

Chronic Obstructive Pulmonary Disease – A Role for High Frequency Chest Compression Therapy

Jane Braverman, PhD, Amy Kulenkamp, MS, RRT

“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.

Management of Chronic Obstructive Pulmonary Disease (COPD) is a topic of unrelenting debate. However, the urgent need for better strategies is not in dispute. Tens of billions of dollars are spent annually to combat a condition soon to become the third most common cause of death worldwide.¹ As the American population ages, if effective interventions remain elusive, healthcare resources will be overwhelmed.² New insights into COPD pathophysiology suggest that, for selected patients, high-frequency chest compression (HFCC) therapy may be a simple, practical way to stabilize or slow disease progression and provide symptomatic relief.

Introduction

COPD is complex, variable and incompletely understood. The term, used to classify an heterogeneous spectrum of non-cystic fibrosis (CF) obstructive lung disorders, defies consensus definition.³ It is agreed, however, that COPD encompasses an array of chronic respiratory disorders distinguished by obstructive-pattern alterations of the respiratory system. Pathological features include structural changes of the small airways, loss of alveolar attachments and decreased elastic recoil of the lung.⁴ Airflow limitation, impaired gas exchange, dyspnea, inflammation and impairment of mucociliary clearance (MCC) mechanisms are characteristic. Significantly increased sputum production, or chronic bronchitis (CB), is common but not universal.^{5,6}

Until recently, COPD has been considered progressive, irreversible, and incurable.^{7,8} Therapeutic interventions, largely unrewarding, were limited to relief of symptoms and management of acute exacerbations.

After decades of therapeutic nihilism, understanding of the pathophysiology of COPD has advanced significantly. New insights have encouraged development of novel strategies with the potential to modify or control some causes and effects of disease progression.⁹ Discoveries concerning inflammation, oxidative stress and proteolysis within the lungs drive the search for targeted drugs.¹⁰ Recognition that mucus hypersecretion and airway hyperreactivity trigger episodes of acute illness motivate efforts to manage pulmonary secretions.^{11,12} The implications are immense.

Airway Mucus and COPD: The British hypothesis

Historically, airway mucus has been dismissed as an annoying but benign feature of COPD. In 1977, Fletcher and Peto published an influential paper affirming the view, widely known as the “British hypothesis,” that the effects of mucus hyperproduction on lung capacity were insignificant.¹³ In a subsequent paper, they reported results of a 20-year prospective questionnaire-based assessment and follow-up of nearly 3,000 British occupational cohort male smokers.¹⁴ The data showed a strong correlation between airflow obstruction - but not mucus hypersecretion- and death. On the strength of this and other evidence suggesting the harmlessness of excess mucus in COPD, most clinicians did not consider it worthy of aggressive treatment.

New insights

In the early 1990s, a rapid succession of robustly powered epidemiological studies challenged conventional views about the role of mucus in COPD. Those observations showed clear, increasingly powerful correlations between chronic mucus hypersecretion and clinical consequences. Outcome findings include increased frequency and severity of disease exacerbation, increased rates of hospitalization, sharply accelerated decline in FEV1 and premature death.

- A ten-year follow-up study of 13,756 randomly selected Danes found that risk of death was significantly higher for individuals with COPD, impaired ventilatory function, and chronic mucus hypersecretion.¹⁵
- A 12-year follow-up study of nearly 4,000 individuals with respiratory symptoms showed that men with chronic mucus production had accelerated rates of decline in FEV1.¹⁶
- A 10-12 year follow-up of 14, 223 COPD subjects showed that mucus hypersecretion together with pulmonary infection is a significant predictor of death, but not of death without pulmonary infection.¹⁷
- An 8-10 year follow-up of nearly 9,500 COPD subjects found that chronic mucus hypersecretion was significantly and consistently associated with both an excess in FEV1 decline and increased risk for hospital admission.¹⁸
- A 12-year study of more than 13,000 Danish men and women found that mucus hypersecretion and reduced FEV1 were important risk indicators for severe pneumonia, hospitalization, and death.¹⁹
- A cross sectional study of ambulatory COPD patients seen in more than 200 pulmonology practices in Spain concluded that chronic mucus hypersecretion is significantly associated with the risk of frequent exacerbations.²⁰

Growing interest in the effects of chronic mucus hypersecretion has inspired a sharp increase in basic research concerning mucus, cilia, and mucociliary interactions. Symposia publications and electronic databases cite hundreds of papers describing the role of mucus in respiratory pathophysiology in general and in COPD in particular.^{21,22} Histological studies of lung tissue affected by stagnant mucus demonstrate epithelial damage, inflammation, alterations in gas exchange structures and dysfunctional or absent airway cilia.^{5,8} Studies of abnormal mucus production, rheology, clearance and cough function reinforce epidemiological and observational evidence.^{11,12,23}

Chronic cough and daily mucus hypersecretion are now recognized as predictive of frequent COPD exacerbations and accelerated decline in health status.²⁴ Evidence unequivocally demonstrates that excess, retained mucus contributes to progressive lung injury and obstructed airflow.^{18,25,26} Health consequences are measurable. Annually, patients with advanced COPD have a median of two acute exacerbations requiring hospitalization.²⁷ An estimated 29-50% of COPD have demonstrable bronchiectasis.^{25,28} Those with lower lobe bronchiectasis generally experience more refractory exacerbations owing to bacterial colonization in the lower lobes.

Rationale for mucus clearance techniques in COPD

Improved understanding of the role of mucus as a vehicle of pulmonary destruction in COPD provides a compelling rationale for the use of assistive secretion clearance interventions. Routine airway clearance therapy (ACT) is accepted universally as a cornerstone of treatment for cystic fibrosis (CF) and primary ciliary dyskinesia (PCD). Both conditions are characterized by impaired MCC, mucus hypersecretion and ultimately, bronchiectasis.^{29,30} Extrapolation of evidence supporting ACT in these diagnoses suggests that COPD patients with a similar pattern of impaired MCC should also show therapeutic benefit.

Despite the intuitive rationale for managing secretions in affected COPD patients, ACT is rarely provided. This neglect is explained, at least in part, by the emphasis upon development of pharmacologic solutions. A second explanation is found in the poor or equivocal outcomes of a small number of dated studies evaluating the usefulness of chest physiotherapy (CPT) in COPD.

Mucoactive drugs

Several pharmaceutical firms have launched major initiatives to develop mucoactive drugs aimed specifically at moderating mucus production and enhancing mucus clearance in COPD.^{31,32} Currently, most patients receive at least one and frequently two such drugs. Clinically, however, the benefits of mucolytic and mucokinetic agents have been disappointing. Among more than fifty such commercially available compounds, fewer than ten are listed consistently in publications for prescribing physicians.³² Randomized controlled trials involving five different drugs failed to show clinical benefit in terms of accelerated recovery from acute exacerbations.³³ Although some COPD/CB patients may show symptom relief from mucoactive drugs, most consensus statements find that current evidence does not justify general use.³²

COPD and chest physiotherapy

For more than 30 years, conventional CPT, defined as any combination of postural drainage, chest percussion and

vibration and cough techniques, has been tried and studied in a limited number of COPD patients. Although most studies confirm that CPT does what is intended to do - transport and help evacuate mucus - few have captured data to support its routine use in patients with COPD.^{34,35,36} On the basis of randomized clinical trial results, consensus statements on the treatment³ of acute exacerbations echo the general view that "chest physiotherapy does not appear to be of benefit."^{24,37}

Absence of evidence of benefit vs evidence of absence of benefit

Re-evaluation of the usefulness of ACT in COPD is urged in a recent critique of the limitations of existing CPT studies.³⁸ Most published CPT/COPD trials have broad inclusion criteria that do not select for clinical evidence of mucus hypersecretion. Unsurprisingly, those studies fail to demonstrate statistically significant benefit from CPT. Poor control of both subject-related and CPT technique-related variables confound outcomes data further. Perhaps equally important, those COPD/CPT studies are limited by failure to recognize barriers to the effective use of the therapy. CPT is a technique-dependent modality requiring considerable skill, physical strength and caregiver commitment. On the patient side of the equation, many individuals with COPD are fragile, obese, disabled and mentally challenged. Physical fragility or deformities increase risk for therapy-related injury. Ventilators, intravenous lines, catheters, pacer wires etc further complicate repeated positioning of patients safely and effectively. Cognitive impairment or depression contribute to unwillingness to cooperate. In fact, patient inability to tolerate required maneuvers may preclude use of CPT altogether. Gravitational postural drainage may increase dyspnea, induce hypoxemia and increase work of breathing. CPT is associated with increased episodes of gastroesophageal reflux (GOR).³⁹ Recent studies have shown that the effects of CPT-induced GOR may have serious adverse respiratory consequences including accelerated progression of lung disease in susceptible patients.^{40,41}

Trials investigating the benefit of CPT in COPD were doomed to failure by enrollment of inadequately screened subjects and disregard for confounding limitations of the interventional therapy. It is unfortunate that results of those studies are often accepted as evidence of absence of treatment benefit.^{24,37} Because the rationale for secretion clearance therapy in COPD is so compelling, negative studies should be subjected to renewed scrutiny. Methodological flaws should be identified and used to guide the design of new trials targeting only those patients whose clinical status suggests the possibility of therapeutic benefit. CPT is simply not a practical therapy for COPD patients. That fact should not discourage the search for a better method.

A practical choice: high-frequency chest compression (HFCC)

In patients lacking the ability to tolerate CPT and other technique and/or effort-dependent forms of ACT, only one therapeutic modality holds promise: high-frequency chest compression (HFCC). HFCC therapy is an FDA-approved airway clearance technology. Phase I and Phase II studies provide qualifying safety data and demonstrate a variety of physiological effects influencing mucus mobilization and clearance.⁴² Dozens of clinical trials demonstrate the safety and efficacy of HFCC in a broad range of patient populations.⁴² The therapy has been used widely and successfully in patients with CF. Patients with

acute illness, serious trauma, status post-operative or with airway clearance compromise arising from an array of other conditions that compromise MCC have shown benefit. In numerous published studies, investigational endpoints include the comparative volume of expectorated secretions, changes in pulmonary function scores, quality of life gains and reductions in healthcare utilization.^{42,42,43,44,45}

HFCC therapy is administered by means of an air pulse generator attached by two lengths of tubing to an adjustable, inflatable jacket garment fitted over the users' thorax. The jacket component of the device transmits compressive forces to the chest wall to produce increased airflow and oscillatory effects within the airways, thus enhancing mucus mobilization and clearance. The therapy is technique-independent and requires no active effort from the user.

HFCC technology allows self-administered therapy; most patients require little or no caregiver assistance. Tolerance barriers and risk for GOR are eliminated because, unlike CPT, the therapy does not require trendelenberg positioning, physical or mental cooperation. During HFCC, all segments of the lung are treated simultaneously. Aerosolized medications may be administered during therapy, thus reducing time and burden of treatment. Because HFCC is automated, treatments are consistent and reliable.

HFCC and COPD

Although some COPD/HFCC studies have been done, they are small in scale and not widely known. Unfortunately, the comparatively limited resources of medical device manufacturers usually do not permit studies matching the power, rigor and complexity of those conducted by major pharmaceutical firms. Nevertheless, existing COPD/HFCC studies are consistently positive and suggest benefit sufficient to pursue further studies.

- HFCC therapy may alleviate COPD symptoms by: 1) improving respiratory muscle function, resulting in better ventilation and gas exchange; 2) improving secretion clearance, resulting in reduced airway obstruction and dyspnea; and 3) facilitating better disease self-management.⁴⁶
- HFCC therapy may augment respiratory muscle training by strengthening respiratory muscles.⁴⁷
- HFCC may facilitate inspiratory muscle work and enhance both gas exchange and inspiratory muscle function in patients with severe COPD thus facilitating pulmonary rehabilitation.³²
- In a 90-day trial of high frequency chest compression (HFCC), COPD patients that completed the trial program and then elected to continue HFCC therapy experienced statistically and/or clinically significant improvements in treatment and quality-of-life outcomes measured by validated instruments. Outcome domains include: 1) dyspnea; 2) six-minute walk distance; 3) quality of life (general health category); 4) treatment satisfaction and; 5) treatment adherence.⁴⁸
- A comparison of the safety and efficacy of percussion and postural drainage (P&PD) and high frequency chest compression (HFCC) in treatment of long-term mechanically ventilated patients showed equivalent safety and efficacy; 80% of therapists believed HFCC reduced their workload.⁴⁹

Conclusion

In selected COPD patients, the rationale for aggressive secretion clearance interventions is compelling. The strong relationship

between mucus hypersecretion and poor clinical outcomes, escalating healthcare expenditure and premature death is indisputable. Poorly designed studies, chiefly investigating CPT, have yielded conclusions suggesting that ACT offers little or no benefit. Uncritical acceptance of those conclusions may have devastating consequences. Failure to scrutinize counterintuitive data and to identify methodological flaws in such studies may delay identification of therapies potentially useful to many patients.

Results of studies investigating the use of HFCC in COPD are uniformly positive. Because HFCC technology eliminates virtually all the extrinsic and intrinsic limitations associated with CPT, it is also practical. Negative attitudes about the use of physiotherapy in COPD should be suspended until clinicians and investigators have tried HFCC in appropriately selected patients. HFCC may prove to be a simple, effective way to stabilize or slow disease progression and provide symptomatic relief for many COPD sufferers. Further studies should be encouraged.

References

- 1 Yelin E, Trupin L, Cistermas M, Eisner M, Katz P, Blanc P. A national study of medical care expenditure for respiratory conditions. *Eur Respir J* 2002; 19: 414-421.
- 2 Afessa B, Morales U, Scanlon PD, et al. Prognostic factors, clinical course, and hospital outcomes of patients with chronic obstructive pulmonary disease admitted to intensive care for respiratory failure. *Crit Care Med*. 2002; 30: 1610-1615.
- 3 Rodriguez-Roisin R: Towards a consensus definition for COPD exacerbations. *Chest* 2000, 117:398S-401S.
- 4 Decramer M, De Benedetto F, Del Ponte A, Marinari S. Systemic effects of COPD. *Resp Med* 2005; 99, S3-S10.
- 5 Hogg JC. Chronic obstructive pulmonary disease: an overview of pathology and pathogenesis. In: *Chronic Obstructive Pulmonary Disease: Pathogenesis to Treatment*. Novartis Foundation Symposium 234; (John Wiley and Sons, New York, 2001) pp. 4-19.
- 6 Rogers DF. Mucus pathophysiology in COPD: differences to asthma, and pharmacotherapy. *Monaldi Arch Chest Dis* 2000 Aug; 55(4): 324-32. Review.
- 7 Cella BR. Current thoughts regarding treatment of chronic obstructive pulmonary disease. *Med Clin N Am*. 1996; 80:589-609.
- 8 Rodriguez-Roisin R, MacNee W. Pathophysiology of chronic obstructive pulmonary disease. In: *Management of Chronic Obstructive Pulmonary Disease*, European Respiratory Monographs Vol. 3 (7), Postma DS, Siafakas NM, eds. U.K.: ERS Journals Ltd, 1998.
- 9 Barnes, PJ. Potential novel therapies for chronic obstructive pulmonary disease. In: *Chronic Obstructive Pulmonary Disease: Pathogenesis to Treatment*. Novartis Foundation Symposium 234; (John Wiley and Sons, New York, 2001). PP. 255-267.
- 10 Rennard SI, Farmer SG. COPD in 2001: a major challenge for medicine, the pharmaceutical industry and society. *Chest* 2002, 113S-115S.
- 11 Takisima T, Shimura S. Airway hypersecretion in bronchial asthma and chronic obstructive pulmonary disease. In: *Airway Secretion: physiological bases for the control of mucous hypersecretion*. Takisima T, Shimura S., eds. *Lung Biology in Health and Disease*, Vol. 72 (Marcel Dekker, New York 1994) pp. 527-578.
- 12 Chodosh S. Sputum production and chronic bronchitis. In: *Airway Secretion: Physiological Bases for the Control of Mucous Hypersecretion*. Takishema T, Shimira S, eds. (Lung

- Biology in Health and Disease, Vol 72; Marcel Dekker, Inc., New York 1994) pp. 579-628.
- 13 Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977; 1 (6077): 1645-1648.
 - 14 Peto R, Speizer FE, Cochrane AL, et al. The relevance in adults of air-flow, but not of mucus hypersecretion, to mortality from chronic obstructive lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis*. 1983 Sep; 128(3):491-500.
 - 15 Lange P, Nyboe J, Appleyard M, et al. Relation of ventilatory impairment and chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; 45 (8): 579-585.
 - 16 Sherman CB, Xu X, Speizer FE, et al. Longitudinal lung function decline in subjects with respiratory symptoms. *Am Rev Respir Dis* 1992; 146: 855-859.
 - 17 Prescott E, Lange P, Vestbo J. Mucus hypersecretion identified as significant predictor of COPD-related death with pulmonary infection. *Eur Respir J* 1995; 8 (8): 1333-1338.
 - 18 Vestbo J, Prescott E, Lange P. Chronic mucus hypersecretion in patients with COPD associated with increased FEV1 decline and increased risk of hospitalizations. *Am J Respir Crit Care Med* 1996; 153: 1530-1535.
 - 19 Lange P, Vestbo J, Nyboe J. [Risk factors of death and hospitalization due to pneumonia. Results from the Osterbro Study.] *Ugeskr Laeger* 1997; 10: 159 (7): 956-959
 - 20 Miravittles M, Guerro T, Mayordomo C. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients; a multiple logistic regression analysis. The EOLO Study Group. *Respiration* 2000; 67 (56): 495-501.
 - 21 Cilia and Mucus: From Development to Respiratory Disease. Matthias Salathe, Ed., (Marcel Dekker, Inc., New York, NY, 2001)
 - 22 Cilia, Mucus, and Mucociliary Interactions Feb 27-Mar 4, 2005; Buellton, CA., (Richard Boucher and Matthias Salathe, Chairs). <http://www.grc.uri.edu/programs/2005/cilia.htm>
 - 23 King M, Rubin BK. Rheology of airway mucus: relationship with clearance function. In: *Airway Secretion in Health and Disease: Physiological Bases for the Control of Mucous Hypersecretion*, Takishima T and Shimura S, eds. (Marcel Dekker, Inc., New York, 1994), 283-314.
 - 24 Fabbri LM, Hurd SS. Global strategy for the diagnosis, management and prevention of COPD: 2003 update. *Eur Respir J* 2003; 22: 1-2.
 - 25 Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, Reznick RH, Wedzicha JA. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004 Aug 15; 170(4):400-7.
 - 26 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998; 157: 1418-1422
 - 27 Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000; 161: 1608-1613.
 - 28 O'Brian C, Guest PJ, Hill SL, Stockly RA. Physiological and radiological characterization of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635-642.
 - 29 Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care: consensus conference report. *Chest* 2004; 125:1 S-39S.
 - 30 Bush A, Cole PJ, Hariri M, et al. Primary ciliary dyskinesia: diagnosis and standards of care. *Eur Respir J* 1998; 12: 982-988.
 - 31 Rogers DF. Mucoactive drugs for asthma and COPD: any place in therapy? *Expert Opin Invest Drugs* 2002; 11 (1): 15-35.
 - 32 Poole PJ, Black PN. Mucolytic agents for chronic bronchitis (Cochrane Review). In: *The Cochrane Library, Issue 2*. Cochrane Database Syst Rev 2000; URL: www.update-software.com.
 - 33 McCorry DC, Brown C, Gelfand SE, et al. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest* 2001; 119: 1190-1209.
 - 34 Bateman JR, Newman SP, Daunt KM, Pavia D, Clarke SW. Regional lung clearance of excessive bronchial secretions during chest physiotherapy in patients with stable chronic airways obstruction. *Lancet*. 1979; 1 (8111):294-297.
 - 35 Bateman JR, Newman SP, Daunt KM, Sheahan NF, Pavia D, Clarke SW. Is cough as effective as chest physiotherapy in removal of excessive tracheobronchial secretions? *Thorax*. 1981; 36:683-687.
 - 36 Gallon A. Evaluation of chest percussion in the treatment of patients with copious sputum production. *Respir Med* 1991; 85:45-51.
 - 37 Bradley JM, Moran FM, Stuart Elborn J. Evidence for physical therapies (airway clearance and physical training) in cystic fibrosis: An overview of five Cochrane systematic reviews. *Respir Med* 2006; 100:191-201.
 - 38 Holland AE, Button BM. Is there a role for airway clearance techniques in chronic obstructive pulmonary disease? *Chron Respir Dis* 2006; 3: 83-91.
 - 39 Bendig DW, Seilheimer DK, Wagner ML, Ferry GD, Barrison GM. Complications of gastroesophageal reflux in adult cystic fibrosis patients. *J R Soc Med* 1998; 91 (1): 7-9.
 - 40 Button BM, Heine RG, Catto-Smith AG, Olinsky A, Phelen PD, Ditchfield MR, Story I. Chest physiotherapy in infants with cystic fibrosis: To tip or not to tip? A five-year study. *Pediatr Pulmonol* 2003; 35 (3): 208-213.
 - 41 Vandeplass Y, Dietrich A, Blecker U, Lanciers S, Deneyer M. Esophageal pH monitoring data during chest physiotherapy. *J Pediatr Gastroenterol Nutr* 1991; 13:23-6
 - 42 Milla CE, Hansen LG, Weber A, Warwick WJ. High-frequency chest compression: effect of the third generation compression waveform. *Biomed Instrum Technol* 2004; 38:322-328.
 - 43 Kluff J, Beker L, Castagnino M, Gaiser J, Chaney H, Fink R. A comparison of bronchial drainage treatments in cystic fibrosis. *Pediatr Pulmonol* 1996; 22:271-274
 - 44 Braggion C, Cappelletti LM, Cornacchia M, Zanolla L, Mastella G. Short-term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a cross-over randomized study. *Pediatr Pulmonol* 1995; 19:16-22.
 - 45 Warwick WJ, Hansen LG. The long-term effect of high-frequency chest compression therapy on pulmonary complications of cystic fibrosis. *Pediatr Pulmonol* 1991; 11:265-271.
 - 46 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.
 - 47 Piquet J, Brochard L, Isabey D, De Cremoux H, Chang HK, Bignon J, Harf A. High frequency chest wall oscillation in patients with chronic airflow obstruction. *Am Rev Respir Dis* 1987; 136:1355-1359.
 - 48 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).
 - 49 Whitman J, Van Beusekom R, Olson S, Worm M, Indihar F. Preliminary evaluation of high-frequency chest compression for secretion clearance in mechanically ventilated patients. *Respir Care* 1993; 38:1081-1087.