

## Airway Clearance in Cystic Fibrosis

Airway clearance is considered an integral component of standard therapy for cystic fibrosis (CF) patients. Although the pathophysiology of CF has not been conclusively delineated, most of the theories revolve around the development of viscous airway secretions.<sup>1-4</sup> These secretions are thought to be poorly cleared from the lung, leading to airway obstruction and infection with *Staphylococcus aureus* and *Haemophilus influenzae* early in the disease, followed by *Pseudomonas aeruginosa* later in the disease.<sup>5,6</sup> Chronic inflammation either secondary to abnormal mucus and bacterial infection or related to the underlying defect then leads to airway injury, airway fibrosis, and bronchiectasis.<sup>7</sup> There is clear evidence that CF patients have abnormal mucociliary clearance and mucus plugging very early in the disease.<sup>8,9</sup> Pathophysiologic reasoning suggests airway clearance makes sense and could modify the course of the disease. The goal of airway clearance techniques is to enhance clearance of airway secretions, thus potentially limiting the bacterial burden and decreasing inflammation in the conducting airways. Theoretically, to substantially alter the natural history of the disease, airway clearance should be started early in the course of the disease. Thus the scientific basis for this therapy is very sound.

---

SEE THE ORIGINAL STUDY ON PAGE 24

---

The range of techniques and devices to enhance airway clearance is very diverse, ranging from simple cough or physical exercise to high-frequency chest wall compression (HFCWC) with *The Vest*, a \$16,000 external device that uses high-frequency chest compressions to enhance clearance. Two of the more complete recent reviews of this topic were published in *RESPIRATORY CARE*.<sup>10,11</sup> One of the major problems with the entire body of literature on CF airway clearance is that most of the clinical trials have been small, under-powered, run over short periods of time, and without clear meaningful clinical end points. The end points of studies to date have included clearance of radio-labeled isotopes, lung function, sputum weight (wet and dry), gas exchange, and chest radiograph changes. There has been very little conclusive evidence of the efficacy of many, if not all the techniques and devices with CF patients.

A more recent meta-analysis looked specifically at positive expiratory pressure, forced expiratory technique, exercise, autogenic drainage, and standard chest physiotherapy (CPT) for CF, reviewing and summarizing a total of 35 articles that met the authors' quality criteria.<sup>12</sup> That study concluded that standard CPT enhances sputum production, compared to no treatment, and a combination of standard CPT and exercise increases forced expiratory volume in the first second (FEV<sub>1</sub>) more than standard CPT alone. In a Cochrane database meta-analysis of CPT versus no CPT, only 7 trials (126 patients) met their criteria for inclusion in the analysis. Because of differences among patient groups, the studies could not be pooled, and the researchers concluded that there was no evidence to either support or refute the use of CPT for chronic obstructive lung disease or bronchiectasis.<sup>13</sup> Van der Schans et al came to the same conclusions when doing a meta-analysis to compare the effect of standard CPT to cough or no CPT, finding that no studies met their inclusion criteria.<sup>14</sup> Like the prior analyses, they found that there was a lack of "robust" evidence to support the conclusion that CPT is beneficial in CF.

Given the current understanding of the disease pathophysiology, lack of clear efficacy in the literature need not indicate that CPT is not a useful or effective treatment. Much of medical practice is not evidence-based. Several factors must be assessed when considering the use of a nonpharmaceutical therapy that does not have proven efficacy in clinical medicine. I believe that therapies that fulfill all of the following 3 criteria can be advocated for patient use, without good empirical evidence of efficacy:

1. The therapy/device must be extremely safe. If it is extremely safe and cannot harm a person, one can argue that the weight of the evidence need not be as great to advocate its use.

2. The therapy/device must be inexpensive. In the era of rapidly rising pharmaceutical and medical bills, expensive unproven therapies should be abandoned. There is clearly a gradation of cost.

3. The therapy must be consistent with the current understanding of the pathophysiology of disease.

If all 3 of these criteria are met in a nonpharmaceutical therapy/device, clinicians should not dissuade their patients from using that therapy/device.

An alternative to the above criteria would be an *n*-of-1 trial, which consists of a random sequence of treatments

(which may include a blinded placebo) with a single patient. Objective outcome measures are followed, and the best therapy is selected based on those measures. In many ways an *n*-of-1 trial provides the strongest evidence to use a therapy or device with a particular patient, despite lack of efficacy in clinical trials.

A number of airway clearance methods and devices fulfill some of the above-mentioned requirements: cough, physical exercise, flutter valve, autogenic drainage, and active cycle breathing. These therapies are safe, inexpensive, and have good pathophysiologic rationale. Traditional CPT, particularly with hospitalized patients, may be costly; however, it will probably remain the standard of care, based just on historical views of this intervention.

In this issue of *RESPIRATORY CARE*, Varekojis et al present a non-blinded crossover study of 3 methods of enhancing airway clearance: postural drainage and percussion, intrapulmonary percussive ventilation, and HFCWC.<sup>15</sup> They conclude that intrapulmonary percussive ventilation and HFCWC are "at least as effective as vigorous professionally performed postural drainage and percussion for hospitalized CF patients and . . . equally acceptable to" the patients. The measure of efficacy in the Varekojis et al study was mean sputum weight (wet and dry) over 2 consecutive days of each treatment. Sputum weight has never been proven to be an adequate surrogate for CF clinical outcome. No drug trial could gain Food and Drug Administration approval with such an end point. Varekojis et al conclude that the CPT device or method should be chosen based solely on patient preference, which may enhance compliance.

Is such a conclusion valid? Yes and no. Patient preferences clearly should guide clinical decision-making in this field until better evidence of efficacy is available. However, we in the medical community should not implicitly accept the value of expensive but unproven therapies such as some currently available in respiratory care. Such devices should be considered investigational and not be introduced into the clinical realm until detailed clinical outcome studies have been conducted.

Ideally, future studies related to CPT should include meaningful clinical outcomes, such as hospitalization rate, exacerbation rate, growth/weight, and lung function decline, and should take place over longer periods. Surrogate outcomes such as sputum volume should be advocated only in early-phase studies, prior to pursuing true efficacy end points. Studies should also include economic analyses, given the potential for widely different costs. This would permit clinicians to assess whether a costly but effective

therapy is significantly better to permit its widespread integration into the health care system.

**Christopher H Goss MD MSc**

Division of Pulmonary and Critical Care Medicine

Department of Medicine

University of Washington Medical Center

Seattle, Washington

#### REFERENCES

1. Knowles M, Church NL, Waltner WE, Yankaskas JR, Gilligan P, King M, et al. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med.* 1990;322(17):1189-1194.
2. Bouche RC. Human airway ion transport. Part two. *Am J Respir Crit Care Med* 1994;150(2):581-593.
3. Boucher RC. Human airway ion transport. Part one. *Am J Respir Crit Care Med* 1994;150(1):271-281.
4. Quinton PM. Viscosity versus composition in airway pathology. *Am J Respir Crit Care Med* 1994;149(1):6-7.
5. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *Am J Respir Crit Care Med* 1996;154(5):1229-1256.
6. Cystic Fibrosis Foundation. Patient registry 2000 annual data report. Bethesda MD; 2001:1-2.
7. Chmiel JF, Berger M, Konstan MW. The role of inflammation in the pathophysiology of CF lung disease. *Clin Rev Allergy Immunol* 2002;23(1):5-27.
8. Robinson M, Eberl S, Tomlinson C, Daviskas E, Regnis JA, Bailey DL, et al. Regional mucociliary clearance in patients with cystic fibrosis. *J Aerosol Med* 2000;13(2):73-86.
9. Regnis JA, Piper AJ, Henke KG, Parker S, Bye PT, Sullivan CE. Benefits of nocturnal nasal CPAP in patients with cystic fibrosis. *Chest* 1994;106(6):1717-1724.
10. Hess DR. The evidence for secretion clearance techniques. *Respir Care* 2001;46(11):1276-1293.
11. Davidson KL. Airway clearance strategies for the pediatric patient. *Respir Care* 2002;47(7):823-828.
12. Thomas J, Cook DJ, Brooks D. Chest physical therapy management of patients with cystic fibrosis: a meta-analysis. *Am J Respir Crit Care Med* 1995;151(3 Pt 1):846-850.
13. Jones AP, Rowe BH. Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis. *Cochrane Database Syst Rev* 2000;(2):CD000045.
14. van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev* 2000;(2):CD001401.
15. Varekojis SM, Douce FH, Flucke R, Filbrun D, Tice J, McCoy K, Castile R. A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. *Respir Care* 2003;48(1):24-28.

---

Correspondence: Christopher H Goss MD MSc, Division of Pulmonary and Critical Care Medicine, University of Washington Medical Center, Campus Box 356522, Seattle WA 98195. E-mail: goss@u.washington.edu.