

# HFCWO Therapy: Weighing the Evidence

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High frequency chest wall oscillation (HFCWO), also known as vest therapy, is a form of chest physiotherapy used for airway clearance therapy (ACT). The most common design uses an inflatable vest attached to an air pulse generator that creates rapid compressions to the chest, helping to loosen, thin and mobilize mucus so it can be expelled through coughing or suctioning. This therapy is considered a medically appropriate intervention for a large number of disease states where the normal mechanisms for clearing mucus are impaired or lacking.

Originally conceived to treat cystic fibrosis (CF) in the early 1990's, much of the supporting evidence for the therapy dates from that time, often in the form of small, uncontrolled studies. Since its introduction, the use of HFCWO therapy has expanded well beyond CF to include a long list of hereditary and acquired conditions, including non-cystic fibrosis bronchiectasis (referred to as NCFB or "bronchiectasis" in this paper). Airway clearance plays an important role in treating symptoms and reducing health care utilization for bronchiectasis and other chronic respiratory conditions.<sup>1</sup> The clinical community has long sought a definitive study unequivocally demonstrating that HFCWO is shown to improve clinical outcomes.<sup>2,3</sup> The existence of such evidence would further bolster what many clinicians have seen in everyday practice—the maintenance or improvement of lung health in individuals with chronic respiratory conditions.

Many studies do exist, however, demonstrating the value of HFCWO as part of an ACT treatment regimen. To better understand the current evidence landscape, it is useful to explore the challenges inherent in implementing a large-scale, long-term study in these patient populations. At the same time, this review of the currently available evidence addresses the popular misconception that few valuable ACT studies exist. There are in fact many studies from across the globe that examine the utility of various methods of ACT within respiratory conditions featuring chronic mucus hypersecretion. This article will review what is known about the evidence behind HFCWO and suggest a pathway for strengthening the research base for the future.

## The Need for ACT

A healthy individual clears mucus from the respiratory system through ciliary action and coughing. Cystic fibrosis, non-cystic fibrosis bronchiectasis, some forms of chronic bronchitis,



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chronic obstructive pulmonary disease (COPD), and certain neurological disorders can exhibit the production of excess mucus and/or the inability to adequately clear secretions. Patients with these conditions often experience accumulation of secretions in bronchi, particularly in the small airways, limiting adequate gas exchange in the lungs. Inadequately cleared secretions can become a culture medium for pathogens, leading to serious complications including degradation of lung function<sup>4</sup> and increased lung infections.<sup>4,5</sup> In addition, mucus blockage may lead to further infections and inflammation resulting in bronchiectasis.<sup>6</sup> Bronchiectasis can also be a co-morbidity of chronic bronchitis.<sup>7</sup>

Goblet cells in the respiratory tract secrete mucus to form a protective lining of the inner airways. Bacteria and other airborne particles trapped in this mucus are mobilized by cilia and eventually cleared by expectoration or swallowing. Excess mucus is further expelled from the airways through coughing or suctioning. Acute illness and a progressive decline in lung function can occur when this normal mucus-clearing function is impaired or disrupted on a chronic basis.<sup>8</sup> Secretions that are not cleared can promote chronic inflammation, repeated infections, irreversible lung damage and impaired respiratory function.<sup>9,10</sup> Other symptoms and signs of chronic respiratory diseases include dyspnea, cough, wheezing, hyperventilation and hemoptysis. Conditions that result in chronic mucus hypersecretion are considered candidates for ACT, including HFCWO. ACT is intended for patients who are unable to clear excess secretions without external manipulation or therapeutic intervention, and the range of such conditions is wide and often overlapping.

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### HFCWO Therapy May Be Considered for ACT for Patients with the Following Conditions

- Cystic Fibrosis
- Bronchiectasis (NCFB)
- COPD
- Neuromuscular disorders associated with impaired airway clearance such as:
  - Acid maltase deficiency
  - Anterior horn cell diseases, including amyotrophic lateral sclerosis
  - Cerebral palsy
  - Familial dysautonomia
  - Hereditary muscular dystrophy
  - Multiple sclerosis
  - Myotonic disorders
  - Other myopathies
  - Paralysis of the diaphragm
  - Post-polio
  - Quadriplegia

### The Challenges of ACT Research

Studies involving airway clearance therapy are intrinsically difficult to perform.<sup>11</sup> Many of the disease states have small populations making recruitment of adequate numbers of subjects challenging and expensive. This factor makes it problematical to define an appropriate control group as the disease itself may be heterogeneous, making it hard to understand and control for hidden confounding factors. Even if potential confounders are recognized, they may be numerous and it is often unclear which of them are independently associated with outcomes. Additionally, it is impossible to fully blind subjects to the use of airway clearance devices; therefore, studies of effectiveness will always blend the outcome with the patients' perceptions and responses to their own treatment. Some means of ACT require patient cooperation, and many require continuous, conscious effort to be effective. However, no therapy can be effective if it is unused, and studies that do not measure, let alone control for, adherence suffer from a serious deficiency.<sup>12</sup> Moreover, there has been no agreement about which outcomes are clinically relevant. Many early studies use sputum production as an outcome,<sup>13</sup> which is a reasonable proxy for airway clearance effectiveness. However, sputum production relies on patient effort and the proportion of hydration of the sputum, both of which are highly variable. Many studies have simply relied on self-reported sputum volume, or self-reported success of airway clearance in general, with the unsolved issue of biased self-reporting. Lastly, studies have shown that the degree of education and support given to a chronically ill patient can have major effects on the success of any therapy, particularly one that requires extended voluntary effort.<sup>14</sup> It is, perhaps, an academic concern whether success is due to the device itself or the support surrounding it; both are intertwined in actual clinical practice, and both are necessary for successful treatment.

### Cystic Fibrosis and Origin of HFCWO Therapy

Various forms of percussion therapy have long been used for patients with CF. Conventional chest physical therapy (CPT) has been shown to improve respiratory function. Percussion may be combined with postural drainage (P&PD), which uses gravitational flow, diaphragmatic breathing and controlled coughing to mobilize secretions. These methods were among the first to help patients with cystic fibrosis manage their airway clearance; however, the need for trained caregiver

involvement on a daily basis with these methods often leads to poor adherence to the prescribed treatment plan.<sup>14</sup> Hence, HFCWO was introduced as an alternative to these more manual approaches. In the U.S., HFCWO is often considered standard care in cystic fibrosis treatment.<sup>15</sup> Multiple studies in cystic fibrosis patients found vest therapy equivalent<sup>16-23</sup> or superior<sup>13,24-27</sup> to other airway clearance methods including positive expiratory pressure (PEP), postural drainage, CPT, and intrapulmonary percussive ventilation (IPV). A randomized comparison of PEP and HFCWO found no significant difference in pulmonary function tests, quality of life scores or patient satisfaction scores between the two ACT methods.<sup>21</sup> In this study, average forced expiratory volume in one second (FEV<sub>1</sub>) lung function improved in both the HFCWO and PEP groups, and there were statistically fewer exacerbations for all study participants, including the HFCWO patients, than in the general CF population.

Most adult patients can use vest therapy without the aid of caregivers.<sup>24</sup> Health care providers rely on the consistency of treatment that vest therapy offers. Vest therapy is technique-independent and simple to do correctly,<sup>28</sup> and effective treatment contributes to ongoing compliance.<sup>25</sup> For payers, successful ACT treatment with vest therapy may improve or maintain health status, reducing medical and ancillary care costs associated with refractory lung disease.<sup>29</sup>

A Cochrane review of 15 studies<sup>30</sup> compared CPT to PEP, active cycle of breathing, autogenic drainage, and mechanical devices including airway oscillators, mechanical percussion devices, and HFCWO. No significant difference was shown between CPT and other airway clearance therapies in terms of lung function, and studies of acute lung infections showed improved lung function regardless of type of treatment. Ten of the 15 studies in the review showed patient preference for self-administered techniques such as HFCWO.

Several studies have compared chest physiotherapy to HFCWO alone. A retrospective chart review comparing prior CPT use to HFCWO showed that the introduction of HFCWO slowed or reversed degradation of FEV<sub>1</sub>.<sup>31</sup> These improvements were sustained over the four-year period included in the review. A different 30-month study compared HFCWO to no treatment: the HFCWO group had less pulmonary function decline than non-HFCWO group, and males showed FEV<sub>1</sub> improvement.<sup>27</sup> Two additional retrospective chart reviews showed that FEV<sub>1</sub> stabilized or improved after HFCWO was initiated.<sup>25,32</sup>

HFCWO has been demonstrated to deliver superior secretion clearance<sup>26</sup> and superior sputum volume relative to CPT. A long-term crossover study further demonstrated that both superior sputum production and improved pulmonary function tests (PFTs) were maintained with the use of HFCWO over 1.5 years.<sup>13</sup> Triangle waveform HFCWO specifically was found to produce more sputum than sine wave devices<sup>33</sup> or CPT delivered by certified respiratory therapists.<sup>27</sup> The triangle waveform HFCWO is intended to mimic the sharp, brief "thumps" of CPT via a caregiver, yet can be self-administered.<sup>33</sup>

The majority of patients prefer the independence afforded by vest therapy.<sup>34</sup> A short-term prospective study (n=50) comparing HFCWO to CPT indicated that 88% of the CF patients favored HFCWO in terms of patient satisfaction.<sup>16</sup> Another short-term study of similar size (n=51) found that 47% of hospitalized CF

patients preferred HFCWO compared to 26% for percussion and postural drainage (P&PD).<sup>35</sup> The patient satisfaction component of ongoing care for chronic conditions is a notable factor as higher satisfaction may lead to better therapy adherence.<sup>30</sup>

### **Neurological Conditions and HFCWO Therapy**

HFCWO therapy is useful for many patients with neuromuscular/neuromotor conditions who require airway clearance.<sup>36</sup> These disorders often result in respiratory muscle disability, making patients more susceptible to pneumonia and infection due to the inability to clear accumulated secretions through coughing. The secretions may contain microorganisms, environmental substances or other debris that activate pulmonary defense mechanisms, which can lead to ciliary dysfunction, additional secretion development and inflammatory response.<sup>37</sup>

A randomized controlled trial comparing CPT to HFCWO in 23 patients with severe neuromotor/neuromuscular disease showed that adherence to HFCWO was markedly superior to CPT, with HFCWO adherence rates exceeding 70%.<sup>38</sup> Additionally, the HFCWO group showed a strong trend toward fewer hospitalizations. Similar results were found in a study of 15 children with severe neuromuscular or neuromotor disorders, which showed a three-fold reduction in hospital days after HFCWO treatment for at least one year compared with days hospitalized during a retrospective year of CPT.<sup>39</sup> None of the patients in this study required ICU care during HFCWO therapy. Another study of children with severe quadriplegia compared 12-month retrospective clinical data to CPT therapy with 12-month prospective HFCWO therapy data. Analysis showed a 50% reduction in pneumonias and a 67% reduction in hospitalizations after the introduction of HFCWO therapy for 20 minutes per day.<sup>40</sup> A randomized controlled study of changes in respiratory function in patients with ALS found that HFCWO users had less breathlessness and more coughing than untreated patients.<sup>41</sup> The authors also concluded the HFCWO showed a slowing in the decline of forced vital capacity (FVC). A cohort study of 426 patients (adults and children) compared healthcare claims before and after initiation of vest therapy for patients with chronic neuromuscular disease.<sup>42</sup> The study found that monthly medical costs per member decreased by \$1,949 (18.6%) after initiation of vest therapy ( $p=0.002$ ). Inpatient admission costs decreased by \$2,392 (41.7%,  $p=0.001$ ), and pneumonia costs decreased by \$514 (18.1%,  $p=0.015$ ).

### **Non-Cystic Fibrosis Bronchiectasis and HFCWO Therapy**

HFCWO has found growing acceptance for addressing the airway clearance needs of patients with bronchiectasis. This is a pulmonary disorder characterized pathologically by permanent bronchial dilatation and severe bronchial inflammation, clinically by chronic productive cough and recurrent infectious exacerbations, and confirmed with computed tomography (CT) scans. The presence of cystic fibrosis, immune disease and recurrent infections are all contributing factors in the development of bronchiectasis, which is considered to be the end point of various lung disorders.<sup>43</sup>

There are ample data showing that untreated or undertreated bronchiectasis is a risk factor for increased hospitalizations, reduced quality of life, and ultimately mortality.<sup>7,44</sup> Earlier intervention may avoid worsening conditions and the need for more serious interventions at a later stage of care.<sup>45</sup> Nicolini et al compared the safety and efficacy of HFCWO with CPT

in patients with NCFB.<sup>46</sup> Participants were randomized into three groups: HFCWO, positive expiratory pressure (PEP) and a control group of medical therapy only. The authors reported that the HFCWO group showed a significant increase in FVC and in FEV<sub>1</sub> after treatment. The HFCWO group also showed a greater increase of sputum volume, significantly reduced cough, and significant improvement in both dyspnea and quality of life measures. The authors concluded that HFCWO should be among the main choices for chest physiotherapy.

A Cochrane review, Lee et al, evaluated the results of seven ACT studies involving patients with clinically stable NCFB.<sup>2</sup> The authors concluded that ACT is beneficial for treatment of NCFB and results in improved pulmonary outcomes. The authors noted that the positive effects of HFCWO on sputum production, dyspnea and health-related quality of life are important clinical outcomes. In contrast, a different study of 75 NCFB patients found adherence to standard medical treatment was low, with only 16% of patients adhering to all treatments.<sup>47</sup> As chronic conditions persist, the ability to consistently adhere to prescribed therapy is a significant factor in maintaining or improving health status.

Though lung function measures are often used as a surrogate for ACT device performance, patient-centered outcomes are becoming increasingly important in assessing therapies.<sup>48</sup> An outcomes database proprietary to Respiratory Technologies, Inc. involving NCFB patients showed measurable benefits associated with the use of vest therapy.<sup>49</sup> Updated numbers from the same source<sup>50</sup> show the number of patients who required no respiratory-related hospitalizations increased from 49% in the year before vest therapy to 76% in the year after starting vest therapy. During this time, the yearly rate of hospitalization dropped 60%. Those who rated the “ability to clear your lungs” as good, very good, or excellent increased from 11% to 72% over the same time. Though the improvements cannot exclusively be attributed to the use of HFCWO therapy, the data strongly suggest a positive role for vest therapy in these improvements and others.

### **Increasing Awareness of COPD/Bronchiectasis Overlap**

There is growing awareness of the association between moderate-to-severe COPD and bronchiectasis.<sup>51</sup> This overlap appears to be so common, in fact, that some experts have proposed the use of a term that captures the frequent, concurrent nature of these two disease states – “Bronchiectasis-COPD Overlap Syndrome.”<sup>52</sup> Some authors consider COPD to be a cause of bronchiectasis,<sup>53</sup> while others describe it as being associated.<sup>54</sup> Nevertheless, there is a high prevalence of airway wall abnormalities (thickening, dilatation) in COPD. A meta-analysis of six observational studies involving 881 patients shows the mean prevalence of bronchiectasis in patients with moderate-to-severe COPD to be nearly 54.3%, with ranges from 25.6% to 69%.<sup>55</sup> In the U.S., approximately 7.48 million patients have currently been diagnosed with moderate-to-very severe COPD (GOLD stages II-IV).<sup>56</sup> Applying a ~50% prevalence rate to this population yields a figure of more than 4 million people who may have bronchiectasis, yet up to 681,000 have been diagnosed.<sup>57</sup>

The use of HFCWO in adults with a COPD-only diagnosis has been studied very little.<sup>58-60</sup> A 2011 study compared the use of HFCWO to conventional treatment for patients with

COPD, defined as patients following their existing COPD management regimen including use of prescription medications (bronchodilator, inhaled corticosteroid, anticholinergic inhaler), regular exercise, and cough clearance of sputum.<sup>61</sup> The results showed the vest therapy device was well tolerated with good reported compliance, reduced symptoms and improved quality of life.

While the use of vest therapy for COPD-only diagnoses is evolving, the clinical and cost consequences of the COPD-bronchiectasis overlap may be significant. (In 2011, the cost of COPD-related readmissions, which included bronchiectasis cases, was estimated to be \$924 million).<sup>62</sup> A study of 201 COPD patients with bronchiectasis-like airway abnormalities demonstrated an association with exacerbation and was predictive of mortality over a two-year period.<sup>63</sup> Another study showed patients with NCFB and associated COPD having a 5-year mortality rate of 55% compared to 20% in those with bronchiectasis without COPD.<sup>63</sup> Changes in the airways caused by bronchial tree dilation and damage can reduce the ability to clear secretions,<sup>64</sup> which can contribute to declining pulmonary function, recurring respiratory infections, and eventually, death.<sup>43</sup> Moreover, there is a clear association between chronic mucus hypersecretion and hospitalization due to COPD.<sup>65</sup>

Recent European guidelines suggest that bronchiectasis should be evaluated in COPD patients who demonstrate chronic mucus hypersecretion and severe airflow obstruction ( $FEV_1 < 50\%$ ), who have been hospitalized for an exacerbation in the previous year, or whose sputum cultures have indicated the presence of potentially pathogenic microorganisms. These are all risk factors of the presence of bronchiectasis.<sup>66</sup>

### Path to Better Understanding

Many studies conclude that “additional data are needed” when it comes to demonstrating the impact of various ACT methods.<sup>2</sup> The need becomes more acute as the burden of proof for medical therapies evolves, and as new evidence emerges to draw our focus to disease states whose importance has been under recognized in the past. The problems of conducting airway clearance studies in rare diseases will not change, just as the difficulties of designing fair, clinically relevant studies will always be present. Nonetheless, the medical community, partnered with industry, must take responsibility to show that these devices improve patients’ lives and justify the costs of using them.<sup>67</sup> A valuable but untapped resource will be large and growing registries of patients.<sup>67</sup> Often, the information necessary to conduct post-hoc observational research is already available and offers an avenue to answer pertinent questions regarding efficacy and other outcomes. At this writing, Respiratory Technologies’ database of NCFB patients contains over 14,000 records, followed closely by the European Bronchiectasis Registry (EMBARC) database with greater than 12,000.<sup>68</sup> Such observational studies will outline the association of HFCWO therapy with clinically relevant outcomes such as hospitalization rate and quality of life. Extending these data to demonstrate the cost effectiveness of vest therapy is possible as well as necessary. However, without larger, better controlled trials, it will never be clear whether the effectiveness found in observational studies is truly due to HFCWO treatment or to association only. Accordingly, despite their known difficulties, randomized control trials will be necessary, and such trials will require significant time and resources.

Until then, consensus statements and guidelines<sup>66,69,70</sup> will need to fill the gap.<sup>8</sup> Cystic fibrosis,<sup>15,71</sup> certain neuromuscular<sup>72</sup> and other conditions<sup>73,74</sup> have guidelines for airway clearance, but in most cases the use of HFCWO therapy is governed by coverage considerations. Presently, HFCWO can be reimbursed by Medicare for most of the conditions listed above, but coverage by private payers is variable, and determinations of “experimental” and “not medically necessary” regularly occur. The disconnect between patient need and approved treatment is the result of a reimbursement system that relies on disease categories rather than a patient’s symptomatic need. Recently, there has been increasing attention given to the concept of “treatable traits.”<sup>75</sup> This simple but useful idea states that teasing out the underlying mechanisms and comorbidities of a complex disease is not necessary for effective medical therapy. In the case of airway clearance therapy, evidence of the patient’s need is underscored by the presence of excess sputum that cannot be coughed out or cleared without help. Addressing this treatable trait can greatly enhance the patient’s outcome.

### Conclusion

Diseases and conditions requiring airway clearance therapy tend to be serious and progressive, with declining respiratory function due to recurrent infections, permanent changes in the architecture of the airways, and co-morbidities. In reviews, there is general agreement that all airway clearance methods can be effective, and that the choice among them depends on the particular circumstances of the patient and the method most likely to be used.<sup>19,23,28,35,45,76,77</sup> As an ACT option, HFCWO therapy is safe for use with a broad range of acute and chronic conditions, and a growing body of evidence supports the clinical, economic and quality of life advantages of this form of therapy.

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