

Annotated Bibliography

Chronic Obstructive Pulmonary Disease (COPD):

Rationale and Evidence for Secretion Management with High-Frequency Chest Wall Oscillation (HFCWO)

This Annotated Bibliography provides an overview of recent literature concerning the causes and effects of mucus hypersecretion/retention in COPD with emphasis upon comorbid chronic bronchitis (CB) and bronchiectasis. The document includes citations and summaries of articles and studies arranged in four sections: Section I - Mucus Hypersecretion/Retention and Associated Complications in COPD; Section II – Prevalence and Characteristics of Comorbid Bronchiectasis in COPD; Section III – Selected Articles and Studies Supporting HFCWO Therapy in COPD; Section IV – Supplemental Literature. Articles and studies are arranged chronologically. Literature citations in Section IV are arranged alphabetically by author.

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Overview: Background and Significance

Chronic obstructive pulmonary disease (COPD) and chronic bronchitis (CB) are major causes of morbidity and mortality worldwide [1-4]. Recent estimates suggest that at least 15 million people in the United States have COPD and an additional 12 million have CB [1,4]. These estimates are likely to be conservative. World-wide, current prevalence estimates stand at 210 million cases [4]. Consistent with its high prevalence, complications of COPD are a major cause of respiratory and/or systemic illness and represent a rapidly escalating societal and economic burden. Acute exacerbations are a major cause of disability, hospital admissions, skyrocketing healthcare costs and high rates of premature mortality. [5,6] Defining COPD has been and continues to be a matter of considerable controversy. [6] In the simplest terms, there is consensus agreement that the generic term “COPD” describes an obstructive pattern of alterations of the respiratory system as seen in conditions including emphysema, CB, chronic asthma and bronchiectasis [2,5-11]. These conditions may occur alone or in combination. The classic definition of CB is chronic cough and sputum production for at least 3 months per year for two consecutive years. [7,8] Current understanding of COPD includes a spectrum of clinical presentations, or phenotypes, arising from a variety of complex etiologies. [2-5,8]. Pathological features include structural changes of the small airways and decreased elastic recoil of the lung [1-6,9]. Airflow limitation, impaired gas exchange, dyspnea, inflammation and impairment of mucociliary clearance (MCC) mechanisms are characteristic. [9] Significantly increased sputum production (CB) in COPD is common but not universal [3,7-9]. In recent decades, a growing body of evidence, including numerous robustly powered epidemiological studies, has demonstrated clear correlations between chronic mucus hypersecretion and serious clinical consequences [6,8]. These include acute exacerbation, defined as episodes of increased dyspnea, sputum production and/or sputum purulence requiring clinical intervention. Chronic cough and daily mucus hypersecretion are recognized as predictive of COPD exacerbations and accelerated decline in health status. [5] Evidence unequivocally demonstrates that excess, retained mucus contributes to progressive lung injury and obstructed airflow [6,10,11]. Health consequences are measurable. Annually, patients with advanced COPD have a median of two acute exacerbations requiring hospitalization [5,6]. Recognition that COPD complications triggered by mucous hypersecretion and retention are responsible for unsustainable demands on limited healthcare resources underscores an urgent need for effective interventions to manage pulmonary secretions [12]. Therapeutic goals are to target the different pathological mechanisms of COPD/CB. Effective treatment should work to reduce mucus overproduction, control inflammation, modify cough and facilitate mucus elimination by increasing ciliary transport, reducing mucus tenacity and increasing sheer stress to augment mucus detachment from airway walls [7]. HFCWO has been shown to impact all these parameters. [13]

1. Miravittles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. *Respiratory Medicine*, 2011; 105 (8), 1118-1128.
2. Novstad SA, Barker AF. Chronic obstructive pulmonary disease and bronchiectasis. *Curr Opin Pulm Med* 2013; 19: 133-139.
3. Ramos FL. Clinical issues of Mucus accumulation in COPD. *International J COPD* 2014; 9: 139-150.
4. Soriano JB, Rodriguez-Roisin R. Chronic obstructive pulmonary disease overview. *Epidemiology, Risk factors and clinical presentation. Proc Am Thorac Soc.* 2011; 8: 363-367.
5. Burgel PR, Nesme-Meyer P, Chanez P, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD Subjects. *Chest* 2009; 135:975–982.
6. Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD – A review of potential interventions. *International J COPD*; 2009; 4: 203-233.

7. Kim V, Criner GJ. Chronic bronchitis and Chronic Obstructive Pulmonary Disease. *Am J Resp Crit Care Med* 2013 Feb 1; 187(3):228-37.
8. Burgel PR. Cough and sputum production in COPD patients: clinical phenotype or markers of disease activity? [Editorial] *International J Clin Pract* 2013;1218-1219.
9. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *NEJM* 2004; 350 (26): 2645-2653.
10. Patel IS, Vlahos I, Wilkinson TM, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Resp Crit Care Med.* 2004; 170: 400-407.
11. O'Brien CO, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characteristics of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635-642.
12. Miravittles M, Garcia-Polo C, Domench A, et al. Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease. *Lung* 2013; 191: 523-530.
13. Hansen LG, Warwick WJ, Hansen KL. Mucus transport mechanisms in relation to the effects of high frequency chest compression (HFCC) on mucus clearance. *Pediatr Pulmonol* 1994; 17: 113-118.

I. Mucus Hypersecretion/Retention and Associated Complications in COPD

"It has long been speculated that mucus clearance is important for airway defense, but only recently have important details of this system become available...as long as mucus clearance is maintained, chronic airway infections do not occur."
— Knowles MR, et al., *J Clin Invest* 2002; 109 (5): 571-577.

1. Ramos FL, Krahnke JS, Kim V. Clinical issues of mucus accumulation in COPD. *International J COPD* 2014; 9: 139-150.

In this review of current literature, authors discuss the prevalence of CB in COPD, mechanisms and consequences of mucus hyperproduction/retention and treatment options. Tables list and characterize studies demonstrating the effects of excess/retained airway secretions on several important COPD outcomes including lung function, health-related quality of life, exacerbations, hospitalizations, and mortality. Pharmacological and physical treatment options are discussed. Authors state that high-frequency compression vests (HFCWO) may be of value, but note the lack of large clinical trials focused upon COPD patients.

2. Kim V, Criner GJ. Chronic bronchitis and Chronic Obstructive Pulmonary Disease. *Am J Resp Crit Care Med* 2013 Feb 1;187(3):228-37.

This review considers the most recent information on the epidemiology of COPD, new understanding of the pathophysiology of goblet cell hyperplasia and mucous hypersecretion in the disorder, and current therapeutic approaches. Epidemiological data show that chronic bronchitis (CB) is a common but variable phenomenon in COPD. Recent studies indicate that most patients lie somewhere in the middle of the classic COPD spectrum, with emphysema on one end and CB on the other, but that many patients with severe emphysema can also develop CB. The condition is caused by overproduction and hypersecretion of mucus by goblet cells, resulting in mucus obstruction of the small airways and progressively worsening airflow obstruction. Clinical consequences include accelerated decline in lung function, increased risk for lower respiratory tract infections, increased frequency of exacerbations and worse overall

mortality. Treatment goals are to target destructive pathological mechanisms including mucous hyperproduction and accumulation. HFCWO is listed among physical measures that may facilitate mucous clearance by increasing ciliary transport, reducing mucous tenacity, and increasing shear stress to augment detachment from airway walls. Authors call for large clinical trials, currently lacking, to demonstrate HFCWO benefit in COPD.

3. Miravitles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. *Respiratory Medicine*, 2011; 105 (8): 1118-1128.

In this observational study investigating clinical outcomes and care costs of outpatients with moderate to severe exacerbated COPD, the course of the exacerbation was evaluated at follow-up visits at 4 weeks and a cost analysis of the use of treatment-related healthcare resources was performed. Subjects included 260 COPD patients (mean age: 68.3 years; mean FEV1 = 58.9% of predicted) % predicted; 22% with significant cardiovascular comorbidity). Patients were prescribed, in compliance with local guidelines, a four-week course of various antibiotics (n = 137 moxifloxacin; n= 50 amoxicillin – clavulanate; n =70 – other antibiotics). Outcomes showed that exacerbation characteristics were generally similar across treatment groups although more patients in the moxifloxacin group than in the amoxicillin group reported increased sputum and fever > 38 °C (96% and 48.9 vs. 86% and 20.4% respectively; P < 0.03 for both). The rate of treatment failure at 4 weeks was 12.5 %, with no differences between the two most prescribed antibiotics. The calculated mean cost of exacerbation showed that 9.6 % of costs were for drugs and 72.9 % for hospital care of patients for whom treatment had failed. Two patients required lengthy in-patient stays and 9 were treated intensively in ER facilities (total hospital/ER days = 63 hospital days). The small percentage of patients that required in-patient or ER hospital attention generated almost two-thirds of the total costs of the exacerbations. Sputum hyper-production and/or purulence were a nearly universal characteristic in COPD exacerbation.

4. Burgel PR, Nesme-Meyer P, Chanez P, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. *Chest* 2009; 135:975–982.

In this cross-sectional analysis to identify features associated with chronic cough and sputum production, data were obtained in a multicenter (17 hospitals) cohort of 433 COPD patients (mean age: 65 ±11 yrs; FEV1: 50 ±20% predicted). Those with and without chronic cough and sputum production were assigned to 2 groups for comparison. (n = 321 and n= 112 respectively). Results showed no significant differences between groups for age, FEV1, body mass index, and comorbidities. Group I patients with chronic cough and sputum production had increased total mean numbers of exacerbations per patient per year (2.20 ± 2.20 vs 0.97 ± 1.19, respectively; p < 0.0001); increased moderate exacerbations (1.80 ± 2.07 vs 0.66 ± 0.85, respectively; p < 0.0001), and increased severe exacerbations requiring hospitalizations (0.43 ± 0.95 vs 0.22 ± 0.56, respectively; p < 0.02). Frequent exacerbations (two or more per patient per year) occurred in 55% vs 22% Group I and Group II patients, respectively (p < 0.0001). The total number of exacerbations per patient per year was the only variable independently associated with chronic cough and sputum production. Chronic cough and sputum production and decreased FEV1 were independently associated with an increased risk of frequent exacerbations and frequent hospitalizations. Results indicate a strong relationship between chronic cough and sputum production in COPD and frequent exacerbations, including severe exacerbations requiring hospitalization.

5. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *NEJM* 2004; 350 (26): 2645-2653.

In this recent PR study to better understand the evolution of pathological effects of airway obstruction, the small airways in surgically resected lung tissue of 159 COPD patients with disease severity ranging from 0-4 as defined by the Global

Initiative for Chronic Obstructive Lung Disease (GOLD) scale were assessed for various markers of disease progression. Findings demonstrated, among other variables, a strong correlation between the accumulation of inflammatory mucous exudates in airway lumen and disease progression.

II. Prevalence and Characteristics of Comorbid Bronchiectasis in COPD

A paradigm shift is underway in the understanding of the overlap between COPD and bronchiectasis. Accumulating studies demonstrate compelling correlations between high – resolution computed tomography (HRCT) imaging findings of bronchiectatic changes in a subset of COPD patients and increased bacterial colonization, airway inflammation and frequency and intensity of exacerbations [1, 3-5]. Increasingly, it has been shown that COPD and bronchiectasis often co-exist and may represent a unique phenotype [1,7]. Recent studies have shown a prevalence of bronchiectasis ranging from 30%-50% among patients with COPD [1,3,4]. Such patients demonstrate persistent mucus production and impairment of mucociliary transport mechanisms, have more frequent and severe exacerbations and are often colonized with difficult to eradicate airway pathogens and associated poor prognosis [1,2,3,5]. With longer survival among COPD patients, co-existing bronchiectasis is being diagnosed in a growing proportion of those who are older [8]. Regardless of underlying cause, all cases of bronchiectasis share the common denominator of mucus plugging and bacterial colonization. [1,3,8] Poor clearance of mucus from bronchiectatic airways is the proximate cause of bacterial colonization, progressive lung damage and related symptoms and complications. The articles and studies in this section support the conclusion that removal of impacted mucus from the airways of affected patients is both rational and medically necessary. HFCWO technology has the potential to contribute significantly to improving clinical management of COPD/ Bronchiectasis.

1. Novstad SA, Barker AF. Chronic obstructive pulmonary disease and bronchiectasis. *Curr Opin Pulm Med* 2013; 19: 133-139.
2. Soriano JB, Rodriguez-Roisin R. Chronic obstructive pulmonary disease overview. *Epidemiology, Risk factors and clinical presentation. Proc Am Thorac Soc.* 2011; 8: 363-367.
3. Martinez-Garcia MA, Soler-Cataluna JJ, Donat Sanz Y, et al. Factors associated with bronchiectasis in patients with COPD. *Chest* 2011; 140: 1130-1137.
4. Patel IS, Vlahos I, Wilkinson TM, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Resp Crit Care Med.* 2004; 170: 400-407.
5. O'Brien CO, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characteristics of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635-642.
6. Gursel G. Does coexistence with bronchiectasis influence intensive care outcomes in patients with chronic obstructive pulmonary disease? *Heart Lung* 2006; 35: 58-65.
7. Burgel PR. Cough and sputum production in COPD patients: clinical phenotype or markers of disease activity? [Editorial] *International J Clin Pract* 2013; 1218-1219.
8. Whitters D, Stockley RA. Bronchiectasis in older patients with chronic obstructive pulmonary disease: prevalence, diagnosis and therapeutic management. *Drugs Aging* 2013; 30: 215-225.

1. Novostad SA, Barker AF. Chronic obstructive pulmonary disease and bronchiectasis. *Curr Opin Pulm Med* 2013; 19: 133-139.

Chronic obstructive pulmonary disease (COPD) and bronchiectasis are two pathologically distinct yet related conditions that occur separately but can coexist. This literature review and discussion focuses upon emerging recognition of distinct COPD phenotypes (clinical presentations) with the goal of changing outcomes using tailored therapies. Research supports the likelihood that patients with both COPD and bronchiectasis represent a unique phenotype characterized by more severe disease, worse outcomes, a higher prevalence of potentially pathogenic organisms – especially *Pseudomonas aruginosa* – and more frequent exacerbations. It is speculated that the overlap of these morbidities provide an opportunity for implementation of targeted therapies.

2. Martinez-Garcia MA, Soler-Cataluna JJ, Donat Sanz Y, et al. Factors associated with bronchiectasis in patients with COPD. *Chest* 2011; 140: 1130-1137.

Bronchiectasis and COPD share many characteristics. Several studies have shown a high prevalence of bronchiectasis in patients with moderate to severe COPD, but the factors associated with bronchiectasis remain unknown. The aim of this study is to identify those factors using routine data collected during medical visits from patients with moderate to severe COPD. One hundred and six consecutive patients with moderate (50%, FEV1 < 70%) or severe (FEV1 < 50%) COPD were included prospectively. Ninety-two patients (51 severe and 41 moderate illness) met inclusion criteria. All subjects filled out a clinical questionnaire, including information about exacerbations. Peripheral blood samples and baseline PFT were obtained and sputum samples were provided for monthly microbiologic analysis for 6 months. At the time of testing, all patients had been stable for at least 6 weeks. High-resolution (HRCT) scans of the chest were used to diagnose bronchiectasis. Imaging interpretations showed evidence of bronchiectasis in 53 patients (57.6%). Variables independently associated with the presence of bronchiectasis were severe airflow obstruction, isolation of a potentially pathogenic microorganism (PPM) and at least one hospital admission due to COPD exacerbations in the previous year.

3. Patel IS, Vlahos I, Wilkenson TM, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400-407.

This study aimed to identify relationships between HRCT findings and the prevalence of bronchiectasis, bacterial colonization, airway inflammation and exacerbation indices among COPD patients. Patel, et al recruited 54 stable COPD patients from an East London clinic, excluding those with known bronchiectasis. Subjects had a mean age of 69 years, a history of smoking and mean FEV1 scores of 38.1 % predicted (\pm 13.9%). Exacerbation indices were determined from diary cards over two years and quantitative sputum bacteriology and cytokine measurements were performed. Evidence of bronchiectasis was seen on HRCT scans in 27 of 54 subjects (50%). Presence of bronchiectasis was associated with more severe exacerbations, lower airway colonization and increased sputum inflammatory markers.

4. O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterization of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Am J Respir Crit Care Med* 2000; 55:635-642.

In this screening study of COPD patients for coexisting bronchiectasis, O'Brien et al examined 110 stable patients aged 40-80 drawn from primary care clinics. HRCT scans and PFTs revealed a wide range of lung function impairment, secondary pathologies and disease severity. Among findings, 29% of subjects demonstrated evidence of bronchiectasis. Authors conclude that bronchiectasis, discovered by HRCT imaging in an unexpected nearly 30% of COPD patients, is significantly underdiagnosed. Under-diagnosis is likely to be highest in smokers where cough and sputum production are assumed to be consequences of COPD.

5. Gursel G. Does coexistence with bronchiectasis influence intensive care outcomes in patients with chronic obstructive pulmonary disease? Heart Lung 2006; 35: 58-65.

The aim of this study is to evaluate whether co-existing bronchiectasis/COPD influences morbidity and mortality during intensive care unit (ICU) stays. Among 93 mechanically ventilated (MV) patients in the respiratory ICU of a university hospital, 29 (31%) had both COPD and bronchiectasis. Medical records data showed that patients with COPD/bronchiectasis had more frequent hospitalizations, more severe airflow limitation, and higher pulmonary artery pressure than patients without bronchiectasis. Duration of ICU days in patients with bronchiectasis were significantly longer than in patients without bronchiectasis (27 ± 32 days [median: 14]; 16 ± 16 days [median: 9]; $P=.01$), respectively. The same was true for total hospital days (44 ± 44 days [median: 24.5]; 28 ± 26 days (median: 20); respectively $P=.046$). Bronchiectasis was an independent predictor for ICU stay longer than 10 days ($P=.043$). The incidence rate of ventilator-associated pneumonia (VAP), especially with *Pseudomonas aeruginosa*, was significantly higher in patients with bronchiectasis ($P=.034$). In this study population, however, COPD/bronchiectasis did not show greater mortality rates than those with COPD only ($P=.865$). Results suggest that the coexistence of bronchiectasis in patients with COPD may significantly increase the duration of ICU stay and hospitalization but appears not to influence the mortality.

6. Whitters D, Stockley RA. Bronchiectasis in older patients with chronic obstructive pulmonary disease: prevalence, diagnosis and therapeutic management. Drugs Aging 2013; 30: 215-225.

Despite an urgent need for a rational approach to management, information concerning effective treatment of COPD-related bronchiectasis is scanty. In this review, the epidemiology, diagnosis, pathophysiology and known factors associated with COPD/Bronchiectasis among older patients is discussed, followed by an assessment of the strength of evidence supporting current pharmacologic therapeutic approaches to control symptoms and exacerbations. Non-pharmacologic interventions are not discussed. Authors call for well-designed studies to answer important questions focused upon the recognition and treatment of a rapidly growing population of elderly COPD/bronchiectasis patients.

7. Nicolini A, Cardini F, Landucci N, et al. Effectiveness of treatment with high-frequency chest wall oscillation in patients with bronchiectasis. BMC Pulm Med 2013; 13: 21. <http://www.biomedcentral.com/1471-2466/13/21>

High frequency chest wall oscillation (HFCWO) is a widely used ACT that, in recent years, has been among the most frequently studied techniques. It is considered standard of care for cystic fibrosis (CF) management in the U.S. Treatment guidelines recommend mucous clearance in bronchiectasis, but, until this study, no clinical trials of HFCWO clearance have been conducted in patients with bronchiectasis. In this investigation to assess whether HFCWO is more effective than traditional ACT in this patient population, 30 of 37 enrolled patients (aged 18-85 with HRCT-scan confirmation of bronchiectasis) were accepted and randomized to three groups of 10. Pre-treatment, each patient had blood tests, sputum volume and cell counts, pulmonary function tests (PFTs) and completed quality of life (QOL) inventories (MMRC, CAT, BCSS).

- 10 group I subjects were treated with HFCWO for twice daily 30 minute sessions for 5 days.
- 10 group II subjects were treated for twice daily 45 minute sessions for 5 days with a variety of ACTs that included chest physiotherapy (CPT) with ELTGOL breathing techniques (expiration with the glottis open in the lateral posture) and positive expiratory pressure (PEP) mask or bottle).
- 10 group III subjects (control group) received medical therapy only.

Results showed that the HFCWO group alone showed significant improvement in blood inflammation parameter C-RP ($p \leq 0.019$), parameters of lung functionality associated with bronchial obstruction (FVC, FEV1) ($p \leq 0.006$ and $p \leq 0.001$ respectively), and in dyspnea scores. Both the HFCWO and CPT groups showed QOL improvement (BCSS, CAT) (both $p \leq 0.001$). Total cell counts in sputum samples remained similar, but the HFCWO group showed a significant reduction of neutrophils percentage ($p \leq 0.002$) and a significant increase of macrophages percentage ($p \leq 0.012$). Data suggest that HFCWO therapy may improve both pulmonary function and QOL-related parameters in patients with non-CF bronchiectasis.

8. Goeminne PC, Nawrot TS, Ruttens D, et al. Mortality in non-cystic fibrosis bronchiectasis: A prospective cohort analysis. *Respir Med* 2014; 108: 287-296.

There is limited data on mortality and associated morbidity in non-cystic fibrosis bronchiectasis (NCFB). The aim of this study was to analyze the overall mortality in newly diagnosed NCFB patients from June 2006 – October 2012 and to evaluate risk factors for mortality in this cohort. Two hundred and forty-five patients with HRCT scan – confirmed NCFB and productive cough were included. Death rates were compiled until end of November 2013. Overall mortality in NCFB patients (median follow-up = 5.18 years) was 20.4%. Patients with NCFB and associated COPD had a mortality of 55% during the study interval. Univariate analysis showed higher mortality according to age, gender, smoking history, *Pseudomonas aeruginosa* status, spirometry, radiological extent, total number of sputum bacteria and underlying etiology. Multivariate hazard ratio (HR) analysis showed significant higher mortality with increasing age (HR = 1.045; $p = 0.004$), with increasing number of lobes affected (HR = 1.53; $p = 0.009$) and when patients had COPD-associated NCFB (HR = 2.12; $p = 0.038$). The majority of the 50 deaths were respiratory related ($n = 29$; 58%). Compared to other NCFB patients, those with comorbid bronchiectasis/COPD had dramatically higher rates of mortality.

III. Selected Articles and Studies Supporting HFCWO Therapy in COPD

Studies of the effects and utility of HFCWO in patients with COPD and/or bronchiectasis have been small in scale and are not widely known. The comparatively limited resources of medical device manufacturers usually do not permit clinical trials matching the power and rigor of those conducted by major pharmaceutical firms. This trend is changing with increasing recognition of the rationale for aggressive secretion clearance interventions in patients with COPD, CB, and COPD/Bronchiectasis. Currently, the preponderance of existing studies is positive and suggests benefit sufficient to pursue larger, better designed studies.

1. Esquina A, Patel B, Pravinkumar E. High-frequency chest wall oscillation in infective exacerbation of COPD. Is airway secretion clearance the cornerstone? *Clin Rehabil* 2014; 28 (2): 206-207. [Editorial]

In this editorial commenting on the importance of accurately assessing the role of HFCWO in COPD therapy, authors identify major weaknesses in a recent study that may negatively influence clinical decision-making. (Goktalay T, et al. *Clin Rehabil* 2013; 27: 710-718) In particular, authors question 1) the use of “fixed application” rather than “patient-specific” therapy individualized on the basis of physiologically relevant parameters; 2) lack of data showing correlations with airway secretions and ACT techniques, noting the difficulty of estimating variable patient responses to HFCWO in clinical practice; 3) failure to use objective predictive parameters to distinguish infective and non-infective acute COPD, possibly affecting study outcomes; 4) failure to distinguish between subjects with classic COPD and those with COPD/bronchiectasis, thus obscuring the possibility that differences in secretion characteristics may influence the effectiveness of HFCWO therapy. Authors conclude that, “further clinical studies with more patient-specific parameters such as airway

secretion score and intrinsic predictive factors associated with acute COPD. . ." would best advance understanding of the utility of HFCWO in the treatment of acute disease exacerbations.

2. Mahajan, AK, Diette GB, Hatipoglu U, et al. High frequency chest wall oscillation for asthma and chronic obstructive pulmonary disease exacerbations: a randomized sham-controlled clinical trial. *Resp Res* 2011; 12:120.

Many patients with COPD and acute asthma suffer from airway mucous hypersecretion and impaired mucociliary clearance (MCC). Resulting airway plugging may reduce the deposition, and therefore response, to important aerosolized medications. In this study to evaluate the early use of HFCWO in the treatment of adults hospitalized for acute exacerbations of either COPD or asthma, 52 qualifying patients (n = 31 asthma, 19 COPD, 2 acute asthma and COPD) were randomized to receive within 24 hours of admission either double-blinded HFCWO active (A) or sham (S) device therapy for 15 minutes three times a day for 4 treatments. Both COPD and asthma HFCWO users showed clinically significant improvement of dyspnea compared with sham device users (70.8% vs. 42.3%; P = 0.04). Secondary outcomes including FEV1 and sputum production were equivalent. Both active HFCWO and sham groups demonstrated high levels of treatment satisfaction and tolerance.

3. Chakravorty I, Chahal K, Austin G. A pilot study of the impact of high-frequency chest wall oscillation in chronic obstructive pulmonary disease in patients with mucus hypersecretion. *International Journal of COPD* 2011; 6: 693-699.

Thirty patients hospitalized with acute exacerbations of COPD were recruited to a randomized controlled crossover study to investigate the impact of 4 weeks of HFCWO versus 4 weeks of conventional treatment on symptom relief. Twenty – two patients completed the study; 8 were withdrawn owing to worsening illness. Results showed that, during HFCWO treatment phase, patients with moderate to severe COPD and mucous hypersecretion showed clinically but not statistically significant reduced sputum production, improved symptom relief and quality of life (QOL) scores.

4. Bhowmik A, Chahal K, Austin G, Chakravorty I. Improving mucociliary clearance in chronic obstructive pulmonary disease. *Respir Med* 2009; 103: 496-502.

In this review article, authors compile recent research and expert opinion on physiotherapy techniques to improve MCC that may be potentially useful in improving outcomes and promoting self-management in patients with COPD. In their discussion of HFCWO, evidence of positive physiological effects in laboratory studies and of clinical studies showing benefit in non-COPD patients is acknowledged, but its value in COPD remains unclear owing to a lack of good quality studies in this patient population. On the basis of good evidence of the benefit in cystic fibrosis and the comparative advantages of HFCWO over several alternative approaches to MCC, authors call for intensified efforts to investigate clinical and quality of life (QOL) outcomes in COPD patients.

5. Rumbak MJ, Marchione VL, Kennedy TC, Rolfe MW. Ninety-day assessment of the effect of high-frequency chest wall oscillation (HFCWO) on exercise tolerance and quality of life of patients with chronic obstructive pulmonary disease. *Chest* 2001; 120:4(Suppl): 250S. (Presented at ACCP Chest Conference, November 2001).

Patients with COPD may improve their symptoms, function and QOL with airway clearance therapy (ACT) provided by HFCWO. This 90 day trial - use study to assess the effects of HFCWO on pulmonary function, symptoms, exercise tolerance and QOL enrolled 85 patients (confirmed COPD; age > 40 yrs; FEV1 < 70% of predicted; evidence of retained secretions, dyspnea and decreased functional ability) Baseline medical history, PFTs, 6-minute walk distance, dyspnea (Borg and

baseline transitional dyspnea); symptom and SF-QOL scores were determined. Patients received in-home HFCWO training. Patients were asked to perform therapy for 15-30 minutes daily; treatment adherence and satisfaction was monitored during the trial period. At 90 days, 59/85 patients completed the study (69.4%). Among the 59 who completed the trial, 38 (64.4%) sought lifetime prescriptions. Analysis of data for this subset of participants who both completed the trial program AND then elected to continue HFCWO therapy found that they experienced statistically significant and/or clinically important trend improvements in all treatment and QOL outcomes as measured by validated instruments. Results suggest that a trial period of HFCWO therapy can help identify COPD patients who are most likely to use and benefit from treatment.

6. Diette GB, Rand C, Thompson K, et al. A pilot study of high frequency chest wall oscillation (HFCWO) to reduce acute exacerbations of COPD: Poster Presentation. Chest 2007; 132 (4): Suppl: 531S.

Chronic mucus hypersecretion is common in COPD and associated with acute exacerbations (AE). In this pilot sham-controlled double-blinded parallel group trial to assess the efficacy of HFCWO airway clearance therapy (ACT) in reducing AE, 50 patients with COPD were randomized to receive either ACT 30 minutes daily for 12 weeks with either standard HFCWO equipment (A Group; n=26) or a sham device (S group; n=24). Patient characteristics included FEV1/FVC < 70%; > 20 pack years tobacco; age > 45; > 1 AE-COPD in past 6 mos. Outcomes after 12 weeks showed the AE-COPD was common in both A and S groups (92% vs 95% respectively), but the rate was lower in the A group (4 vs. 5.5/12 weeks; P = < .02 by Poisson regression). At 12 weeks, daily phlegm production decreased in a large number of A group subjects (75% to 52%) but increased in the S group (54% to 67%). (P = .35 for difference). QOL improved for both A and S groups (P= .02 and .04 respectively), but self-reported adherence was somewhat lower in the A group (57% vs 80%). Authors conclude that the significant reduction in the rate of AE-COPD in the A vs the S group, together with a similar trend toward improved QOL justify further investigation.

7. Diette GB, Bilderback A, Becker B, et al. Adherence to high-frequency chest wall oscillation (HFCWO) improves quality of life in COPD: Poster Presentation. ERS International Congress 2009; 34: Suppl 53: 359S.

In this pilot sham-controlled double-blinded parallel group trial to assess the efficacy of HFCWO airway clearance therapy (ACT) in reducing acute exacerbation (AE) in COPD, treatment adherence (TA) was analyzed as a secondary outcome. Fifty patients with COPD were randomized to receive either ACT 30 minutes daily for 12 weeks with either standard HFCWO equipment (A Group; n=26) or a sham device (S group; n=24). (Patient characteristics included FEV1/FVC < 70%; > 20 pack years tobacco; age > 45; > 1 AE-COPD in past 6 mos). Both HFCWO and sham TA were assessed by an automatically activated electronic monitor and by self-report. Regression models were developed to assess adherence as a predictor of improved health status. Results showed median HFCWO usage of 23.4 min/day with electronic monitoring vs 28.6 min/day by self-report. Both QOL (P= <0.01) and phlegm frequency and severity (P=0.03) improved with greater TA. Improved QOL appears to be mediated by phlegm reduction, underscoring the importance of TA in managing secretions in COPD.

8. Perry RJ, Man GCW, Jones RL. Effects of positive-end expiratory pressure on oscillated flow rate during high-frequency chest compression. Chest 1998; 113 (4): 1028-1033.

The aim of this study was to investigate effects of positive end-expiratory pressure (PEEP) on end-expiratory lung volume (EELV) and mean oscillated flow rate (OSC) during HFCWO in normal subjects and in patients with severe COPD. Six normal subjects and six with stable COPD received HFCWO at 10 Hz with a mean chest wall pressure of 16 cm H₂O while a closed circuit spirometer system measured HFCWO and PEEP – induced changes in EELV. No adverse events were noted. Results showed that, in the COPD group, the addition of a small amount of positive end expiratory pressure (PEEP)

during HFCWO therapy prevents decreased EELV and increases OSC during both phases of spontaneous breathing. Investigators speculated that the higher oscillated flow rates achieved during HFCC+ the addition of a modest amount of PEEP may improve the effectiveness of HFCWO in clearing mucus from the lungs of patients with airway disease.

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Patients with severe COPD experience debilitating respiratory muscle fatigue. Investigators reasoned that the application of HFCWO during the expiratory phase of normal tidal breathing could provide advantageous ventilator effects in such patients. In this study, 12 male patients with severe COPD and dyspnea received HFCWO for 15 minutes during the expiratory phase of spontaneous breathing. Fifteen minute pre and post gas exchange and breathing patterns were compared. Results showed decreased respiratory rates, increased tidal volumes, increased arterial PO₂, decreased arterial PCO₂, and decreased duty cycle (time of inspiration/total breath period), suggesting that HFCWO may facilitate inspiratory muscle work and enhance both gas exchange and inspiratory muscle function. The potential of HFCWO to strengthen respiratory muscle function and improve ambulatory care in patients with severe COPD merits further investigation.

IV. Supplemental Literature

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