

Cystic Fibrosis: Current Trends in Respiratory Care

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Summary

Cystic fibrosis is a genetic disease that typically produces malnutrition and chronic respiratory infections. Prolonged bronchial obstruction, infection, and inflammation result in bronchiectasis and permanent lung damage. Most cystic fibrosis patients die because of this progressive respiratory disease. Thus, in the absence of a cure, effective respiratory therapy is the primary means to extend and improve the quality of life for the cystic fibrosis patient. Aerosol therapy, airway clearance techniques, and noninvasive ventilation can all improve quality of life and possibly extend survival. Close patient monitoring with pulmonary function testing, chest radiography, and induced sputum can result in earlier treatment, potentially reducing permanent lung damage. Earlier diagnosis has prevented serious complications through early initiation of preventive therapies such as improved nutrition. *Key words: pediatric, respiratory, pulmonary, cystic fibrosis, respiratory care, airway clearance.* [Respir Care 2003;48(3):234–245. © 2003 Daedalus Enterprises]

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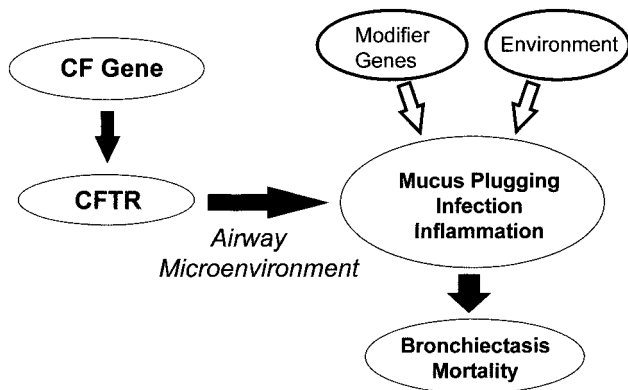


Fig. 1. Pathogenesis of cystic fibrosis-related lung disease. CF = cystic fibrosis. CFTR = cystic fibrosis transmembrane conductance regulator.

Introduction

Since the gene responsible for cystic fibrosis (CF) was isolated in 1986, there have been great advances in understanding the pathophysiology of this disease (Fig. 1). Most of the over 1,000 identified gene mutations result in a malfunctioning of the cystic fibrosis transmembrane conductance regulator protein. This malfunction creates an abnormal airway surface microenvironment, leading to thickened mucus, chronic infection, and chronic inflammation. Eventually, the mechanical obstruction plus high concentrations of pro-inflammatory cytokines and neutrophil-derived oxidants and elastases damage the airway, leading to bronchiectasis and permanent lung damage. As a result the life expectancy for CF patients is markedly shortened, with many patients dying in their early 20s and 30s.

Though the discovery of the CF gene improved understanding of cystic fibrosis transmembrane conductance regulator-related cell biology, clinical care advances have developed from improved understanding of mucus rheology and airway infection. In addition there are many new therapies being developed that combine the understanding of cell biology with the understanding of mucus and airway pathology. Almost all of these new therapies will require a good understanding of early detection and disease progression, since they are largely preventive and will not reverse serious airway damage. Additionally, there is increasing evidence that existing therapies are effective, and possibly optimal, when begun prior to permanent airway damage. In this report we discuss the diagnosis and early monitoring of CF lung disease, available aerosol therapies and delivery devices, and the many airway clearance techniques used to improve airway mucus clearance.

Cystic Fibrosis Lung Disease

Diagnosis

Most CF patients are diagnosed during childhood, with the median age of diagnosis being 6 months and the mean 3.2 years.¹ Conventional diagnosis is usually made in a patient with both respiratory disease and malnutrition. These children are often poorly grown because they have pancreatic insufficiency leading to protein-calorie malabsorption. The malnourished patient more frequently has more severe respiratory disease.² Additionally, the patient with more severe respiratory disease has greater energy requirements, leading to a greater chance of malnutrition. Thus, good nutrition and growth are essential for normal lung development and to reduce the frequency of lung infections. This recognition of the need to avoid malnutrition has led several states and a few countries to institute routine newborn screening for CF. Early detection by newborn screening provides a chance to treat malabsorption with oral pancreatic enzymes and supplemental calories, plus it provides a chance to start preventive respiratory therapies to improve mucus clearance and reduce lung infections.

Some patients are not diagnosed until a much later age. These patients often do not have pancreatic insufficiency and severe malnutrition, and usually have less lung disease, but they still have a higher risk of serious lung infections and they have a shorter life expectancy. Additionally, patients diagnosed at an older age are more likely to have complications of CF, such as male infertility, pancreatitis, atypical mycobacteria lung infections, and allergic bronchopulmonary aspergillosis as presenting complaints.

Clinical Monitoring

Respiratory disease is the major cause of morbidity and death in CF patients. However, nutritional health is closely related to respiratory health, suggesting that the first priority in clinical monitoring is to follow weight and growth. Every respiratory practitioner should know the importance of CF patients maintaining normal body growth in order to assure normal lung development, to allow for normal exercise, and to reduce the frequency of respiratory infections. Currently the United States Cystic Fibrosis Foundation suggests that patients should be seen every 3 months to assure appropriate weight and height development. During the first year of life this monitoring often needs to be more frequent. Additionally, because of the malabsorption of fats, CF patients are at risk for zinc and vitamin deficiencies, particularly during the first year of life. Certain vitamins, particularly vitamin E and β carotene, are essen-

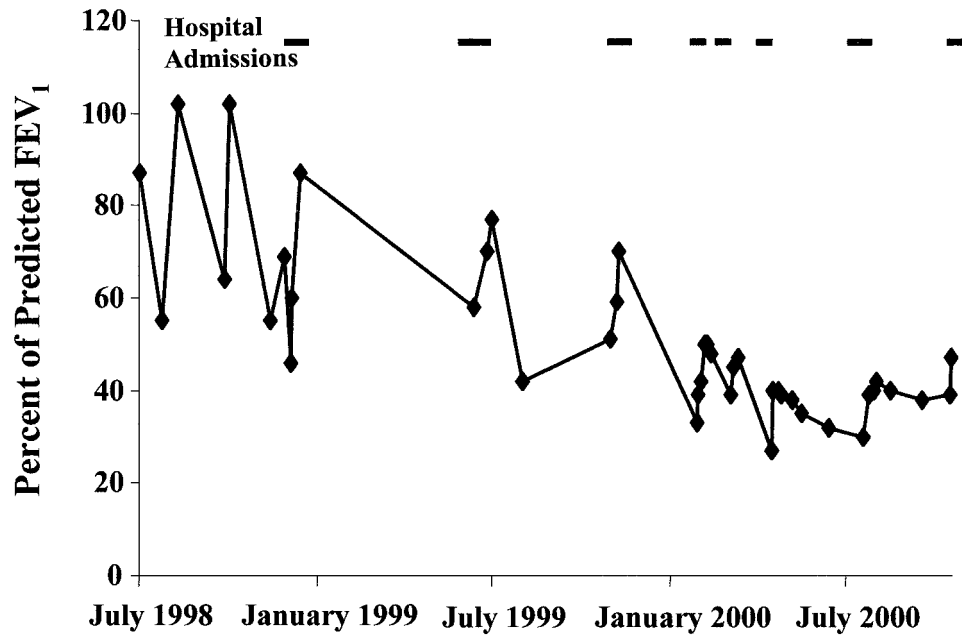


Fig. 2. Pulmonary function test results from a single patient, plotted over time. FEV₁ = forced expiratory volume in the first second.

tial for protecting the airways from oxidant injury and lung damage.

In addition to nutrition, all CF patients should be monitored for clinical signs and symptoms of respiratory compromise. Persistent cough is never normal. Even prior to developing cough, some patients may have chronic throat clearing, a possible sign of increased mucus production. Similar to cough, crackles on chest examination are never normal. Crackles in a patient with a previously clear chest are one of the best indicators of a respiratory exacerbation. Rarely will crackles resolve without increasing therapy directed toward airway obstruction and infection. Other historical symptoms related to the respiratory system that are important to assess include exercise tolerance, wheezing, sputum production, sputum appearance, hemoptysis, and sleep quality. Other clinical signs suggesting chronic lung disease include clubbing, chest hyperinflation, increased second heart sound, and kyphosis.

Pulmonary Function Monitoring

Spirometry is one of the most sensitive and specific monitoring tools for following the clinical status of CF patients. Initially the lung function is normal in all CF patients. Over time, airway obstruction develops and usually involves the smaller, more peripheral airways first. Thus, spirometry (either a volume-time or flow-volume curve) will initially show changes in flow at lower lung volume (forced expiratory flow during the middle half of the forced vital capacity), followed by decreased flow at higher lung volumes (forced expiratory volume in the first

second [FEV₁]), and eventually by decreased volume (forced vital capacity [FVC]). When plotted versus time, these changes are more obvious (Fig. 2). With actively growing children, pulmonary function values are plotted as percent-of-predicted values, whereas with adult patients the absolute values may be plotted. Although defining a significant drop in lung function depends on the variability of the test, in general a 10% FEV₁ decrease is considered a sign of worsening lung disease, and if acute, is a sign of a respiratory exacerbation. Post-bronchodilator spirometry should be performed with patients who have detectable airway obstruction to see if bronchodilator therapy would be helpful and to look for complicating conditions such as asthma.

Respiratory rate and pulse oximetry can provide early signs of worsening lung function, particularly in young children in whom abnormalities of smaller airways are more likely to decrease oxygenation. For older patients tachypnea and poor oxygenation are signs of more severe disease or an acute respiratory exacerbation. Oxygenation during sleep is an important measurement that should be done in all patients with acute respiratory deterioration or who show signs of pulmonary hypertension. Nighttime desaturation can be quite severe in patients who have normal daytime saturation. Patients with FEV₁ < 30% of predicted are at particular risk of nocturnal hypoxia and hypercarbia.

Other pulmonary function tests can be valuable in selected situations. Lung volume measurements are important whenever there is spirometric evidence of restrictive changes. Since CF produces primarily an obstructive lung

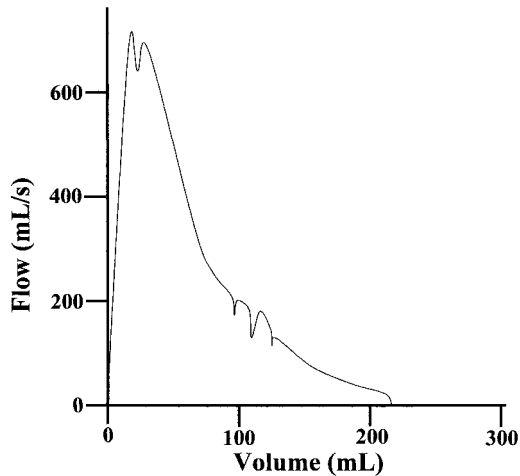


Fig. 3. Expiratory flow-volume curve produced by lung distention followed by chest wall compression in an infant with cystic fibrosis.

disease, spirometric evidence of restrictive changes usually reflects substantial gas trapping. Rarely, however, there may be complicating conditions producing true restrictive lung disease (such as hypersensitivity pneumonitis). If FEV_1 and FVC are both low and the FEV_1/FVC ratio is normal (suggesting restrictive changes), then total lung capacity and residual volume should be measured. Exercise studies can be used to evaluate exercise-induced bronchospasm. Additionally, exercise tolerance can be a very sensitive measure of worsening (or improving) lung function. Exercise studies should always include monitoring of oxygen saturation, since desaturation during exercise is a common complication. In patients with severe obstructive disease ($FEV_1 < 40\%$ of predicted), carbon dioxide monitoring during exercise is also recommended. Diffusing capacity is rarely measured, although this can be a sensitive technique for detecting early airway disease. In general, spirometry and lung volume measurements are more specific, and rarely do CF patients have isolated diffusion abnormalities.

Recently infant pulmonary function testing has become practical. Airway obstruction can be detected and monitored longitudinally with flow-volume measurements. Exhalation is forced by rapid chest wall compression, and air flow is measured at the mouth with a pneumotachograph. A refinement of this test is to first raise lung volume with positive airway pressure, followed by the rapid compression. Using this technique, flow-volume curves nearly identical to those in adults can be recorded (Fig. 3). Additionally, lung volumes can be measured in a body plethysmograph, similar to older patients. Unfortunately, all of these tests require the child to be sedated. This makes the tests less convenient, more costly, and raises their risk slightly. However, numerous investigators have shown that lung function changes often predate clinical symptoms, and following lung function

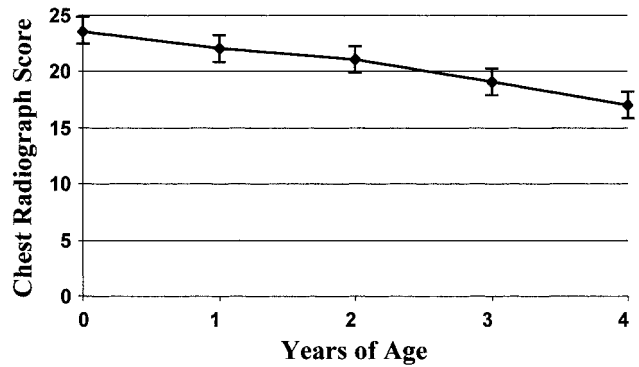


Fig. 4. Chest radiograph scores from a group of cystic fibrosis infants detected by newborn screening and followed for several years. Lower scores indicate hyperinflation, hilar streaking, peripheral nodules, and atelectasis. (Adapted from Reference 5.)

measurements in infants can be as valuable as following them in older patients.^{3,4}

Radiographic Monitoring

Though pulmonary function testing can detect airway functional abnormalities, radiography detects structural changes. Routine chest radiographs are recommended yearly for all CF patients. Various systems for grading radiographs have been developed, providing for longitudinal monitoring of both individuals and groups of patients (Fig. 4).⁵ Recent studies of high-resolution computed tomography show improved sensitivity and specificity for



Fig. 5. High resolution chest computed tomogram demonstrating bronchiectasis in a child with normal pulmonary function test results.

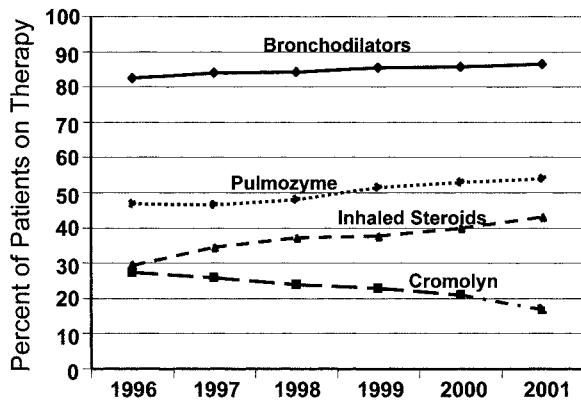


Fig. 6. Five-year trends for use of various inhaled therapies among cystic fibrosis patients. (Adapted from Reference 7.)

early lung disease.⁶ This may prove particularly valuable for early detection of airway disease and bronchiectasis in the middle aged child with normal pulmonary function (Fig. 5).

Aerosol Therapies and Delivery Devices

Inhaled Bronchodilators

Clinicians frequently prescribe bronchodilators for CF patients in an effort to maximize airway size and improve mucociliary clearance (Fig. 6).⁷ All CF patients develop obstructive airway disease and most will have airway hyperreactivity at some time.^{8,9} Most, however, will not show a consistent bronchodilator response in pulmonary function testing. Occasionally, air flow obstruction may actually worsen with bronchodilators. Unfortunately there are few studies showing significant, long-term clinical improvement with routine bronchodilator use. Eggleston et al¹⁰ showed that routine albuterol improved lung function over 1 month only in patients with demonstrated airway hyperreactivity to methacholine. Longer-acting bronchodilators have also been studied. In high doses (4 puffs twice daily) during in-patient therapy for respiratory exacerbations, salmeterol had a significantly greater pulmonary function benefit than albuterol.¹¹ Salmeterol is also effective in decreasing nocturnal hypoxia related to CF lung disease.¹²

Inhaled Anti-inflammatory Agents

Neutrophil-dominated airway inflammation occurs even in CF patients who have mild lung disease. Long-term systemic steroid therapy improves lung function in CF patients, but complications from therapy (including glucose intolerance, hypertension, and poor height growth) limit its value. Inhaled corticosteroids would be a logical

extension of these findings, but most studies have not shown inhaled corticosteroids to have great benefit. Despite that lack of evidence, the use of inhaled corticosteroids has been increasing over the last few years (see Fig. 6). Currently, inhaled corticosteroids for CF patients are best used for treating complicating conditions such as asthma and allergic bronchopulmonary aspergillosis. Inhaled corticosteroids may also be beneficial early in the course of the lung disease, when the inflammation is potentially more reversible. Risks from inhaled corticosteroids that should be monitored include delayed height growth and adrenal insufficiency (with high doses).

Nonsteroidal anti-inflammatory inhaled therapy (cromolyn sodium) is decreasing in popularity as inhaled corticosteroid use has increased (see Fig. 6). There have been no studies indicating benefit from cromolyn in CF care, and frequent nebulized medications may increase the risk of acquiring *Pseudomonas aeruginosa* infection.

Inhaled Mucolytics

Since the primary, initiating event for airway obstruction in CF is the dry, thick mucus, mucolytics are a logical first-line therapy. There are many constituents in airway mucus, but one of the most common is deoxyribonucleic acid (DNA) derived from the many neutrophils attracted to the airway by the chronic infection. Shak et al¹³ noted the extremely effective mucolytic properties of dornase alfa, a naturally-occurring anti-DNA, on CF mucus. When recombinant human dornase alfa (Pulmozyme) was studied in a large, randomized, controlled study, patients on the therapy had a significant improvement in pulmonary function and a significant decrease in respiratory exacerbations over 6 months.¹⁴ Further study in patients with only mild lung disease showed similar benefits of daily Pulmozyme therapy over 2 years.¹⁵ These benefits of Pulmozyme therapy may not be simply due to improved mucus clearance.¹⁶ Thus, daily, twice-daily, or every-other-day Pulmozyme therapy should be considered early in the care of CF patients.

Hypertonic saline (3–7%) improves pulmonary function similarly to Pulmozyme over the short-term (one month).¹⁷ However, hypertonic saline is not as effective as Pulmozyme over a longer period.¹⁸ This may be related to the airway-irritating effects of hypertonic saline and unrelated to its mucolytic properties. N-acetyl-cystiene (Mucomyst) has not been compared with other mucolytic therapies.¹⁹ One potential advantage of Mucomyst is that it is also an anti-oxidant. Since oxidant injury contributes to airway destruction in CF, this may be an important benefit. However, in vivo studies have not been preformed and this advantage can only be surmised. Mucomyst is also an airway irritant and over the long term may actually increase mucus production and airway obstruction. Because

of that irritant effect, the risk of Mucomyst outweighs its theoretical benefit.

Inhaled Antibiotics

Inhaled antibiotics are logical therapies for CF, because most patients eventually develop chronic endobronchial infection.²⁰ Inhalable tobramycin was developed to provide long-term therapy for CF patients suffering *Pseudomonas aeruginosa* airway infection. Treatment with 300 mg inhaled tobramycin twice daily resulted in a marked improvement in lung function, significant decreases in the bacterial density on sputum, and decreased systemic markers of inflammation during a 6-month, randomized, placebo-controlled study.²¹ That study, as well as additional studies of patients with *Pseudomonas* infection and normal lung function, indicate that inhaled Tobramycin also decreases respiratory exacerbations and the need for hospitalization. Over the long term there is an increase in bacterial antibiotic resistance, but because the airway levels of the antibiotic delivered via inhalation are so high, the resistance does not seem to reduce the response.

Colistin (Coly-Mycin) is also frequently nebulized for CF patients with *Pseudomonas aeruginosa* airway infection.²² Typically 150 mg is nebulized twice daily. Resistance is difficult to evaluate, and no long-term, randomized controlled trials have been conducted. The results of routine therapy with colistin, however, suggest it is effective in reducing chronic colonization and infection with *Pseudomonas*. Trials of other nebulized antibiotics have been reported, but none are routinely used for CF.

Delivery Devices

Airway administration of an inhaled medication is highly related to the delivery technique.²³ This is most dramatically demonstrated with nebulized therapy, because nebulizers and compressors can affect various medications in various ways.²⁴ Additionally, administration technique is extremely important. When using a mask to deliver nebulized medication to a young child, simply moving the mask away from the face by 2 cm reduces drug delivery by 85%.²⁵ Probably the single most important aspect of effective therapy with nebulized medications is to educate the patient or parent in proper delivery. Ideally, the patient should use a mouthpiece (usually possible in children over 3 years old), breathe through the mouth (occasionally requiring nose clips), use the appropriate nebulizer, and complete the entire dose. For younger children a face mask should be used and always placed snugly onto the face. With infants, delivery appears to be equally effective whether the patient is awake or asleep.²⁵

A metered-dose inhaler should always be used with a spacer, which improves delivery and decreases adverse

Table 1. Disinfection Options for Reusable Items Contacting the Patient

Boil in water for 5 minutes, or
Use a standard cycle dishwasher if water > 70°C is maintained for > 30 minutes, or
Microwave for 5 minutes, or
Immerse in one of the following:
• 1:50 dilution of 5.25–6.15% sodium hypochlorite (bleach) for 3 minutes
• 70% isopropyl alcohol for 5 minutes, or
• 3% hydrogen peroxide for 30 minutes

Note: Following disinfection by immersion, the device should be rinsed with sterile water (not tap or distilled water) and allowed to air dry. An alternative is to rinse with tap water, followed by rinsing with 70–90% alcohol.

effects (particularly for inhaled corticosteroids). Medications can be equally effective when given via nebulizer or via metered-dose inhaler with spacer. However, more than 2 metered-dose inhaler puffs are frequently required to provide a comparable total dose, since the dose per puff is often much less than the dose in the nebulizer (particularly with inhaled bronchodilators). Dry powder inhalers are increasingly popular, but there needs to be good patient education to assure the patient can generate an adequate inspiratory flow. In general, dry powder inhalers should not be used by children under 4–6 years old.

Delivery devices are a potential cause of nosocomial infection, and infection control standards need to be rigidly followed.²⁶ In addition to cleaning with soap and water, equipment needs to be disinfected, rinsed (with sterile water), and air-dried (Table 1). Standards for disinfecting need to be similar in both in-patient and out-patient settings, given the risk of reintroducing and perpetuating infections by CF-related pathogens.²⁷

Airway Clearance Techniques

Airway clearance therapy should be a routine activity for all CF patients.^{28,29} Even during the early phase of CF lung disease, when the patient is asymptomatic, there can be benefits from airway clearance. Waiting until the patient has had his or her first pneumonia or waiting until daily coughing or mucus production is present will delay the benefits of airway clearance and may contribute to the deterioration in lung function. Many airway clearance techniques exist,^{30–32} but only a few long-term studies have compared the various options.^{33–36} The decision on which technique to use should be based on the patient's age and preference after trying different approaches (Table 2).³⁷ Generally, airway clearance therapy should be done prior to eating, to avoid the potential for stomach upset during any coughing. Often bronchodilators or mucolytic medications are given prior to or during airway clearance ther-

Table 2. Airway Clearance Techniques by Age Group

Technique	0–3 years	3–9 years	> 9 years
Chest physiotherapy	Yes	Yes	Yes
Active cycle of breathing	No	Yes	Yes
Autogenic drainage	No	No	Yes
Positive expiratory pressure (PEP)	No	Yes	Yes
Oscillating PEP (Flutter or Acapella)	No	Yes	Yes
Intrapulmonary percussive ventilation	No	No	Yes
High-frequency chest compression (<i>The Vest</i>)	No	Yes	Yes
Exercise	Yes	Yes	Yes

apy. Inhaled corticosteroids and inhaled antibiotics should be given *after* airway clearance therapy so that the airways are first cleared of secretions, allowing the medications to maximally penetrate into the lung.

Chest Physiotherapy

Most forms of airway clearance therapy are similarly effective, but the accepted standard for airway clearance is chest physiotherapy (CPT), also known as percussion-and-drainage or chest clapping.^{38,39} CPT is typically performed with a cupped hand or a plastic cup and rapid “clapping” onto the chest. Usually, an assistant is required; however, patients can perform their own CPT on the front and sides of the chest. Mechanical devices are available, although they do not clear the airways better than manual techniques.⁴⁰ During CPT the patient is placed in several positions to enhance mucus clearance. Percussion is usually performed for 1 or 2 minutes in each position, followed by encouraging the patient to cough. Infants will occasionally cough spontaneously if mucus is present, but the goal is to move peripheral mucus into more central airways, and this will happen even in the absence of coughing. During CPT the oxygen saturation may decrease, and patients with severe lung disease should be watched for signs of low oxygen.⁴¹ To reduce desaturation, inspiratory pressure-support ventilation can be added during CPT.⁴² Gastroesophageal reflux can be exacerbated during CPT, so the head-down position should be avoided in all patients.^{43,44}

Active Cycle of Breathing

Active cycle of breathing technique is a form of airway clearance that improves lung function without decreasing oxygenation.⁴⁵ Unlike CPT, active cycle of breathing technique does not require an assistant. This technique is a combination of breathing control, thoracic expansion, and the forced expiratory technique. Breathing control is normal tidal breathing with the lower chest, allowing the up-

per chest and shoulders to relax (also referred to as diaphragmatic breathing). During active cycle of breathing technique, breathing control is used between periods of thoracic expansion and forced expiratory technique.

Thoracic expansion exercises involve deep breathing, focusing on active inspiration. Deep inspiration is often followed by a several-second breath-hold, which is particularly valuable for the postoperative patient, in whom it aids in avoiding atelectasis. Thoracic expansion is repeated 3–4 times, followed by a period of breathing control.

The forced expiratory technique combines 1 or 2 huffs (forced exhalations) with periods of breathing control.⁴⁶ In general, the forced expiratory technique should be combined with other forms of airway clearance.^{38,47} However, huffs can be more effective than coughing, and patients often use a modified forced expiratory technique when they need to move mucus (such as while in the shower or other moist environment). Huffing can be performed at various lung volumes. At low lung volumes, the huff moves mucus primarily from the more peripheral airways, whereas at high lung volume, the huff clears the secretions from the larger, more proximal airways. The forced exhalation produces a dynamic compression of the airway, leading to airway collapse downstream (toward the mouth) from the point where pressure outside the airway is similar to inside the airway (referred to as the equal pressure point or flow-limiting segment). Any mucus within this distance of compressed airway will be exhaled from the lung by increased air turbulence. As lung volume decreases, the area of airway compression moves upstream (toward the alveolus), resulting in movement of more peripheral mucus. A prolonged huff, or a series of coughs without intervening breaths, moves the compressing segment deep into the segmental bronchi. Huff results in lower transpulmonary pressure than a sequence of coughs, resulting in less complete airway collapse. The huff is a forced but not violent maneuver and can be varied by length and force to optimize mucus clearance. Young children can be taught to huff by playing games. It is important to remember the goal is not to do a maximal flow maneuver such as that performed for pulmonary function testing.

Autogenic Drainage

Autogenic drainage has many of the attributes of active cycle of breathing technique. The goal is to breathe at different lung volumes and create the highest possible air flow in different airway generations. As a result, the mucus is “unstuck” at low lung volume, “collected” at middle lung volume, and “evacuated” at high lung volumes (Fig. 7).⁴⁸ With autogenic drainage, there is a balance between the tendency for airway collapse and the need to move air rapidly enough to move secretions. Initially the patient breathes tidally below his or her normal functional resid-

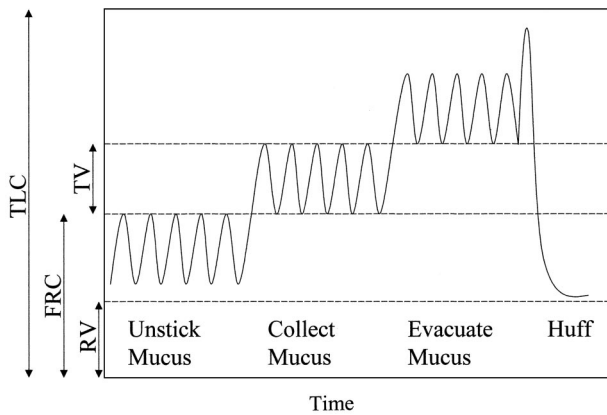


Fig. 7. Tidal breathing at various lung volumes during autogenic breathing. TLC = total lung capacity. FRC = functional residual capacity. RV = residual volume. TV = tidal volume.

ual capacity (the volume where the lung normally rests at the end of an exhalation). This causes mucus to be cleared from the more peripheral airways. Exhalation is mildly forced, to shear mucus from the airway walls. After breathing for a few minutes at this volume, the patient inspires a small amount, raising the volume for tidal breathing. This cycle is repeated several times, eventually raising lung volume to well above functional residual capacity. Often mucus is expectorated without the need for forced coughing.⁴⁹ Because of this, oxygenation is unaffected during autogenic drainage.⁴¹ Frequently, autogenic drainage is combined with several aspects of active cycle of breathing technique, including doing the forced expiratory technique between different levels of lung inflation. Given the similar benefits of these techniques, patients should be encouraged to experiment with the different techniques to find the optimal way to clear secretions.⁵⁰

Positive Expiratory Pressure and Flutter

Airway collapse is a major problem with more advanced CF lung disease. Bronchiectasis results in weakening of airway walls, and even with normal breathing there can be airway collapse, causing secretions to be trapped in the smaller airways. Positive expiratory pressure (PEP) is an airway clearance technique developed to reduce the airway collapse caused by bronchiectasis.⁵¹⁻⁵⁴ There are 3 modifications of the PEP technique: low-pressure PEP, high-pressure PEP, and oscillating PEP (Flutter or Acapella).

Low-pressure PEP consists of a mouthpiece or face mask attached to a low-pressure, expiratory resistor.^{55,56} Usually there is some form of manometer to measure the expiratory pressure. The degree of expiratory resistance can usually be varied so that the patient can exhale, without exertion, and maintain pressures of 10–20 cm H₂O. Inspiration is passive and exhalation slightly active against the resis-

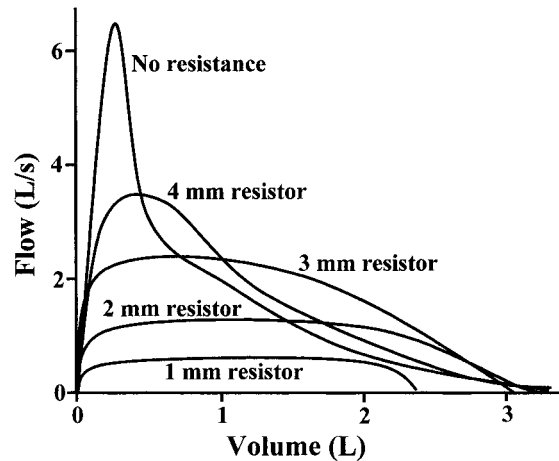


Fig. 8. Maximum expiratory flow-volume curves produced with various degrees of expiratory resistance to assess the optimal settings for high-pressure positive expiratory pressure therapy. As the diameter of the expiratory resistor is decreased (increasing resistance), the curvilinearity of the expiratory curves decreases, indicating successful distal airway distension. Note that at very high resistance (1 mm diameter) the resistance is so high that full exhalation is not possible.

tance. Techniques differ, but usually involve 1–2 min of tidal breathing or 15–20 expiratory breaths of 3 seconds each. The PEP is removed and the patient does several forced exhalations and coughs. This cycle is repeated 3–4 times, with the entire treatment lasting 15–20 min. Low-pressure PEP is similar to CPT for airway clearance, although there may be less oxygen desaturation.⁵⁷⁻⁶⁰ In one of the few long-term studies of airway clearance, PEP resulted in better lung function than conventional CPT.³⁵

High-pressure PEP is similar, but instead of slightly active exhalation, this technique uses forced expiratory maneuvers against the resistor, creating high pressure.^{61,62} The patient inhales to total lung capacity and performs an FVC maneuver, creating pressures between 40 and 100 cm H₂O. As with low-pressure PEP, the expiratory resistor is adjusted to provide for optimal airway distention. Optimal distention should prevent airway closure and can be determined by plotting the flow-volume curve at different resistances (Fig. 8).

Oscillating PEP is most commonly performed with the Flutter device or the Acapella device. Both short-term and long-term studies with CF patients have shown the Flutter to be similar to CPT or PEP.^{36,63-66} The patient exhales into the Flutter device; during exhalation the steel ball inside the device bounces, causing vibratory obstruction to air flow, which oscillates both the pressure and air flow during exhalation. The angle at which the device is held determines the oscillation frequency (usually between 6 and 26 Hz), and the patient's expiratory effort determines the pressure. As with other PEP techniques, the patient repeats the maneuver for 10–15 breaths and then does

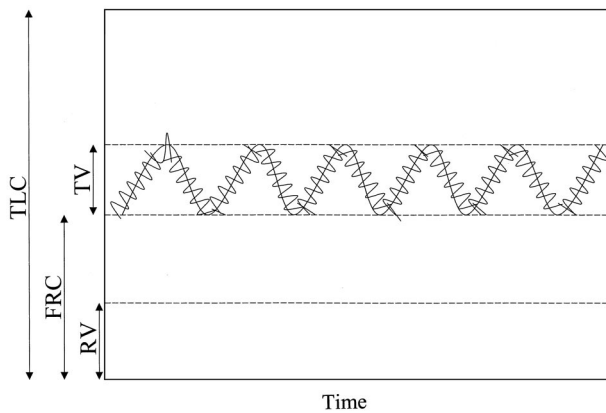


Fig. 9. Intrapulmonary percussive ventilation creates oscillating machine volumes on top of the patient's spontaneous breathing. TLC = total lung capacity. FRC = functional residual volume. RV = residual volume. TV = tidal volume.

several huffs or coughs without the device. This cycle is repeated 3–4 times, resulting in a 15–20 min airway clearance session.

Intrapulmonary Percussive Ventilation

Intrapulmonary percussive ventilation (IPV) has many attributes similar to oscillating PEP. However, with IPV there are continuous oscillating pressures during both inhalation and exhalation.⁶⁷ The pressure and frequency of these oscillations can be varied, but typically the frequency is 6–12 Hz and the pressures are 10–20 cm H₂O. Following IPV therapy, sputum production and pulmonary function improvement is similar to that following standard CPT.^{68–71} However, fluid can be delivered during IPV, similar to intermittent positive-pressure breathing. Unlike intermittent positive-pressure breathing, however, there is no attempt to breathe for the patient. Instead, the oscillating pressure is layered on top of the patient's normal tidal breathing (Fig. 9). Although there are no studies of medication delivery via IPV in CF patients, there have been studies of other pressure-assisted techniques, and those studies showed enhanced drug deposition without changes in lung distribution.⁷² Further study of drug deposition via IPV is needed to assure clinical efficacy, since some medications, such as dornase alfa, may be broken down when delivered via nonapproved nebulizers.

High-Frequency Chest Compression

High-frequency chest compression (HFCC) was developed to provide oscillation to the external chest, similar to the airway oscillation provided by oscillating PEP and IPV.^{71,73} Oscillation has potential benefit both by shearing mucus from the airway wall and by modifying the vis-

coelastic properties of the mucus. Shearing occurs at the mucus/airway-surface interface and results from the kinetic energy released by high-velocity air flow. Peak flows during HFCC are similar to those produced with coughing, although for briefer duration. The result, however, is to enhance release and downstream flow of mucus. Mucus viscoelasticity can be altered mechanically as well as chemically.^{74–76}

High-frequency chest compression is clinically safe and effective in CF patients.^{77–79} Unlike CPT, however, the patient can independently perform HFCC.⁸⁰ Patient acceptance, and therefore adherence with prescribed routine, may also be better with HFCC.⁸¹ In-patient HFCC therapy is also effective, and, although the initial equipment cost is high, subsequent savings in therapist time can be expected.⁸²

Exercise

Many investigators have studied the effects of exercise and exercise programs on CF.⁸³ Closely supervised programs encourage patient adherence to exercise routines and provide for close monitoring; however, these programs are difficult to organize and may not be feasible for the typical patient. Additionally, many patients are unable to maintain prolonged, high-intensity programs. Whether the exercise actually improves mucus clearance is debated,⁸⁴ although several studies indicate that patients in regular exercise programs have better lung function than less active patients.⁸⁵ Patients also report improved quality of life when they exercise regularly, and the quality-of-life improvement is directly related to the patient's exercise tolerance increasing with regular aerobic training. Aerobic fitness may also be an indicator of disease status and prognosis. There is lower mortality among CF patients who exercise regularly, even when controlled for pulmonary function.

Prior to initiating an exercise program, all patients should be assessed clinically and physiologically. Oxygenation during exercise should be monitored to assure that subjects do not substantially desaturate (> 3–4% drop). In general, CF patients with mild lung disease (FEV₁ > 80% of predicted) will not have exercise-related desaturation. Patients with severe pulmonary disease (FEV₁ < 40% of predicted) are likely to experience both hypoxia and hypercarbia with exercise. These patients are at risk for adverse events during exercise and should have close cardiopulmonary monitoring if they plan to exercise. Continuous positive airway pressure or supplemental oxygen during exercise may help these patients by reducing the work of breathing.^{86,87} Once a patient is cleared for exercise, he or she can be encouraged to exercise for at least 30 min, 3 times a week. Exercise, however, is not superior to routine airway clearance and should be used as supplemental therapy.³³ The reduced

deterioration of lung function related to exercise is seen only when combined with routine airway clearance.

Noninvasive Ventilation

Noninvasive ventilation, most commonly biphasic positive airway pressure, has increasing value for “bridging the gap” between respiratory failure and lung transplant in CF patients.^{88–91} However, other uses may prove increasingly valuable. Though nocturnal oxygen therapy has not been shown to improve long-term prognosis,⁹² nighttime biphasic positive airway pressure therapy reduces hypoxia, hypercarbia, and work of breathing, and may enhance airway clearance and reduce pulmonary hypertension.^{93–97} Alternatively, nighttime desaturation related to decreasing end-expiratory lung volume during rapid-eye-movement sleep can be reduced with nasal continuous positive airway pressure.⁹⁸

Summary

Advances in understanding the genetics and pathophysiology of CF have improved patient care and survival. Currently, every patient born with CF should be expected to live well into adulthood, with most patients having productive careers and families. Because of these advances, prevention and care of the lung disease associated with CF have taken on increasing importance. The future definitive treatment or cure for CF will probably help only patients with normal or good lung function. Thus, the goal has to be to maintain clear airways, to avoid airway infections, and to reduce airway inflammation. This can only occur in a patient who has a good nutritional state. The respiratory therapist is a key figure in knowing all available techniques for airway clearance so that the patient and his or her parents can be provided with every option. Additionally, the respiratory therapist needs to know the many available inhalable therapies and needs to educate the patient in their uses. Finally, by assuring that infection control techniques are followed closely, the care provider can reduce the chance that a patient will acquire a complicating nosocomial infection.

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Discussion

Davis: Could you comment on the use of ibuprofen as an anti-inflammatory medication in CF?

Wagner: I mentioned the one long-term study of alternate-day steroids that showed benefit, but also showed a concerning complication rate.¹ A comparable study with the anti-inflammatory ibuprofen showed similar benefit with less deterioration in lung function.² But there is concern about potential complications with high ibuprofen doses.

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Davis: Could you also comment on the utility of antibiotics in eradicating *Pseudomonas* in infants?

Wagner: The large, controlled, inhaled tobramycin study I mentioned did not show *Pseudomonas* eradication in patients with chronic *Pseudomonas*.¹ A study was recently completed of inhaled tobramycin for infants and young children with early onset of *Pseudomonas*.² As you might expect, the drug was adequately delivered and effective in infants. Although that study had a limited number of patients, there was 100% eradication of the *Pseudomonas* at the end of 1 month of treatment. However, at the end of 2 months, there was a 25% recurrence in the upper airway. So it seems inhaled tobramycin is more effective when used early on in this disease.

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Wiswell: Bronchoscopic evaluation of surfactant levels indicates that certain lipids and surfactant proteins (especially anti-inflammatory ones such as surfactant proteins A and D) are low in the majority of CF patients. Potentially, an aerosolized surfactant would be useful, since you don't need to get the surfactant all the way down to the alveoli, but rather just to the more proximal airways for it to be helpful.

Wagner: Surfactant proteins A and D are low in lavage fluid from older CF patients, suggesting that replacing or adding these surfactant proteins may be of some value. The remaining components of surfactant (the non-proteins and the B and C proteins) seem to be in the normal range. Because this deficiency is selective, if replacement is to be tried, we may need a more focused approach than that of the neonatal product.

Wiswell: The commercially available surfactants do not contain surfactant proteins A or D. There were human surfactant trials performed in the 1980s by T Allen Merritt and Mikko Hallman, but I don't know whether there were surfactant proteins A or D in the human surfactants that they were using.^{1,2} It's also very difficult, if not impossible at this point, to try to use recombinant protein technology to produce those particular proteins. So I don't know if we're going to get there. There is seemingly some anti-inflammatory effect from surfactant proteins B and C, but they don't seem to play as major a role as surfactant proteins A and D.

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Wagner: I find this very exciting. As we develop technology to identify and produce these selective products, I am sure we will see benefit for conditions such as CF, particularly if we can intervene early in the disease.

Kercsmar: I have 2 questions regarding the data about using inhaled corticosteroids and about using short-acting bronchodilators in CF patients. Does it make a difference if you dissect out that subset who have either allergy or increased airway reactivity or who have demonstrated a positive response to the bronchodilator? Also, do you want to comment on possible risks of any form of airway therapy, particularly with IPV?

Wagner: Many investigators have separated the bronchodilator-responsive patients from the nonresponsive patients. In fact, Hordvik et al¹ found the benefit from long-acting bronchodilators almost exclusively in the bronchodilator-responsive patients. This demonstrates the importance of obtaining pre- and post-bronchodilator pulmonary function tests with CF patients. The inhaled steroid studies have not separated out the patients who had bronchial hyperresponsiveness. Unfortunately, none of these studies are large enough to do subset analysis. Since 50% of CF patients are on inhaled steroids and only about 25% have demonstrated bronchial hyperactivity, we should be questioning what we are treating.

Concerning your question about the risks of airway clearance techniques, there are a few anecdotal reports of complications with PEP and with IPV.

With both of those there have been rare reports of pneumothorax, but whether the pneumothorax was related specifically to the therapy or was spontaneous—which is a known complication of CF—is not completely clear. The second anecdotal complication, which has been seen by computed tomography in patients on IPV, is dilation of bronchiectatic airways. Until controlled studies clarify these potential complications, you have to use those forms of therapy judiciously. Autogenic drainage, chest physiotherapy, high-frequency chest compression (*The Vest*), and Flutter devices do not seem to carry those same risks.

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Hansell: Are the patients in whom you've initiated this "exercise therapy," if you will, more likely to also adhere to their other therapies, such as taking their drugs at home? We have a fair number of patients at our institution who come in simply because they just don't take care of themselves while at home. It seems to be more prevalent in the pre-teen and teenager group. Also, I'd like to ask about how you do chest physiotherapy. We have a clinic on Thursdays, and often after the clinic we have a substantial number of CF patients who are admitted. Over the weekend we often have a fair number of our respiratory therapists who work predominantly in pediatrics starting to complain of repetitive motion injury. A few staff have needed surgical correction of carpal tunnel syndrome. A lot of that is attributed to a high volume of CPT. Obviously, these other therapies make that less likely, but has anyone studied it that that you're aware of?

Wagner: First, as far as exercise, there was definite improved quality of

life in patients randomized to the exercise group. Only 5 of the 35 individuals randomized to the exercise group dropped out. The researchers did not measure if the improved quality of life corresponded to improved adherence to other CF therapies. Carpal tunnel syndrome and repetitive motion injury is a definite complication of chest physiotherapy. Hospital respiratory care directors need to address whether to change to other techniques, now that there are equally effective alternatives such as *The Vest* and IPV. Even with younger children, we're beginning to find alternatives to the classic chest physiotherapy.

Rotta: In general, CF patients' airways are colonized with bacteria, and we recognize the impact of exacerbation of pulmonary infection and the deterioration of lung function. Can you comment on what is the state of the art in early diagnosis of an infectious exacerbation, so that we can act on it quickly, particularly in light of the recent literature about chronic lung disease in adults, in which a change in bacterial profile in the airway signals an infectious exacerbation?

Wagner: Only recently have people begun to do routine monitoring of airway bacteria. Historically, CF centers have done once-a-year cultures unless the patient was sick. Now that we see more frequent monitoring for bacteria, 2 questions have arisen; one is what to do with the results, and the second is whether this frequent monitoring makes any difference. For example, the Danish Cystic Fibrosis Center has done monthly cultures and they respond 100% of the time to the result of those cultures. As a result, they report a persistently high eradication rate of *Pseudomonas*.¹ I think that in the future we are going to follow the course that you mentioned. Bacteria identification will be early and treatment will start in the presymptomatic phase. The Cystic Fibrosis Foundation

in the United States is currently planning a study to look at the question of treating early *Pseudomonas* infection.

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Cheifetz: I want to ask about heliox [helium-oxygen mixture]. There is a case report,¹ and I am aware of anecdotal evidence, indicating that heliox might be useful with CF patients suffering severe exacerbation and impending respiratory failure, to help avoid intubation. I acknowledge that the use of heliox might be simply "buying time" for more definitive therapies to take effect. Do you know of any more definitive evidence concerning the use of heliox with CF patients, or if you have had any experience with using it?

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Wagner: Heliox for CF is anecdotally discussed, similar to the question of noninvasive ventilation. I think it has to be on the list of possible therapies for patients with impending respiratory failure. A second gas to think about is nitric oxide, which improves ventilation-perfusion matching and also may reduce the number of bacteria and alter the inflammation process.¹ Thus, there is some interest in using nitric oxide with CF patients, either long-term or during acute exacerbations prior to respiratory failure.

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