

**TITLE**

A short-term comparative study of high frequency chest wall oscillation and European airway clearance techniques in people with cystic fibrosis

**CORRESPONDENCE**

Leyla Osman,

St. Thomas' Hospital, Department of Physiotherapy, Westminster Bridge Road,  
London, SE1 7EH, UK.

E-mail: [leyla.osman@gstt.nhs.uk](mailto:leyla.osman@gstt.nhs.uk)

Telephone: (0)207 188 5082. Fax: (0)207 188 5096.

**AUTHORS**

Leyla P. Osman<sup>\*†</sup>, Michael Roughton<sup>†</sup>, Margaret E. Hodson<sup>\*†</sup>, Jennifer A. Pryor<sup>†</sup>

<sup>\*</sup>Population Genetics and Gene Therapy, National Heart & Lung Institute, Imperial College, London, UK

<sup>†</sup>Royal Brompton & Harefield NHS Trust, London, UK

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## **ABSTRACT**

High frequency chest wall oscillation (HFCWO) is standard treatment for airway clearance in the United States of America, and has recently been introduced to the United Kingdom (UK) and Europe. There is little published research comparing HFCWO with airway clearance techniques (ACTs) frequently used in the UK and Europe. The aim of this study was to compare the short-term effects of HFCWO with usual ACTs in people with cystic fibrosis hospitalised with an infective pulmonary exacerbation.

A four-day randomised cross-over design was used. Patients received either HFCWO on Days 1 & 3 and usual ACTs on Days 2 & 4 or vice versa. Wet weight of sputum, spirometry and oxygen saturation were measured. Perceived efficacy, comfort, incidence of urinary leakage and preference were assessed. Data were analysed by mixed model analysis.

Twenty-nine patients, (72% male) mean age in years (sd) 29.4 (8.4) and mean FEV<sub>1</sub> as percent predicted (FEV<sub>1</sub>%) (sd) 38 (16.7) completed the study. Statistically significantly more sputum was expectorated during a single treatment session and over a 24 hour period (mean difference 4.4g and 6.9g respectively;  $p < 0.001$ ), with usual ACTs than HFCWO. No statistically significant change in FEV<sub>1</sub>% or oxygen saturation was observed after either HFCWO or usual ACTs, compared with baseline. Seventeen (55%) patients expressed a preference for their usual ACT.

During both a finite treatment period and over 24 hours less sputum was cleared using HFCWO than usual ACT. HFCWO does not appear to cause any adverse physiological affects and may influence adherence.

## INTRODUCTION

The last four decades have seen improved survival in people with cystic fibrosis (CF). The latest figures estimate the median life expectancy of individuals with CF, born between 2000-03, to be approximately 40 years [1]. Respiratory failure is the major cause of morbidity and mortality in those with CF [2]. Accumulation of secretions in the CF airway precipitates chronic infection, causing a progressive deterioration in lung function and eventually respiratory failure and death [3]. Airway clearance techniques (ACTs) are an essential component of the management of people with CF and are considered standard care [4]. There is a range of ACTs which augment the normal mucus clearance mechanisms of the lung to facilitate expectoration. These techniques generally aim to promote secretion clearance by altering airflow and mucus viscosity.

Typically, high frequency chest wall oscillation (HFCWO) produces compression of the chest wall via an inflatable jacket linked to an air-pulse generator. The generator delivers an intermittent flow of air into the jacket, which rapidly compresses and releases the chest wall at a variety of frequencies. Consequently, an oscillation in airflow within the airways is achieved. HFCWO has been shown to enhance central and peripheral mucus clearance [5]. A number of underlying mechanisms have been hypothesised including increased airflow-mucus interaction causing a reduction in viscoelasticity, production of an expiratory airflow bias which promotes a cephalad movement of mucus and the enhancement and stimulation of ciliary activity [6;7]. Published short-term evidence has demonstrated increased sputum clearance and improved pulmonary function with HFCWO compared with no treatment [8]. This and other studies have also compared HFCWO with alternative ACTs. Some have demonstrated increased sputum clearance with HFCWO compared with postural drainage and percussion (PD&P) [9-11]. Others found no significant difference in sputum clearance between HFCWO and PD&P [8;12;13], positive expiratory pressure [8], high frequency oral oscillation [13] or intrapulmonary percussive ventilation [14]. Furthermore, some of these studies found no differences in efficacy related to pulmonary function between HFCWO and PD&P [8;12;13], PEP[8;15], oscillating positive expiratory pressure (Flutter<sup>®</sup>) [16] and high frequency oral oscillation [13]. One study reported an improved outcome in forced expiratory volume in one second (FEV<sub>1</sub>) in the longer term using HFCWO compared with PD&P [17].

Few trials have compared HFCWO with alternative ACTs which are commonly used in the United Kingdom (UK) and Europe by people with CF. Phillips *et al* [18] compared HFCWO (using the Hayek Cuirass) with the active cycle of breathing techniques (ACBT) in hospitalised paediatric patients. Significantly more sputum was cleared with the ACBT. The authors concluded that HFCWO was not an effective airway clearance treatment for children with CF. It is difficult to compare this study directly with those above, as the Hayek Cuirass machine has a different operating mode to the inflatable vest system.

A series of Cochrane systematic reviews have demonstrated that no one ACT is superior in terms of respiratory function and efficacy [19]. Of a number of published studies on HFCWO, only two were deemed of sufficient quality to be included in these randomised control trial systematic reviews [8;12].

HFCWO is widely used in the United States of America (USA), where it is considered standard care in CF [20]. HFCWO has recently been introduced to the UK and Europe, where the mainstay of care for airway clearance in CF is the ACBT, autogenic drainage (AD) and other airway clearance regimens using small devices [4]. In the USA these techniques and devices tend to be considered adjuncts, with PD&P and HFCWO remaining the most common ACTs [20]. While there is a body of evidence which equates HFCWO and PD&P, there is a need for further trials to compare HFCWO with alternative ACTs to provide a more relevant evidence base for HFCWO in the UK and Europe.

The aim of the present study was to compare the short-term effects of HFCWO with patients' usual ACTs in those with CF admitted to hospital with an acute exacerbation of pulmonary infection. The hypothesis was that HFCWO was superior to patients' usual ACTs.

## **METHODS**

### **Study participants**

All patients admitted to hospital, who met the entry criteria, were invited to participate in the study. The inclusion criteria were a diagnosis of CF (established by genotype or sweat sodium >70mmol/litre or sweat chloride of >60mmol/litre), FEV<sub>1</sub> ≥ 20% predicted and ≥16 years and an infective pulmonary exacerbation as defined by Thornton *et al* [21]. Exclusion criteria were current severe haemoptysis, rib fractures, pregnancy, inability to give consent and those who's usual ACT was HFCWO. Informed written consent was obtained for all patients and the study was approved by Brompton Harefield and National Heart & Lung Institute Research Ethics Committee.

### **Study Design**

A randomised cross-over design was used to compare HFCWO with patients' usual ACTs, which allowed within-patient variability to be controlled. Over four consecutive days, patients received either HFCWO therapy on Days 1 & 3 and their normal ACT on Days 2 & 4 or vice versa. Allocation to HFCWO or usual ACT on day one was determined using a computer generated randomisation table.

### **Protocols**

Patients performed their usual ACT or received HFCWO, twice daily at the same time. Before starting the study, each patient's usual ACT was reviewed by an experienced senior respiratory physiotherapist. In addition, patients were familiarised with HFCWO (The Vest<sup>®</sup>). This involved the patients using The Vest<sup>®</sup> for a trial period the day before the start of the study, during which time they were given the opportunity to experience all three protocol frequencies at a variety of pressures. Each airway clearance treatment session lasted 30 minutes and was supervised by the same physiotherapist, to ensure optimisation and standardisation of usual ACT and HFCWO performance. All nebulised and inhaled medications were taken before each treatment session as per patients' individual regimens.

### **High frequency chest wall oscillation**

The following regimen was identified as current best practise following an in-depth review of the literature and discussion with clinical experts in the USA. Using the

Vest<sup>®</sup> Airway Clearance System Model 4 (Hill-Rom<sup>®</sup> UK Ltd, Leicestershire, England), each patient was fitted with an appropriately sized, full torso, inflatable, disposable vest, connected to the air-pulse generator via two flexible tubes. Patients remained in an upright sitting position throughout the 30-minute treatment session. HFCWO was applied for eight minutes at each of three frequencies in sequence (10, 13 and 15Hz) with each frequency followed by a two-minute rest period. The pulse-pressure was set according to individual patient's reported comfort at all three frequency settings. During both the HFCWO and rest periods, patients were instructed to huff or cough as they felt necessary in order to expectorate loosened bronchial secretions.

#### Usual airway clearance techniques

Usual ACTs were in accordance with the guidelines of the International Physiotherapy Group for Cystic Fibrosis [22]. Patients performed their usual ACT for 30 minutes, and for patients practising an assisted ACT, the physiotherapist provided percussion. Patients were allowed to perform combined ACTs where this was their usual practice. This reflected current international practice more accurately and recommendations that ACTs be adapted on an individual basis [23].

#### Outcome measures

The primary outcome measure was wet weight of sputum expectorated during a treatment session. Patients were instructed to expectorate all sputum into a pre-weighed pot during and for 30 minutes following each treatment session. They were also instructed to collect sputum expectorated at all other times during each 24-hour period. All sputum collected was weighed immediately following collection on weighing scales with an accuracy of 0.01g (BL310; Sartorius UK Ltd, Epsom, England).

FEV<sub>1</sub> was measured using a hand held spirometer (2120; Vitalograph<sup>®</sup> Ltd, Buckingham, England) in accordance with internationally agreed standards [24]. Measurements were taken immediately before and after a 30-minute period following each treatment session. Data was analysed using Spirotrac IV Version 4.30 software (Vitalograph<sup>®</sup> Ltd, Buckingham, England).

Pulsed arterial oxygen saturation (SpO<sub>2</sub>) was measured transcutaneously at rest, for five minutes immediately before, 30 minutes during and 30 minutes immediately following each session. SpO<sub>2</sub> was measured with a fingertip pulse oximeter (Konica-Minolta Pulsox<sup>®</sup>-300i; Stowood Scientific Instruments Ltd, Oxford, England). The data was analysed using Download<sup>™</sup> 2001 Version 2.8.0 software (Stowood Scientific Instruments Ltd, Oxford, England).

The perceived efficacy and comfort of each ACT and the incidence of urinary leakage during treatment were measured using 10cm visual analogue scales (VAS). Each day, after the last treatment session, patients completed three 10cm VAS with reference to the ACT used that day. On the VAS used, 0 represented not at all effective/comfortable or no urinary leakage and 10 represented extremely effective/comfortable or a lot of urinary leakage. On the fourth and final day participants were also asked to indicate which ACT they would prefer.

An independent observer, blind to the daily method of airway clearance used, performed the spirometry, weighed the sputum samples and collected the 10cm VAS throughout the study.

### Statistical Analysis

A sample size calculation determined the number of patients required to test for superiority of HFCWO. This was based on a difference of four grams of sputum between the usual ACT and HFCWO during a single treatment session. A square-root of within mean standard error of four grams at the 5% significance level would require 24 patients to achieve 90% power. Data are presented as mean (sd), median (IQR) or n (%) as appropriate. Continuous variables were analysed using a mixed-effects linear regression model. This was to allow the results to be adjusted for a number of factors which inherent to the design of a crossover trial. The order of treatment randomisation and the day and time of treatment were all entered into the model, and their effect on the outcomes was tested. For this trial the results were also adjusted for the method and position of treatment in the ACT session. In these models patients were entered as random effects, since it was not of interest to quantify the differences between individual patients, but it was important to account for the repeated measurements on each patient. The estimates of the fixed effect of ACT versus HFCWO are presented as mean (95% CI). A p value of 0.05 was taken to be statistically significant. All analysis was conducted using STATA 9.2 (StataCorp LP, Texas, USA).

## RESULTS

### Participants

Fifty patients were invited to participate in the study, twenty declined, twenty nine patients completed the study and one patient was withdrawn due to a hypoglycaemic episode. Table 1 shows patient demographics and baseline characteristics of the patients who completed the study.

**Table 1: Patient demographics and baseline characteristics (n=29)**

Age (years)	29.4 (8.4)
Male (%)	21 (72%)
Height (cm)	171 (9)
Weight (kg)	60 (11)
BMI (kg/m <sup>2</sup> )	20.4 (2.6)
FEV <sub>1</sub> (L)	1.46 (0.72)
FEV <sub>1</sub> % predicted	38 (16.7)
SpO <sub>2</sub> (%)	94.3 (2.1)

BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in one second; SpO<sub>2</sub>, pulsed arterial oxygen saturation.

Data are presented as mean (standard deviation) or n (%) as appropriate.

Twenty-nine patients were treated with intravenous antibiotics as part of their medical management. All participants received two treatment sessions on each study day and all treatment sessions were 30 minutes in duration. The mean length of stay for patients was 14 (5) days and the mean day of entry to the study was day 8 (3) days.

### Usual airway clearance techniques

Usual ACTs included the ACBT with modified PD&P (41%; n = 12) and with modified PD alone (7%; n = 2), AD in sitting (28%; n = 8) and with modified PD (7%; n = 2), PEP (7%; n = 2) and Flutter® (10%; n = 3).

### Sputum weight

The wet weight of sputum expectorated with usual ACT compared with HFCWO is shown in table 2.

Table 2 Wet weight of sputum expectorated: high frequency chest wall oscillation compared with usual airway clearance technique

Period of sputum collection	Expectorated sputum wet weight (g)					p value
	Usual ACT		HFCWO		Mean difference	
	Mean (sd)	Median (IQR)	Mean (sd)	Median (IQR)		
A single Rx session	9.1 (7.9)	7.2 (3.0 - 14.2)	4.6 (4.1)	3.4 (1.5 - 6.7)	4.4 (3.5 to 5.4)	p < 0.001
24 hours (excluding Rx)*	22.4 (26.8)	12.9 (4.0 - 29.9)	24.9 (25.8)	15.3 (3.9 - 40.1)	- 1.5 (-4.6 to 1.6)	p = 0.352
24 hours (including Rx)	39.8 (36.3)	25.5 (14.0 - 57.1)	34.3 (30.7)	26.3 (12.1 - 46.0)	6.9 (3.1 to 10.8)	p < 0.001

ACT, airway clearance technique; HFCWO, high frequency chest wall oscillation; Rx, treatment.

Data are presented as mean (standard deviation) or (95% confidence interval) or median (inter-quartile range) as appropriate. Data are adjusted for randomization, day, time and position of treatment using a mixed-effects linear regression model.

\*Of 116 24-hour sputum samples collected, two were discarded as they were incomplete.

The mean weight of sputum expectorated during a single treatment session and over a 24-hour period was statistically significantly greater with usual ACT than with HFCWO. The mean difference in wet weight of sputum expectorated during a treatment session was 4.4g (p<0.001) and the mean difference in wet weight of sputum expectorated over a 24-hour period was 6.9g (p<0.001). These findings were not affected by order, time, day or position of treatment.

No statistically significant difference was observed in the amount of sputum expectorated when using HFCWO or usual ACT, between treatments in a 24-hour period.

### Physiological measures

FEV<sub>1</sub> and SpO<sub>2</sub> measured before, during and after usual ACT and HFCWO treatment sessions are shown in table 3.

Table 3 Forced expiratory volume in one second and pulsed arterial oxygen saturation at baseline, during and after treatment with usual airway clearance technique and high frequency chest wall oscillation

	Usual ACT			HFCWO		
	Baseline	During Rx	30 mins after Rx	Baseline	During Rx	30 mins after Rx
FEV <sub>1</sub> % predicted	39.1 (16.9)	N/A	38.9 (17.1)	38.9 (16.8)	N/A	39.2 (16.7)
SpO <sub>2</sub> (%)	94.4 (2.0)	94.4 (1.9)	93.9 (1.6)	94.5 (1.8)	95.0 (1.7)	94.3 (1.7)

ACT, airway clearance technique; HFCWO, high frequency chest wall oscillation; Rx: treatment; FEV<sub>1</sub>, forced expiratory volume in one second; SpO<sub>2</sub>, pulsed arterial oxygen saturation; N/A, not applicable.

Data are presented as mean (standard deviation).

### Comfort, efficacy and preference

The VAS scores for comfort, efficacy and urinary leakage during usual ACT compared with HFCWO are shown in Table 4. No statistically significant differences were observed in VAS scores for comfort or urinary leakage between HFCWO and usual ACT. Patients scored the efficacy of their usual ACT statistically significantly higher than for HFCWO (mean difference = 14mm; p = 0.002). This was not affected by the order or day of treatment. Of those patients who completed the study, 17 (55%) expressed a preference for their usual ACT over HFCWO. Preference was not predicted by the amount of sputum expectorated.

Table 4 Comfort, efficacy and urinary leakage: high frequency chest wall oscillation compared with usual airway clearance technique

Self reported measure	Visual analogue scale score (mm)			
	Usual ACT	HFCWO	Mean difference	p value
Comfort	69 (23)	70 (22)	-1 (-9 to 7)	p = 0.784
Efficacy	68 (21)	54 (26)	14 (6 to 23)	p = 0.002
Urinary leakage	0 (1)	0 (1)	-0.05 (-0.3 to 0.4)	p = 0.791

ACT, airway clearance technique; HFCWO, high frequency chest wall oscillation; Rx, treatment.

Data are presented as mean (standard deviation) or (95% confidence interval) as appropriate. Data are adjusted for randomization, day of treatment and time of treatment, using a mixed-effects linear regression model.

## DISCUSSION

There have been few published comparisons between HFCWO using a vest system with the ACTs of the ACBT and AD. This short-term study, carried out on individuals with CF admitted to hospital with an acute infective pulmonary exacerbation, demonstrated that statistically significantly more sputum was expectorated during a single treatment session and over a 24-hour period using the patient's usual ACT than with HFCWO. In addition, slightly less sputum was expectorated at all other times (excluding treatment sessions) on usual ACT days compared with HFCWO, but this trend was not statistically significant. These findings were independent of order, time or day and position of treatment. Neither HFCWO nor any of the usual ACTs were associated with any adverse clinical events.

A possible factor contributing to the difference in sputum clearance between HFCWO and usual ACT may have been the number and frequency of forced expiratory manoeuvres (FEMs) and the more gentle expiratory manoeuvres of the AD breath, that were performed with the usual ACTs. Some studies have standardised the number of coughs and FEMs that patients performed, however at the time of designing the protocol the aim was to compare the regimens as currently practised internationally and the frequency of coughs and FEMs was neither standardised, nor counted. In retrospect, it would have been of value to have counted the number of coughs and FEMs undertaken during each regimen, but it had not been anticipated that any differences between HFCWO and usual ACTs may be a consequence of the number of FEMs or AD breaths. Theoretically, during the three eight-minute periods of HFCWO fewer FEMs, coughs or AD breaths would be undertaken than during an equivalent period of the ACBT, AD, PEP or Flutter<sup>®</sup> (all of which inherently include FEMs or AD breaths at regular intervals). This difference was supported by observations of the investigators. However, manual cough counts are subject to observer error. Objective cough monitoring, using The Leicester Cough Monitor, has only recently been validated and should be considered for use in further studies [25]

Components of patient satisfaction include efficacy, comfort and convenience. Some studies have formally evaluated patient satisfaction and compliance. One study reported that 50% of subjects chose HFCWO compared with the Flutter<sup>®</sup> and efficacy was the most frequently cited reason for this choice [16]. A later study reported that HFCWO was not preferred over PD&P and intrapulmonary percussive ventilation, furthermore there was no significant correlation between treatment preference and sputum weight [14]. The current study found that patients perceived the efficacy of HFCWO to be statistically significantly less than that of their usual ACT. However, nearly half (45%) of patients expressed a preference for HFCWO. Preference may have been affected by the novelty of a new treatment and it is unknown whether this would continue in the long-term.

There is no one recommended protocol for the application of HFCWO in the literature. Published studies describe differing numbers and duration of frequencies, length of treatment and airway clearance. Frequencies of 10, 13 and 15Hz were chosen as it has

been reported that maximum mucus transport occurs between 11 and 15Hz with a peak at 13Hz [5;6]. In addition, the highest oscillated tidal volume flow (peak airflow) occurred between 10 and 15Hz in CF patients [26]. More recent research recommends an individual ‘tuning’ method to identify optimum treatment frequencies. These have been shown to vary among individuals and the oscillation waveform [27], but, it is unknown as to whether ‘tuning’ increases efficacy.

It is possible that a practice effect could have occurred as all patients were new to HFCWO. However, the protocol used in this study did not require the patient to perform any newly learned physical technique. In addition, the statistical analysis ensured data was adjusted for day of treatment and found no effect. Alternatively, patients’ familiarity with their usual ACT may also have had an effect on outcomes.

This study was powered to detect a difference of 4g of sputum expectorated during a single treatment session. Other studies have been based on a difference of 3 – 3.5g, which is generally accepted as a clinically important difference [28;29]. Wet weight sputum was felt to be an appropriate primary outcome measure in this short-term study in an acute environment. Previous work has found wet weight to be proportional to dry weight sputum [28;30]. Emerging non-invasive means of measuring airway clearance may be more sensitive indicators in the future, for example, lung clearance index and electrical impedance tomography.

Considering the cost benefit of HFCWO, compared with other ACTs, and the differing healthcare systems in the USA and the UK, it is unlikely that HFCWO will become the first choice ACT for most individuals in the UK. Further work needs to be undertaken to identify the place of HFCWO in Europe. Patient preference for a treatment regimen may positively influence adherence to treatment in the short-term and nearly half the patients who participated in this study preferred HFCWO to their usual ACT. HFCWO is a safe treatment that facilitates airway clearance in CF, but when compared with patients’ usual airway clearance techniques HFCWO led to the clearance of statistically significantly less sputum during a single treatment session and over a 24-hour period.

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