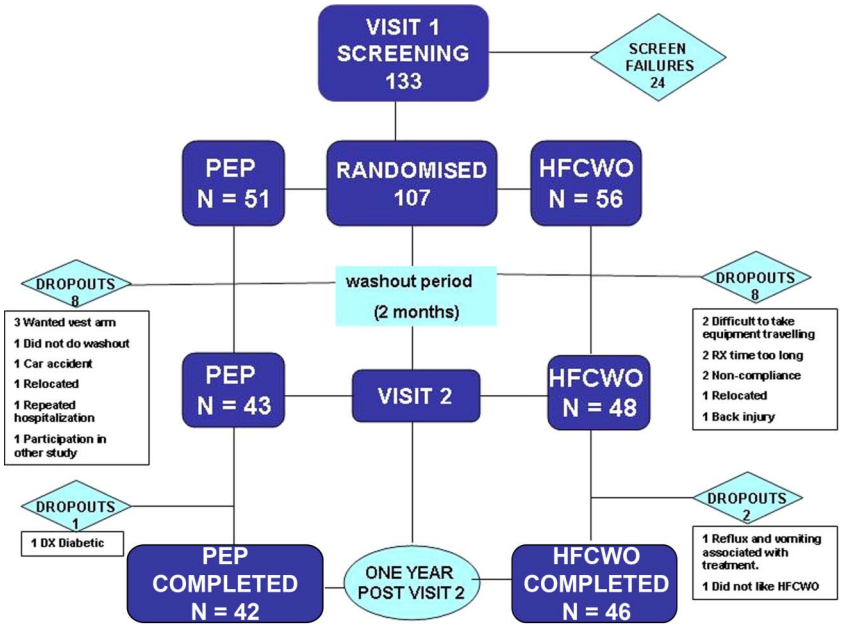

Figure 1 Flow chart of enrollment. HFCWO, high frequency chest wall oscillation; PEP, positive expiratory pressure.

Table 2 Pulmonary exacerbations (PEs) reported for the two study groups

	PEP	HFCWO	p Value
Number of PEs requiring antibiotics	49 Median1.00 (0.00, 2.00)	96 Median 2.00 (1.00, 3.00)	0.007*
Number of PEs requiring intravenous antibiotics	6 Median 0.00 (0.00, 0.00)	19 Median 0.00 (0.00–1.00)	0.258
Median length in days of intravenous antibiotics per treatment	14.5 (13, 17)	14 (9.5, 15)	0.484
Number of PEs requiring oral/inhaled antibiotics	43 Median 1.00 (0.00, 2.00)	77 Median 2.00 (1.00, 3.00)	0.025*

*Significantly different at the p=0.05 level.
Data are presented as median (25%, 75% percentiles)
HFCWO, high frequency chest wall oscillation; PEP, positive expiratory pressure.

Pulmonary exacerbations

The overall number of PEs requiring oral, inhaled or intravenous antibiotics was 1.59 per participant and was evenly distributed throughout the 12 CF centres. The number of PEs per participant in the PEP group was 1.14 compared with 2.0 in the HFCWO group (p=0.007, table 2). In addition, while the overall incidence was low, the number of PEs requiring intravenous antibiotics in the HFCWO group was more than three times the number in the PEP group. The time to first PE ($T_{½}$) in the PEP group was 220 days compared with 115 days in the HFCWO group (p=0.02), as shown in the Kaplan–Meier plot in figure 2.

Lung function

As seen in figure 3, no significant difference in FVC, FEV_1 and $FEF_{25–75}$ between the two groups was demonstrated. Absolute FVC and FEV_1 increased significantly over the 1-year period (data not shown). FVC and FEV_1 expressed as percent predicted and analysed as change in percent predicted from baseline also increased significantly in both groups.

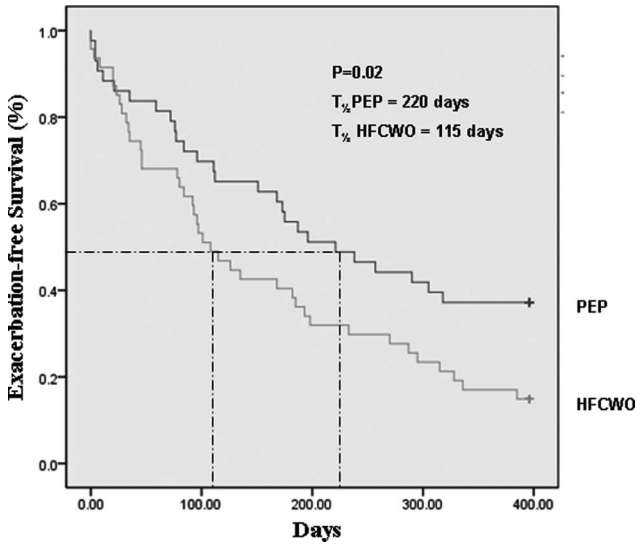

Figure 2 Kaplan–Meier plot of time to first pulmonary exacerbation (PE). $T_{½}$ refers to time when 50% of subjects have experienced their first PE. HFCWO, high frequency chest wall oscillation; PEP, positive expiratory pressure.

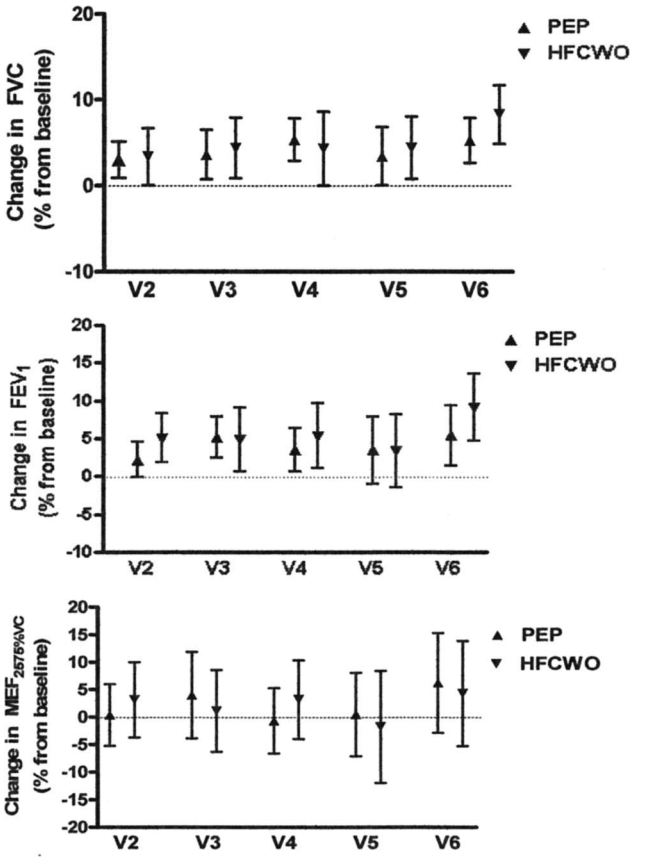

Figure 3 Changes in percent predicted for lung function. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HFCWO, high frequency chest wall oscillation; $MEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; PEP, positive expiratory pressure.

Health-related quality of life

The CF questionnaire data were analysed for change from baseline and are reported as mean±SD for the PEP and HFCWO groups, respectively, for the following domains: physical (−0.84±3.3 vs −3.04±13.0), emotional (0.48±11.9 vs −3.13±11.6), treatment burden (−2.55±20.6 vs −3.60±18.2), respiratory (2.98±17.0 vs 0.19±17.1), digestion/weight (−3.28±19.0 vs −2.12±25.1). The changes in the respiratory symptoms score in either group or between groups did not reach the minimally clinically important difference of 4 reported by Quittner *et al*.[22]

Comfort, independence, flexibility, treatment time and adherence

The visual analogue scores for comfort, independence and flexibility are shown in table 3. No significant differences were observed for comfort and independence between PEP and HFCWO. Participants scored flexibility higher in the PEP group than in the HFCWO group, and this was related to the flexibility in where they could perform their ACT. Treatment time was significantly shorter in the PEP group. The recommended number of treatments per day was equivocal in both groups. Adherence, as reported through daily dairies, was high with participants missing only 6% of treatments in each group.

Table 3 Treatment time, comfort, flexibility and adherence in the two study groups

Self-reported measure	PEP	HFCWO	p Value
Treatment time (min)	20 (15, 20)	30 (20, 35)	<0.001
Comfort 1–5	5 (4, 5)	5 (4, 5)	0.474
Independence 1–5	4 (3, 5)	4 (3, 5)	0.427
Flexibility 1–5	5 (4, 5)	4 (3, 5)	<0.001
Mean number times per day	1.75	1.76	0.962
Mean number of misses per week	0.5	0.5	

Data are presented as median (25%, 75% percentiles).
HFCWO, high frequency chest wall oscillation; PEP, positive expiratory pressure.

Data, presented as median and 25%, 75% percentiles except where stated otherwise, were measured on a Likert scale of 1–5, with 1 being the least comfortable, independent and flexible and 5 being the most comfortable, independent and flexible.

Adverse events

The total number of adverse events was not significantly different between the two groups (163 in the PEP vs 200 in the HFCWO group). However, there were significantly more adverse events related to the lower airways in the HFCWO group than in the PEP group (mean 2.46 vs 1.72, p=0.023). These included increased cough, chest infection, haemoptysis, decreased lung function and chest pain (for further details see online supplement and table 4).

DISCUSSION

This multicentre study is the first long-term randomised trial comparing HFCWO and PEP in the treatment of CF. It included 12 children and adult CF centres in Canada, so the results can be generalised across a broad CF population. The study was limited by the fact that the majority of participants were on PEP prior to the study, although attempts were made to limit any potential bias from this by having a washout period. In addition, although participants were matched for randomisation purposes, this did not take into account whether there were any differences between groups in the number of PEs in the year prior to the study. However, the results did show that the number of PEs in the HFCWO group was significantly higher than in the PEP group. This is an important finding as both the number of PEs and the time to PEs have been associated with greater lung function decline and higher morbidity and mortality.[23]

Table 4 Adverse events

	PEP	HFCWO	Total
n	43	48	91
Total adverse events	163	200	363
Median (lower–upper quartile)	3 (2–6)	4 (2–6)	4 (2–6)
Adverse events leading to study device interruption	7	10	17
Adverse events leading to study device discontinuation	2	3*	5
Serious adverse events (all causes) (all resulted in hospitalisation)	14 (6 patients)	27 (7 patients)	41 (13 patients)
Serious adverse events due to PE (all resulted in hospitalisation)	6 (6 patients)	19 (14 patients	25 (20 patients)

*One adverse event led to study device discontinuation because it coincided with the end of the study for that subject.
HFCWO, high frequency chest wall oscillation; PE, pulmonary exacerbation; PEP, positive expiratory pressure.

Previous AC studies have used pulmonary function and sputum weight as primary outcome measures; however, the number of PEs and the time to first PE may provide a more sensitive measure that captures clinical response to treatment.[19] AC interventions may affect lung function decline, but studies that assess change in the rate of pulmonary function decline require a much larger sample size or longer duration of follow-up.[23] A recent analysis suggested that 50% of lung function decline is explained by PEs, thus quantification of PEs may potentially serve as a surrogate for this outcome measure.[24]

HFCWO was first studied in an uncontrolled retrospective study demonstrating improved lung function after it was introduced.[25] Several short-term studies have suggested that HFCWO may be as effective as PD&P.[26–30] A recent study by Osman *et al*[31] comparing HFCWO with participants' usual ACT found that significantly more sputum was produced with participants' usual ACT. Sontag *et al*[32] recently published the results of a long-term study comparing HFCWO with PD&P and Flutter. The study was discontinued early due to a high dropout rate in the PD&P and Flutter groups. Although the study did suggest higher satisfaction rates with HFCWO, there was a significantly steeper decline in $FEF_{25–75}$ in this group. Previous studies therefore do not provide strong support for the efficacy of HFCWO as the primary form of ACT, and this is supported by the findings of this trial. In our study $FEF_{25–75}$ was trending downwards, but increased again between visit 5 (at 9 months) and visit 6 (at 12 months). When we examined this effect, we found that 30 of 46 subjects in the HFCWO group required antibiotics for a PE during this time. The increase may therefore have been a treatment effect of the antibiotics and warrants further investigation.

Reported adherence rates for both HFCWO and PEP, although of limited reliability, were well above the previously documented adherence rates of 51–74% in childhood, 50% in adolescence and 30–32% in adulthood.[33] Interest in participating in the study due to perceived effectiveness of a treatment may have led to improved adherence and treatment satisfaction.[32] Close contact and telephone calls from study coordinators may also have contributed to increased adherence. The high adherence may explain the significant increase in percent predicted FEV_1 and FVC in both groups from their baseline value.

Although a full cost analysis has not been performed, several cost factors need to be considered when deciding which ACT to use. First, the cost of a PEP mask is significantly less than a HFCWO device (approximately £50 and £7000, respectively). Second, in order to maintain health, the number of hospitalisations for PE in this study was three times more in the HFCWO group than in the PEP group (19 vs 6). The cost of hospitalisation is significant for our health economy and also causes a significant burden for the family of people with CF. Thus, at a time when we are looking to reduce health costs, unless there is strong evidence to support the use of more expensive equipment we cannot justify the cost.

CONCLUSIONS

The relatively lower PE rates and their later onset in patients performing PEP therapy compared with HFCWO supports the use of PEP as the primary ACT in patients with CF aged >6 years. This is the first long-term efficacy trial comparing HFCWO with any other ACT, and the results of this study do not support the use of HFCWO as the primary means of AC therapy in patients with CF. Additional evidence is needed to

evaluate whether HFCWO combined with other forms of ACT is efficacious in these patients. Health costs also need to be a factor when considering which ACT to use.

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Contributors MMcI, NA, GD, LCL, BO, FR, RM and JLA: literature search; MMcI, BO and JLA: data collection; MMcI, NA, RM, BO and JLA: data analysis; MMcI, NA, GD, LCL, FR, RM, BO and JLA: data interpretation; MMcI, NA, GD, LCL, BO, FR, RM and JLA: manuscript preparation, review and approval: all authors. MMcI is the guarantor of the study.

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Competing interests None.

Ethics approval This was a multicentre study involving 12 sites. Ethics approval was obtained from the ethics board of each centre prior to any subjects being enrolled at that centre.

Provenance and peer review Not commissioned; internally peer reviewed.

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Appendices for On-Line supplement.

Study design

Inclusion criteria: a confirmed diagnosis of CF, FEV_1> 45% predicted as calculated by Wang reference equations;[1] a willingness to adhere to the prescribed treatment regimen, study visits, and study procedures. Exclusion Criteria were: diagnosis of Allergic Broncho-Pulmonary Aspergillosis, positive culture for *Burkholderia cepacia* complex within the previous year; active treatment for Non- Tuberculosis Mycobacteria; use of intravenous antibiotics within the previous 14 days of enrollment; initiation and or change in maintenance therapy within 14 days of enrollment; use of systemic corticosteroids (1mg/kg if < 20 kg or 20 mg of prednisone per day) within 14 days of enrollment; concurrent participation in another interventional study; haemoptysis of over 20 milliliters on more than 2 occasions within the previous 30 days; pneumothorax in the preceding six months; or presence of a condition or abnormality that in the opinion of the site CF physician would compromise the safety of the patient.

79 participants (73%) commencing the study were using PEP as their primary airway clearance technique (ACT), although, the method of performing PEP was not standardised across the participants. Other ACTs used at enrollment included, 11 participants were using postural drainage and percussion with no tip, 5 were using oscillating PEP devices, 4 were performing the Active Cycle of Breathing Technique, 4 were performing Autogenic Drainage, 2 were using a High Frequency Chest Wall Oscillation device and 2 were primarily using exercise as their ACT. To avoid any potential bias from using PEP, we included a washout period where the participants had to change to another technique for two months prior to visit 2. At visit 2, the subjects were taught either HFCWO or PEP, both to be performed in a standard method as per study Protocol. Training had been given during the 2 day training session training given to Principal Investigators and Research Coordinators. Thus the study authors took many steps to minimise any effect from subjects entering the study using PEP. In addition in Canada as part of our Physiotherapy Standard of Care, each of the participants enrolled in the study would have known at least 1 -2 other ACTs than PEP and were not dependent on a knowledge of only one technique.

Visit 2 was the beginning of the one year study period. Assessments including pulmonary function tests, satisfaction questionnaires and health Related quality of life scores were performed at 3 monthly intervals with visit 3 at 3 months, visit 4 at 6 months, visit 5 at 9 months and visit 6 at 12 months.

Blinding

Every effort was made to ensure that the Physicians and Respiratory Therapists were blinded as to which technique the study participants were performing. Any clinic papers relating to ACT had labels affixed indicating that this patient was on the Vest study, do not ask any questions about their ACT. In addition, participants were told not to divulge to anyone which ACT they were performing. Physicians were not allowed to ask the subjects which ACT technique they were doing.

PEP technique

There are many PEP devices on the market. The original PEP mask was made by Astra-Meditec and consisted of an Ambu mask to which an inspiratory valve and an expiratory valve are attached. On the expiratory valve, a resistor is attached to create a back pressure of between 10 – 20 cms H_2O. As the Astra-Meditec device is not available in Canada an alternative device called the TheraPEP® was used. It is based on the same physiological principle that the Astra-Meditec

uses. The TheraPEP® consists of an inspiratory one-way valve and a set of expiratory resistors. The expiratory resistor used is the one which creates a back pressure of between 10 – 20 cm H_20 with tidal volume breathing. As the original PEP Mask studies were performed using a facemask and not a mouthpiece, for the purpose of this study we choose to perform PEP using a mask. This helps to ensure that a closed system was kept intact through a series of 12 – 15 breathes through the PEP mask. The regimen used is as follows: Participants were instructed to sit with back straight, and elbows resting on a table. They were asked to hold the mask tight against face with both hands and inspire a slightly larger than normal sized breath (using abdominal breathing) through the mask. They were told that expiration should be slightly active (not forced) against the mask, to create a back pressure of between 10-20 cm of water as measured by manometer. This was repeated for 15 breaths. The mask was then removed from the face and the participant instructed to perform 2 - 3 huffs from a high lung volume to a mid lung volume, followed by a cough and expectoration of any mucus produced. Participants were then to pause for one to two minutes and concentrate on doing relaxed abdominal breathing. The above procedure was to be repeated 6 times.

HFCWO technique

The HFCWO device used in this study was the inCourage System (ICS) ® by RespirTech. This device consists of an air-pulse generator which delivers high frequency air pulses to an inflatable vest that the subject wears. The device has two user-controlled operating adjustments: frequency and pressure. The frequency control determines the air-pulse frequency and is adjustable from 6 to 15Hz. The pressure control adjusts the amount of external chest wall pressure with mean chest wall pressure adjustable from 0 to 15 cm H_2O.

The regimen used was as follows: Participants were instructed to sit comfortably wearing the appropriate size jacket (The participants brought their jacket back at each clinic visit to ensure proper sizing as the participants grew over the year). While wearing the jacket, participants were instructed to breathe normally. For the purposes of this study, the 30 minute pre-programmed ramped Quick Start Program was used. This consists of a programmed ramping up and down between the frequencies of 6 – 15 Hz over a 5-minute period with a pressure set between 60% - 80% as tolerated. This was repeated 6 times. At the end of each 5-minute period, the device automatically paused and the participants were instructed to perform 2 – 3 huffing maneuvers.

Data Safety Monitoring Board

This committee operated under the FDA guidelines for the Establishment and Operation of Clinical Trial Data Monitoring Committees. The committee consisted of a CF Centre Physician who was knowledgeable with clinical trials, a research Physiotherapist with relevant expertise in the area of study and a Methodologist who was knowledgeable about statistical methods for clinical trials. They were an international group from Ireland, England and Australia. The committee were emailed after every cluster of 50 subjects have been enrolled and received SAE's at 3 monthly intervals or sooner if there are more than 10 SAE's within the 3 month period.

They communicated regularly either by email and had teleconferences as issues arose. They had a yearly face to face meeting with the study steering committee. When the DSMB noticed a disproportionate number of pulmonary exacerbations in one arm of the study compared to the

other arm, they requested an interim analysis on the pulmonary function. As there did not appear to be any differences in the pulmonary function between groups, they reported that the study could continue with the number enrolled to completion. Ethic Boards, Health Canada and the FDA were notified of the number of serious adverse events due to pulmonary exacerbations in each group. No further action was taken.

Adverse Events.
A total of 363 adverse events were reported throughout the study period. All 91 patients had at least one adverse event with a median of 4 events (lower quartile: 2, upper quartile:6). A total of 41 Serious Adverse Events (28 patients) were reported throughout the study period, 25 serious adverse events were reported as pulmonary exacerbations (table 2). In terms of the relationship to the study device: 2 events were reported as related, both events occurred in the same patient (HFCWO group) and were reported as abdominal pain during treatment session. Both events were reported as mild, not serious and did not require hospitalization. One event was reported as probably related (PEP group) and consisted of persistent symptoms of an exacerbation not responding to non-pharmacological treatments. The event was reported as severe and serious and the subject was hospitalized for a pulmonary exacerbation. Seventy-six events were reported as possibly related and 284 events were reported as not related. No deaths occurred during the course of the study.

Adverse Event Categories

Adverse Events
Upper airway (cold, sore throat, sinusitis, allergy/sneezing), ear infection, runny nose and dry cough)
Lower Airway (cough, SOB, chest pain, mucus, crackles, secretions, hemoptysis, chest infection, pneumonia, de change in sputum, bronchospasm)
GI (abdominal pain, nausea, vomiting, gastro)
Systemic (fever, decrease appetite, decrease exercise tolerance)
Serious adverse events
Treating physician diagnosed Pulmonary Exacerbation
First Growth of Pseudomonas
Other (headache, polypectomy)

Table. Definition of a pulmonary exacerbation.

The presence of a pulmonary exacerbation is established by the following:

One of the major criteria alone OR two of the minor signs/symptoms and fulfillment of symptom duration

Major Criteria: One finding alone establishes the presence of a pulmonary exacerbation

1. Decrease in FEV1 of ≥10% from best baseline within past 6 months, unresponsive to bronchodilator.
2. Oxygen saturation <90% on room air or ≥ 5% decline from previous baseline
3. New lobar infiltrate(s) or atelectasi(e)s on chest radiograph
4. Hemoptysis (more than streaks on more than one occasion in past week)

Minor Signs/Symptoms: (Two are required with duration criteria in absence of major criteria)

1. Increased work of breathing or respiratory rate
2. New or increased adventitial sounds on lung exam
3. Weight loss ≥ 5% of body weight or decrease across one major percentile in weight percentile for age within the past 6 months
4. Increased cough

5. Decreased exercise tolerance or level of activity
6. Increased chest congestion or change in sputum

- Symptom Duration: (Required with two minor signs in absence of major criteria) Duration of symptoms ≥ 3 days or significant symptom severity.

When a subject was prescribed an antibiotic, the prescribing Physician completed an antibiotic utilization form. This form included the signs and symptoms listed in the definition of a pulmonary exacerbation table above. Antibiotic Utilization form completion was also verified from source documents and from cross referencing with use of antibiotics listed under Conmeds in the Electronic database.

Results.
As noted in Figure 1. 133 subjects were screened and 107 subjects were enrolled into the study. There were 26 screen failures at visit 1 due to not meeting the inclusion criteria. The primary reasons were; i) Subjects were either judged not clinically stable on examination due to having a respiratory exacerbation, ii) They had a respiratory exacerbation within the previous two weeks, iii)They had a change in medications within the previous two weeks.

Table 2A. Cystic Fibrosis Questionnaire reported for the following Domains

	N	**Physical**	**Emotional**	**Treatment burden**	**Respiratory**	**Digestion/ weight**
PEP	58	-0.84 ±3.3	0.48 ±11.9	-2.55 ±20.6	2.98 ±17.0	-3.28 ±19.0
HFCWO	66	-3.04 ±13.0	-3.13 ±11.6	-3.60 ±18.2	0.19 ±17.1	-2.21 25.1

Data reported as mean (SD) change from baseline (visit 2 -6) in each Domain.

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