Positive Expiratory Pressure and Oscillatory Positive Expiratory Pressure Therapies

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Airway clearance techniques, historically referred to as chest physical therapy, have traditionally consisted of a variety of breathing maneuvers or exercises and manual percussion and postural drainage. The methods and types of airway clearance techniques and devices have rapidly increased

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in an effort to find a more efficacious strategy that allows for self-therapy, better patient adherence and compliance, and more efficient durations of care. Mechanically applied pressure devices have migrated from European countries over the last several decades to clinical practice in the United States. I conducted a comprehensive MEDLINE search of two such devices: positive expiratory pressure (PEP) and oscillatory positive expiratory pressure (OPEP) and their role in airway clearance strategies. This was followed by a comprehensive search for cross-references in an attempt to identify additional studies. The results of that search are contained and reported in this review. From a methods standpoint, most of the studies of PEP and OPEP for airway clearance are limited by crossover designs and small sample sizes. While PEP and OPEP do not definitively prove superiority to other methods of airway clearance strategies, there is no clear evidence that they are inferior. Ultimately, the correct choice may be an airway clearance strategy that is clinically and cost effective, and is preferred by the patient so that adherence and compliance can be at the very least supported. *Key words: airway clearance, positive expiratory pressure, PEP, oscillatory PEP, secretion.* [Respir Care 2007;52(10):1308–1326.

Introduction

The description and benefits of airway clearance first appeared in the literature in *The Lancet* in 1901, when William Ewart described postural drainage and percussion as an "empty bronchus treatment by posture in the bronchiectasis of children."[1] Over the past century, airway-clearance strategies have become the primary mechanism to augment mucociliary clearance impaired by structural abnormalities (eg, bronchiectasis), abnormal mucus adhesivity and tenacity (eg, cystic fibrosis [CF]), impaired cough mechanics (eg, neuromuscular disease), or mucociliary-clearance disorders (eg, primary ciliary dyskinesia).

For several decades after their introduction to the medical community, the terms airway clearance and chest physical therapy (CPT) were synonymous with manual percussion, postural drainage, and vibration. Through scientific research and discovery, identification of the vital role of secretion mobilization and elimination in disease processes with impaired secretion clearance and expectoration created a market that led to the development of a large number of devices to assist in airway clearance or, at the very least, allow for effective, self-administered therapy. In addition to enhanced secretion mobilization and elimination, the secondary objective of these airway-clearance devices is to prevent recurring infection, atelectasis, and disease progression, or to improve pulmonary mechanics and facilitate gas exchange.

This manuscript provides a closer look at 2 types of device that were developed to assist in airway clearance: positive expiratory pressure (PEP) devices and oscillatory PEP (OPEP) devices. I will identify the positive (and possible negative) clinical, patient, and financial outcomes of these devices from a review of the literature from 1986 to 2006 that is specific to the use of these devices as adjuncts to airway clearance and secretion mobilization and expectoration.

Definitions of Positive Expiratory Pressure Therapies

Positive Expiratory Pressure Devices

PEP therapy was first developed in Denmark in the 1970s, as a low-pressure system. High-pressure PEP therapy was developed in Austria, as an adjunct or supplement to traditional airway-clearance methods, and the usual patient interface was a face mask.[2] The theoretical benefit of PEP therapy is the ability to enhance and promote mucus clearance by either preventing airway collapse by stenting the airways[3] or increasing intrathoracic pressure distal to retained secretions, by collateral ventilation or by increasing functional residual capacity.[4]

Since the original PEP devices were developed and described,[2] PEP device designs have been modified to allow for the patient interface to consist of either a face mask or a mouthpiece. The traditional main components of the device, however, remain the same, and consist of a one-way valve connected to either a small-exit orifice or, more commonly, an adjustable expiratory resistor. A disposable or permanent manometer is incorporated into the system between the one-way valve and the resistor to measure the expiratory pressure (Fig. 1).

Tightening the expiratory resistor decreases the ability of flow to move rapidly through the device and hence increases the expiratory pressure through flow retard. Low-pressure PEP devices typically generate a pressure range of 5–20 cm H_2O at mid-expiration. The literature commonly defines the high-pressure PEP range as 26–102 cm H_2O, which is typically achieved by performing a forced expiratory maneuver directly into a PEP mask after a maximal inspiration.[3] PEP therapy can be administered with the assistance of a respiratory therapist or caregiver, or independently by the patient (Fig. 2) after the patient receives appropriate instruction and does a return demonstration to the instructor. The duration and frequency of

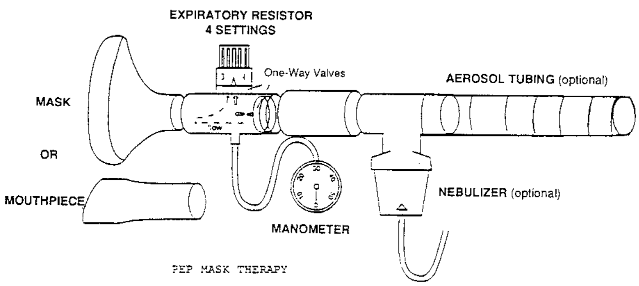

Fig. 1. Positive expiratory pressure therapy setup. The key components are the one-way valve, the small-orifice or (more commonly) adjustable expiratory resistor, and the patient interface (mask or mouthpiece). (From Reference 5. Courtesy of Mercury Medical, Clearwater, Florida.)

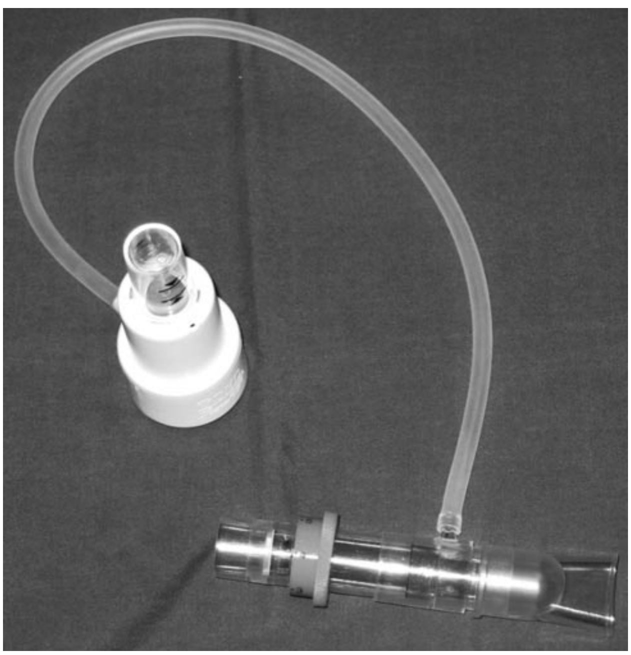

Fig. 2. The TheraPEP positive expiratory pressure therapy device.

Table 1. Patient Instructions for PEP Therapy

1. The patient should sit comfortably and upright while holding the mask firmly over the nose and mouth or the mouthpiece tightly between the lips (a nose clip may be necesary).
2. Adjust the expiratory resistor dial to the prescribed setting.
3. Have the patient breathe from the diaphragm, taking in a larger than normal tidal breath, but not to total lung capacity.
4. Have the patient gently exhale, maintaining a prescribed pressure of 5–20 cm H_2O.
5. Exhalation time should last approximately 3 times longer than inhalation.
6. Patient should perform 10–20 PEP breaths, then perform 2–3 forced exhalation maneuvers or huffs.
7. Repeat steps 3–6 until secretions are cleared, or until the predetermined treatment period has elapsed.

PEP = positive expiratory pressure

Fig. 3. The Flutter oscillatory positive expiratory pressure device: assembled (left), disassembled (right).

treatment should be tailored for each individual, based on the patient's specific indications and response to airway-clearance therapy. Table 1 describes the typical instructional steps for PEP therapy.

Oscillatory PEP Therapy

OPEP therapy was first developed and described in Switzerland, as an adjunct or supplement to traditional airway-clearance methods.[2] OPEP combines the purported benefits previously described for PEP with airway vibrations or oscillations. The theoretical benefits of oscillations have been described as a 2-fold effect in airway clearance. Oscillations reportedly decrease the viscoelastic properties of mucus, which makes it easier to mobilize mucus up the airways, and create short bursts of increased expiratory airflow that assist in mobilizing secretions up the airways.[6] Secretion removal is then facilitated by the patient forcing deep exhalations through the device or with subsequent coughing and/or huffing techniques.

Three OPEP devices are currently available in the United States: Acapella (Smiths Medical, Watford, United Kingdom), Quake (Thayer Medical, Tucson, Arizona), and Flutter (Axcan Scandipharm, Birmingham, Alabama).

The Flutter is a handheld device shaped like a pipe, which contains a high-density stainless steel ball that sits in a circular cone inside the bowl of the "pipe" (Fig. 3). The cover over the ball has perforations that allow expiratory airflow to pass through the device. The Flutter can be used with the patient sitting upright or lying on either side, if a horizontal position is more comfortable and advantageous for the patient. Whatever position the patient uses, the Flutter bowl must be pointed upward (Fig. 4) for maximum efficacy and proper operation.

The basic operation of the Flutter occurs when expiratory flow through the mouthpiece causes the ball to rise and fall within the cone, which creates a PEP between 5 cm H_2O and 35 cm H_2O. The vibrations, which are

Fig. 4. The Flutter device can be used with the patient sitting upright or lying on his/her side. (Photographs used by permission of the patients' parents.)

Table 2. Patient Instructions for Oscillating PEP Technique With the Flutter

1. Position the patient so that they are sitting upright with back straight and slightly extended head upward, with relaxed breathing control technique.
2. Have the patient inhale at 2–3 times greater than a normal breath and breath-hold for 2−3 seconds.
3. Place the Flutter device mouthpiece in the mouth and have the patient exhale at twice the flow of a normal exhalation. Continue the exhalation until lungs reach functional residual capacity.
4. Discourage unproductive coughing episodes during the initial secretion-loosening breaths.
5. During exhalation through the Flutter device, advise the patient to adjust the horizontal tilt of the Flutter to the angle that best gives the sensation of vibration within the lungs.
6. Following multiple loosening breaths, instruct the patient to take a very deep breath, hold it for 2–3 seconds, and then forcefully exhale through the device until lungs reach functional residual capacity.
7. After 1 or 2 high-volume, high-expiratory-flow mucus-clearance breaths, have the patient do a huff or other effective expiratory maneuver.
8. Additional therapy sequences, identical to the above described procedure, should be performed during the therapy session, until lungs are clear or until the predetermined treatment period has elapsed.

PEP = positive expiratory pressure

typically in the range 8–26 Hz,[7] create airflow pulsations throughout the airways. The Flutter can be tilted (frequently referred to as "tuning") slightly upward or downward to change the vibration frequency. Table 2 describes the instructional steps for Flutter therapy.

The Acapella (Fig. 5) uses a counterweighted plug and magnet to create airflow oscillations during expiratory flow. The Acapella comes in 3 models: the green model is for patients with expiratory flow > 15 L/min; the blue model is for patients with expiratory flows < 15 L/min; and the Choice model, which can be disassembled into 4 "easy-to-clean" parts that can withstand autoclaving, boiling, or dishwashing.

Fig. 5. The Acapella oscillatory positive expiratory pressure device (Blue-DM model above, Green-DH model below). (Courtesy of Smiths Medical, Watford, United Kingdom.)

Fig. 6. The Quake oscillatory positive expiratory pressure airway-clearance therapy device. (Courtesy of Thayer Medical, Tucson, Arizona.)

In a bench study comparison of Acapella and Flutter, Volsko et al[8] concluded that Acapella and Flutter have similar operating performance characteristics in pressure amplitudes and frequencies. Volsko et al commented that Acapella's performance is not gravity-dependent (ie, dependent on device and/or patient orientation) and may be easier to use for some patients, particularly at lower expiratory flow.

In my literature search for this review I found no peer-reviewed papers concerning Quake (Fig. 6), using search terms similar to those used for Flutter and Acapella. The Quake device has a manually operated rotating handle that creates the oscillations, and the oscillation frequency is controlled by how quickly the handle is rotated. Rotating the handle slowly creates a low-frequency oscillation and a higher pulsatile expiratory pressure. Rotating the handle quickly provides faster oscillations while decreasing the pulsatile expiratory pressure. Reportedly the Quake can be dissembled for cleaning and its operation and function are not gravity-dependent.

Does PEP Aid in Airway Clearance?

The following section reviews the literature from 1986 through 2006 on both low-pressure and high-pressure PEP therapy, and is based on disease pathophysiology. Table 3 summarizes the studies reviewed.

Cystic Fibrosis

Low-Pressure PEP Therapy for Cystic Fibrosis. Mortensen and colleagues[9] studied the effects of postural drainage and forced expiratory technique (FET) compared to PEP plus FET, in 20-min sessions, on whole-lung and regional tracheobronchial clearance in 10 patients with CF. Both airway-clearance methods demonstrated better whole-lung tracheobronchial clearance at 30 min and 1 hour than did no airway-clearance intervention. PEP plus FET produced significantly greater sputum volume than no airway-clearance intervention. Mortensen and colleagues concluded that postural drainage and PEP plus FET were equally effective on whole-lung and regional tracheobronchial clearance in patients with CF, in that short-term study. Evaluation of effectiveness based solely on sputum expectoration appeared to be inadequate.

Lannefors et al[10] conducted a small crossover study with 9 stable participants, to compare the mucus-clearance effect of 3 different airway-clearance regimens: (1) postural drainage with thoracic expansion exercises plus FET in the left decubitus position, (2) PEP-mask breathing plus FET, and (3) physical exercise on bicycle ergometer plus FET. The mean sputum clearance showed no significant difference between the 3 techniques. Lannefors et al stated that postural drainage was the most effective technique in the left, dependent lung in 7 of the 9 patients.

Van der Schans and colleagues[11] conducted a small crossover study with 8 patients to evaluate the effectiveness of low-pressure PEP (5–15 cm H_2O) versus low-pressure PEP in combination with cough, for peripheral and whole-lung mucus transport. PEP therapy was associated with increases in both functional residual capacity and total lung capacity above baseline. There was no difference in mucus clearance with PEP. Van der Schans et al concluded that, though PEP improved lung function, sputum clearance was not enhanced.

McIlwaine and colleagues[12] conducted a 1-year, comparative out-patient study of PEP technique against conventional postural drainage and percussion. The primary outcome was percent change in FEV_1. To provide balanced study groups, they paired patients according to their FEV_1 (within 15% of predicted value), sex, and age (within 3 years). An adherence rate of $< 85\%$ called for the participant to be removed from the study. Thirty-six patients completed the 1-year study period. Two patients in each group withdrew because of either device or visit nonadherence. The PEP group had significant improvement in FEV_1 ($p = 0.04$) and forced vital capacity (FVC) ($p = 0.02$). Patients subjectively preferred PEP because they believed PEP mobilized greater quantities of mucus and was easier to perform. McIlwaine et al concluded that PEP was superior to postural drainage and percussion in maintaining pulmonary function in patients with CF, and that patients preferred PEP because it requires less time to perform and does not require assistance.

In a study by Darbee et al,[13] a group of CF patients with moderate-to-severe obstructive disease and undergoing treatment for exacerbations were examined for the physiologic effects of high-frequency chest wall compression (HFCWC) versus PEP therapy. Outcome evaluations were conducted before and immediately after HFCWC or PEP treatments. Both airway-clearance methods were associated with significant changes in FVC and FEV_1. There were no differences between the methods or the effect of airway-clearance treatments at admission and discharge on FEV_1/FVC, or the forced expiratory flow in the middle half of the FVC (FEF_{25-75}). Treatment with both HFCWC and PEP at admission and discharge improved ventilation distribution. HFCWC significantly decreased oxygen saturation at both admission and discharge, but oxygen saturation returned to the pretreatment level immediately after treatment, whereas PEP therapy significantly increased oxygen saturation, but the increase was not sustained after treatment. Darbee and colleagues concluded that HFCWC and low-pressure PEP were similarly efficacious in improving pulmonary function, ventilation distribution, and gas mixing in subjects who had CF during exacerbations of their pulmonary disease. People who have low pretreatment pulse-oximetry-measured oxygen saturation values can desaturate to an unacceptable level during HFCWC, and these individuals may benefit from low-pressure PEP during exacerbation of their lung disease.

Placidi and colleagues[14] conducted a randomized crossover study of in-patients with CF to evaluate the short-term effects of directed cough combined with mask PEP, continuous positive airway pressure (CPAP), and noninvasive positive-pressure ventilation (NPPV) on the wet and dry weight of collected sputum. They also measured short-term changes in spirometry and oxygen saturation values and the patients' feelings regarding the effectiveness of these treatments in clearing sputum and the fatigue associated. All the therapies produced an increase in wet-weight sputum, which was attributed to a significant increase in spontaneous cough. PEP significantly increased the rate of spontaneous cough, compared to all other therapies and the control group. PEP wet-weight sputum pro-

Table 3. Studies of PEP Therapy: 1986 Through 2006

First Author	Population	*n*	Study Design	Outcome Variables Measured	Major Findings
Mortensen[9]	Cystic fibrosis	10	Randomized crossover trial of: · Low-pressure PEP + FET · Postural drainage + FET · Control	Spontaneous coughs with sputum expectoration. Mucus clearance via radioactive tracer	Postural drainage + FET and PEP + FET had 4–5 times greater whole-lung tracheobronchial clearance at both 30 min and 1 hour ($p < 0.01$). PEP + FET had significantly (1.4 times) greater output than control ($p < 0.05$). Correlations between tracheobronchial clearance and radioactivity content (Spearman rank r^2 0.76) and number of coughs (Spearman rank r^2 0.65) were better than tracheobronchial clearance and weight of sputum expectorated (Spearman rank r^2 0.39).
Lannefors[10]	Cystic fibrosis	9	Crossover trial of: · Low-pressure PEP + FET · Postural draining and thoracic expansion exercises + FET in the left decubitus position · Exercuse on bicycle ergometer + FET	Radiolabeled sputum clearance from both the right and left lung	No significant difference among the 3 techniques
van der Schans[11]	Cystic fibrosis	8	Crossover trial of: · Low-pressure PEP · Low-pressure PEP with cough	FRC and TLC before, during, and immediately after the interventions. Peripheral and whole-lung mucus transport measured via radioactive tracer.	PEP increased mean FRC 70% and TLC 35% above baseline. Higher PEP measure (15 cm H_2O) created higher lung volumes than did lower PEP pressure (5 cm H_2O). No difference in mucus clearance.
McIlwaine[12]	Cystic fibrosis	40	Prospective randomized trial of: · Low-pressure PEP · Postural drainage and percussion	PFT results Hospitalizations Shwachman score Huang score Cultures Self-reported compliance and questionnaires	Significant improvement in FEV_1 ($p = 0.04$) and FVC ($p = 0.02$). No difference in Shwachman or Huang scores, bacteriologic cultures or treatment adherence.
Darbee[13]	Cystic fibrosis	13	Randomized crossover trial of: · Low-pressure PEP · HFCWC	Distribution of ventilation Gas mixing Lung volumes Expiratory flow Sputum production S_{pO_2}	HFCWC and PEP improved FVC by 13% ($p < 0.001$) during acute stage. Significant FEV_1 improvement in both the acute and subacute stages ($p < 0.01$). No differences in FEV_1/FEV or FEF_{25-75}. HFCWC and PEP for acute and subacute stages improved ventilation distribution ($p < 0.01$). Helium = 8% ($p < 0.001$) Nitrogen = 9% ($p < 0.001$) Sulfur hexafluoride = 10% ($p < 0.001$) HFCWC decreased S_{pO_2} with treatment at both admission and discharge ($p < 0.001$). PEP increased S_{pO_2} with treatment at both admission and discharge ($p < 0.001$)
Placidi[14]	Cystic fibrosis	17	Randomized crossover trial of directed cough with: · Low-pressure PEP · CPAP · NPPV · Control	Sputum Production Cough frequency Pulmonary Function S_{pO_2} Self-reported preference	Increased production of wet-weight sputum with all therapies ($p < 0.05$), due to increased spontaneous cough. Increased production of wet-weight sputum with PEP therapy vs control group ($p < 0.05$) and NPPV ($p < 0.05$). No difference in dry-weight sputum production. Treatment produced increased spontaneous cough ($p < 0.01$). PEP produced higher rate of spontaneous cough than control therapy ($p < 0.01$). PEP produced increase in spontaneous cough, compared to CPAP or NPPV ($p < 0.01$) No difference in directed cough with treatment or spontaneous cough between CPAP and NPPV, compared to control therapy. Correlation between wet weight and number of spontaneous coughs ($r = 0.22$, $p < 0.001$). No difference in spirometry or S_{pO_2} values or self-reported therapy effectiveness. Patients reported feeling less tired ($p < 0.01$) with NPPV therapy than with PEP therapy.

(Continued)

Table 3. (Continued)

First Author	Population	*n*	Study Design	Outcome Variables Measured	Major Findings
Oberwaldner[3]	Cystic fibrosis	20	Crossover trial of: · High-pressure PEP · Postural drainage and percussion	Sputum volume	With PEP, patients cleared a higher percentage of their daily sputum volume than with postural drainage and percussion (78 ± 22% vs 53 ± 17%, $p < 0.01$). PEP significantly increased expiratory flow and significantly decreased hyperinflation.
Pfleger[15]	Cystic fibrosis	14	Crossover trial of: · High-pressure PEP · Autogenic drainage · Cough	Spirometry Sputum production	PEP produced significantly more sputum volume.
Darbee[16]	Cystic fibrosis	6	Randomized crossover trial of: · Low-pressure PEP · High-pressure PEP · Control	Distribution of ventilation Gas mixing Lung volumes Expiratory flow Sputum production S_{pO_2}	Distribution of ventilation improved in the low-pressure and high-pressure PEP groups immediately (25% and 24%, respectively) and 45 min after therapy (35% and 39%, respectively). Distribution of ventilation unchanged in controls. Improved gas mixing at 45 in, with the low-pressure and high-pressure PEP therapy (15% and 23%, respectively), compared to control group (5%). Slow vital capacity increased with low-pressure and high-pressure PEP immediately (5% and 5%, respectively) and 45 min after PEP therapy (9% and 13%, respectively), and after 45 min (20% and 30%, respectively), with minimal to no change in control group (5% and 13%, respectively). Decreases in residual volume with low-pressure and high-pressure PEP immediately (4% and 10%, respectively) and after 45 min FEV_1 increased with both low-pressure and high-pressure PEP immediately (6% and 5%, respectively) and after 45 min (7% and 9%, respectively), compared to <1% in controls. FEF_{25-75} increased with low-pressure and high-pressure PEP immediately (29% and 27%, respectively) and after 45 min (1% and 22%, respectively), with minimal to no changes in control group (2% and 7%, respectively). No differences or changes in S_{pO_2}. Greater cumulative dry-weight sputum in all groups.
Christensen[17]	Chronic bronchitis	44	Prospective randomized trial of: · Diaphragmatic breathing + FET · PEP · Control	Pulmonary function Symptoms Exacerbations Sick-leaves Need for additional medication	No difference in daily airway clearance frequency, dyspnea, missed work, overall pulmonary function status. PEP group self-reported less cough ($p = 0.025$) and mucus production ($p = 0.013$). PEP group had better self-efficacy report at 1 month and at study end ($p < 0.05$ and $p = 0.0001$, respectively). PEP group had fewer exacerbations ($p = 0.011$). Exacerbation rate (exacerbations/observation time) lower in PEP group ($p < 0.001$). Lower antibiotic use rate (antibiotics use days/observation time) in PEP group ($p < 0.05$). Lower supplemental muculytic drugs use in PEP group ($p < 0.05$). Significant difference in FEV_1 in the PEP group in patients treated for 12 months ($p = 0.039$).
Ingwersen[18]	Postoperative patients	160	Prospective randomized trial of: · Postural drainage and percussion · CPAP · PEP · Inspiratory plus expiratory resistance device	FVC P_{aO_2} Chest radiograph reports Device preference survey	No significant differences in any outcomes. Patients preferred the PEP therapy.
Richter Larsen[19]	Postoperative patients	97	Prospective consecutive randomized controlled trial of: · PEP · Postural drainage and percussion · Inspiratory plus expiratory resistance device	FVC P_{aO_2} Chest radiograph reports Device preference survey	No significant difference in FVC, P_{aO_2} or rate of atelectasis. Patient preference for PEP therapy and postural drainage and percussion.

(Continued)

Table 3. (Continued)

First Author	Population	n	Study Design	Outcome Variables Measured	Major Findings
Lagerkvist[20]	Severely disabled children	17	Before and after: · Postural drainage and percussion · PEP + postural drainage and percussion	P_{tcO_2} P_{tcCO_2} Respiratory rate	There were no differences in P_{tcCO_2} or respiratory rate. Significant increase in mean P_{tcO_2} with PEP treatment (66 ± 15 mm Hg vs 73 ± 16 mm Hg, $p < 0.001$).
Plebani[21]	HIV	8	Before and after: · PEP · No intervention	Pulmonary infections Antibiotic use	Decreased infection rate (4.5 d ± 1.0 to 2.1 ± 0.9 infections/y, $p < 0.001$). Decreased antibiotic courses (2.4 ± 0.9 to 1.5 ± 0.7 courses/y, $p < 0.021$).

PEP = positive expiratory pressure. FET = forced expiratory technique. FVC = forced vital capacity. TLC = total lung capacity. FRC = functional residual capacity. FEV_1 = forced expiratory volume in the first second. P_{tcO_2} = transcutaneously measured partial pressure of oxygen. P_{tcCO_2} = transcutaneously measured partial pressure of carbon dixoide. PFT = pulmonary function test. HIV = human immunodeficiency virus. HFCWC = high-frequency chest wall compression. FEF_{25-75} = forced expiratory flow in the middle half of the FVC. S_{pO_2} = blood oxygen saturation measured via pulse oximetry. CPAP = continuous positive airway pressure. NPPV = noninvasive positive-pressure ventilation.

duction was significantly greater than that of the control group or the NPPV therapy group. There was also a significant correlation between the sputum wet-weight and the number of spontaneous coughs. There were no differences in directed cough with treatment or spontaneous cough between CPAP and NPPV compared to control. There were no differences in dry-weight sputum production, spirometry, pulse-oximetry-measured saturation, or self-reported therapy effectiveness before and after the 4 treatments. Patients reported feeling significantly less tired with NPPV than with mask PEP. Placidi and colleagues concluded that there was no difference in sputum clearance between mask PEP, CPAP, and NPPV in patients with CF and severe airway obstruction hospitalized for pulmonary exacerbation.

High-Pressure PEP Therapy for Cystic Fibrosis. Oberwaldner et al[3] trained 20 patients who had previously used postural drainage as their airway-clearance strategy, to receive high-pressure mask PEP therapy. High-pressure PEP produced a significantly greater daily sputum volume than did postural drainage. In this longitudinal study, 11 patients who received high pressure PEP also significantly increased their expiratory flow while significantly decreasing hyperinflation and airway instability. The remaining 9 patients demonstrated a steady and statistically significant improvement of lung function over the entire observation period (18 months). Oberwaldner and colleagues concluded that dilating the airways and evacuating trapped gas with high-pressure PEP therapy improved lung function and mucus clearance in patients with CF.

Pfleger and colleagues[15] conducted a crossover study of 2 self-administered airway-clearance strategies: high-pressure (> 25 cm H_2O) PEP with a mask, and autogenic drainage. All 4 airway-clearance strategies produced a higher volume of mucus than did cough alone, with no adjunctive airway-clearance technique. PEP produced the greatest amount of sputum. There were no significant differences in spirometry among or correlation between improved lung function and increased mucus production. In fact, patients with airway hyperreactivity had increased lung function and significantly lower sputum yields, which led to speculation that these patients may have had PEP-induced bronchospasm. Pfleger et al concluded that PEP clears more sputum than autogenic drainage or some combination of techniques, but patients with airway hyperreactivity might prefer autogenic drainage or should be advised to pre-medicate with bronchodilators prior to high-pressure PEP therapy.

Darbee and colleagues[16] conducted a small study to determine physiologic responses following low-pressure and high-pressure PEP treatments or no intervention (control) in patients with moderate-to-severe lung disease (by American Thoracic Society criteria).[22] Pre-intervention data indicated that all 5 participants had moderate central-airways obstruction, severe peripheral airflow limitation, and unbalanced ventilation distribution and gas mixing. When assessing the diagnostic variables after intervention, both the low-pressure and high-pressure PEP groups had better improvement in ventilation distribution than did the control group. All the groups showed improvement in gas mixing within the lung at 45 min, and both the low-pressure and high-pressure PEP groups had greater improvement than the control group. Lung volumes and expiratory flows increased in both the low-pressure and high-pressure PEP groups immediately and after 45 min of PEP therapy, compared to minimal to no change in the control groups. The study's main finding was that gas mixing improved with all the interventions, and particularly with low-pressure and high-pressure PEP, which indicates that previously closed airways were opened, additional residual-volume gas was exhaled, and a larger inspired volume of gas entered the lung, which might improve gas exchange. Twenty minutes of PEP therapy effectively improved gas mixing in a small group of medically stable patients with moderate-to-severe CF-related lung disease. The subjects also reported less chest unpleasantness due to pulmonary secretions following low-pressure and high-pressure PEP.

Chronic Bronchitis

Christensen et al[17] conducted a study that assessed prophylactic home outcomes in patients with chronic bronchitis who used diaphragmatic breathing plus forced expirations, with or without PEP. Smokers and nonsmokers were included in the study, but patients with disease comorbidities were excluded. Seven patients (4 PEP, 3 control) were removed from the study for lack of adherence. By self-report, the PEP group had significantly less cough and mucus production than did the control group. The PEP group had significantly fewer exacerbations and a significantly lower exacerbation rate (number of exacerbations divided by observation time) than did the control group. The use of supplemental antibiotics (antibiotic rate = number of antibiotics use days divided by observation time) and mucolytic drugs was also significantly lower in the PEP group than in the control group. Both groups reported the treatments useful, but the benefit was more significant for the group who received PEP after 1 month of treatment and at the end of the study. Overall, there was no significant difference in pulmonary function status for the entire group. In the patients treated for 12 months there was an increase in FEV_1 among the PEP group and a decrease in FEV_1 in the control group. There were no differences in other pulmonary function values between the 2 groups or overall pulmonary function status, daily airway-clearance frequency, dyspnea, or missed work. Christensen et al concluded that a simple and inexpensive PEP device can reduce morbidity in patients with chronic bronchitis and may preserve lung function from a more rapid decline.

Postoperative Complications

Ingwersen and colleagues[18] conducted a prospective randomized comparison of CPAP versus PEP versus a device that creates both inspiratory and expiratory resistance, for postoperative complications in surgical patients. Monitored outcome variables were assessed on the fourth and ninth postoperative days. Patients also completed a device preference survey. There were comparable decreases in pulmonary function and P_{aO_2}, and comparable rate of atelectasis in all the treatment groups. The patients preferred PEP to the other therapies. The investigators concluded that there were no significant differences between the airway-clearance regimens, and all the therapies could be used as a supplement to standard CPT.

Richter Larsen and colleagues[19] compared the effects of PEP versus postural drainage and percussion versus a device that creates both inspiratory and expiratory resistance on postoperative complications after thoracic surgery. Sixty-six patients completed the study. There was no significant difference in FVC, P_{aO_2}, or rate of atelectasis from surgery to postoperative day 6. Participants treated with PEP had a borderline significant increase in P_{aO_2} from day 3 to day 6. The questionnaire responses indicated that the participants preferred PEP and postural drainage and percussion over the device that created both inspiratory and expiratory resistance. The investigators concluded that there was a tendency toward less risk of postoperative complications in the groups that used PEP and the device that creates both inspiratory and expiratory resistance.

Multiple Severe Disabilities

Lagerkvist and colleagues[20] conducted a study to investigate if postural drainage and percussion, with and without PEP, could improve P_{aO_2} and/or decrease P_{aCO_2} in severely disabled children with airway mucus accumulation. Participants served as their own controls in this before-and-after intervention study. There was no significant difference in transcutaneously measured P_{CO_2} (P_{tcCO_2}) or respiratory rate after PEP, but PEP significantly increased the mean transcutaneously measured P_{O_2} (P_{tcO_2}). Lagerkvist et al concluded that there was a significant increase in P_{tcO_2}, reproducibility of the PEP treatment was good, and the children accepted the PEP well. Though long-term effects remain to be proven, PEP is effective for severely disabled children.

Infections

Plebani et al[21] conducted a study in patients with human immunodeficiency virus (HIV) and recurrent bacterial pulmonary infections to assess if twice-daily PEP therapy over the course of a year could reduce the infection rate. After the 12-month study, both the mean number of infections and antibiotics use had significantly decreased. The investigators concluded that PEP removes infected secretions and reduces the need for antibiotics in children with HIV.

Summary of PEP Therapy

From these relatively small (total $n = 97$ subjects) and few (6) studies of low-pressure PEP in patients with CF, it is somewhat difficult to draw an objective clinical or scientific conclusion.[9-12,13,14] These studies would lead one to think that PEP therapy may improve pulmonary function status and may facilitate secretion removal, but the methods of airway clearance were not different than other airway-clearance techniques or devices. The same types of conclusions can be extrapolated from the 3 studies in CF patients ($n = 40$ patients) with high-pressure PEP therapy.[3,15,16] There appears to be some improvement in lung function across all 3 studies. Though, again, the number of patients is too few to provide a scientific conclusion, the 3 studies of high-pressure PEP therapy appeared to produce significantly more sputum than their study comparators.

The other 5 PEP studies reported above were conducted in patients with 4 different disease states or conditions (chronic bronchitis, postoperative patients, severely disabled children, and HIV). In the study in patients ($n = 44$) with chronic bronchitis, PEP had little to no impact on mucus production, but provided a clinical benefit in decreasing infections and exacerbations.[17] Two large PEP studies ($n = 257$) in postoperative patients found no significant differences in the outcomes studied, with the exception of a patient preference for PEP therapy.[18,19] The studies in severely disabled children and children with HIV were too small ($n = 17$ and 8, respectively) to draw any conclusion on the effectiveness of PEP therapy.[20,21]

Does Oscillatory PEP Aid in Airway Clearance?

The following section reviews the literature from 1986 through 2006 on OPEP therapy, and is based on disease pathophysiology. All these studies were conducted with the Flutter device. Table 4 summarizes the studies reviewed.

Cystic Fibrosis

Pryor and colleagues[23] compared OPEP (with the Flutter VRP1) to active cycle of breathing technique in a prospective randomized crossover clinical study in subjects with CF. They found no significant improvement in lung function or oxygenation in those subjects. They did find a significant increase in sputum production ($p < 0.001$) in the subjects who received active cycle of breathing technique. Pryor and colleagues concluded that there were no clear differences in efficacy between Flutter and active cycle of breathing technique.

Konstan and colleagues[24] conducted a study to compare the amount of sputum expectorated after use of the Flutter with the amount expectorated with vigorous voluntary coughing, and with postural drainage with chest percussion and vibration. Between these airway-clearance techniques there was no difference in the sputum or sputum pellet weights between week 1 and week 2. All participants expectorated significantly more sputum, as determined by the average weight of the sputum before centrifugation of the sputum pellet, during their sessions with the Flutter device than during either voluntary cough or postural drainage sessions ($p < 0.001$). There was no difference between voluntary cough and postural drainage in the amount of sputum expectorated. Konstan et al concluded that the Flutter was more effective than conventional techniques in clearing mucus from the airways of patients with CF. The Flutter device was simple to use and safe, and they believed that it could improve patient adherence to airway-clearance therapy and reduce the cost of care.

Newhouse et al[25] sought to find an airway-clearance procedure that could be self-administered by adolescents and adults with CF. The study compared the intrapulmonary percussive ventilator and the Flutter device to the standard, manual postural drainage and percussion therapy patients had been receiving. There were no differences in the amount of sputum produced with any of the airway-clearance methods. There were inconsistent but significant improvements in flow with both the intrapulmonary percussive ventilator and Flutter, compared to postural drainage and percussion. Newhouse et al also noted transiently lower oxygen saturation with postural drainage and percussion, compared to the other 2 methods. They concluded that larger and longer studies of these devices compared to standard chest CPT and with each other are warranted to assess their value for independent administration of CPT in CF patients and to determine long-term effects on maintenance of pulmonary function.

Homnick and colleagues[26] conducted a study that compared the Flutter device to standard manual CPT in 22 hospitalized patients (33 total hospitalizations) with exacerbations of CF lung disease. A significant improvement was obtained in both average percent change in clinical score and pulmonary function test results from admission (baseline) to discharge. All the pulmonary function test variables studied improved except total lung capacity with Flutter, and except total lung capacity and FEV_1/FVC with CPT. Homnick et al concluded that the Flutter appears to be safe, efficacious, and cost-effective for CF in-patients capable of undertaking this type of therapy.

Gondor and colleagues[27] conducted a prospective randomized study to compare conventional CPT to Flutter therapy, received 4 times daily, in 23 patients with CF, during a 2-week hospitalization for acute pulmonary exacerbation. Three of the 23 subjects (all from the CPT group) were discharged prior to 14 days of in-patient therapy, and therefore their data were not included in the analysis of the 2-week intervention. A total of 20 patients completed the study. The patients who received CPT and Flutter each had significantly improved FVC and FEV_1 over the 2-week treatment period. Repeated measures for analysis of variance revealed a significant group $\times$ time interaction for both FVC and FEV_1 after 1 week of intervention. Patients in the Flutter group had significantly higher FVC and FEV_1 on day 7, compared to entry day, than did the CPT group, but there was no difference between the groups by day 14. Both treatment groups showed significant increases in FEF_{25-75} and resting arterial oxygen saturation by the end of the 2-week treatment period, and there were no differences between the groups. No significant differences were found between the groups in

Table 4. Studies of Oscillating PEP: 1986 Through 2006

First Author	Population	*n*	Study Design	Outcome Variables Measured	Major Findings
Pryor[23]	Cystic fibrosis	24	Randomized crossover trial of: · ACBT · Flutter + ACBT	Sputum production Spirometry S_{pO_2}	Greater sputum production with ACBT ($p < 0.001$). No differences in spirometry or S_{pO_2} values.
Konstan[24]	Cystic fibrosis	18	Randomized crossover trial of: · Postural drainage and percussion · Flutter	Sputum production	Significantly more sputum production with Flutter ($p < 0.001$).
Newhouse[25]	Cystic fibrosis	11	Randomized crossover trial of: · Postural drainage and percussion · Flutter · IPV	Sputum production Spirometry S_{pO_2}	No difference in sputum production. Significant improvements in flow with both IPV and Flutter. Transient decrease in S_{pO_2} with postural drainage and percussion.
Homnick[26]	Cystic fibrosis	33	Prospective randomized trial of: · Postural drainage and percussion · Flutter	Spirometry Hospital stay Number of treatments Clinical score	No difference in any measured outcome.
Gondor[27]	Cystic fibrosis	23	Prospective randomized trial of: · Postural drainage and percussion · Flutter	Spirometry 6-min walk S_{pO_2} Hospital stay Sputum cultures	Similar significant spirometry and 6-min-walk improvements with postural drainage and percussion and Flutter. No differences in S_{pO_2}, hospital stay, or sputum cultures. Significant improvement in FVC and FEV_1 at 7 days with Flutter.
App[7]	Cystic fibrosis	17	Randomized crossover trial of: · Autogenic drainage · Flutter	Sputum production Spirometry Sputum viscoelasticity	No difference in spirometry or sputum production. Significant decrease in sputum viscoelasticity with Flutter ($p < 0.01$).
Oermann[28]	Cystic fibrosis	29	Prospective randomized crossover trial of: · Postural drainage and percussion · HFCWC · Flutter	Pulmonary function Modified National Institute of Health score Petty score Patient satisfaction score	No difference in pulmonary function, Modified National Institute of Health score, or Petty score. HFCWC had significantly higher patient efficacy score than Flutter. Flutter had significantly higher convenience score than HFCWC or postural drainage and percussion.
Girard[29]	Asthma	20	Before-and-after	Spirometry	Significant improvement in spirometry values with Flutter.
Bellone[30]	Chronic bronchitis	10	Randomized crossover trial of: · Postural drainage and percussion · Flutter · ELTGOL	Sputum production Pulmonary function S_{pO_2}	No difference in pulmonary function or S_{pO_2}. Significant increase in sputum production at 30 min with all ($p < 0.01$). Significant increase in sputum production at 1 hour with Flutter ($p < 0.01$) and ELTGOL ($p < 0.02$)
Burioka[31]	Panbronchiolitis	9	Randomized crossover trial of: · Flutter · Cough	Sputum production Pulmonary function ABG Symptoms scores	Significant increase in mean daily sputum weight and peak expiratory flow ($p < 0.04$ and $p < 0.02$, respectively) with Flutter. Self-reported symptom score improved significantly ($p < 0.02$) with Flutter. No differences in ABG values.
Thompson[32]	Bronchiectasis	22	Randomized crossover trial of: · Flutter · ACBT	Sputum production Spirometry Therapy duration Symptom scores Patient preference survey	Significant improvement in FEV_1 with Flutter. No differences in sputum production, therapy duration, or symptom scores. 11 of 17 patiens preferred Flutter.

ACBT = active cycle of breathing technique. S_{pO_2} = blood oxygen saturation measured via pulse oximetry. IPV = intrapulmonary percussive ventilation. FEV_1 = forced expiratory volume in the first second. FVC = forced vital capacity. HFCWC = high-frequency chest wall compression. ELTGOL = *Expiration lente totale glotte ouverte en infralatéral* (slow expiration with glottis open during the entire exhalation, with the patient in infralateral decubitus position). ABG = arterial blood gas.

their increases in walk distance; however, mean walk distance improved significantly over the 2-week period in both groups. There were no differences in days of hospitalization or prevalent organisms colonizing the respiratory tracts of the groups. Gondor and colleagues concluded that using the Flutter device as a means of airway clearance is comparable to CPT in the short-term, but it remains to be shown whether the Flutter is comparable to or as advantageous as CPT for long-term use by patients.

App and colleagues[7] conducted a study to evaluate the efficacy of autogenic drainage and Flutter. A total of 17 patients with CF entered this long-term study to evaluate the short-term and long-term effects of autogenic drainage and Flutter. Prior to crossing over to the other therapy there was a 1-week wash-out period in which the subjects went without any kind of airway-clearance method. There was no significant difference in FVC, FEV_1, or sputum volume throughout the study. Airway clearance with the Flutter produced a significantly lower sputum viscoelasticity (rigidity) than did autogenic drainage, at both analytical frequencies. The lower sputum viscoelasticity analytic frequency allowed calculation of a mucociliary clearance index, and the higher frequency calculated cough clearance index increased significantly. App and colleagues concluded that applied oscillations can decrease mucus viscoelasticity within the airways at frequencies and amplitudes achievable with the Flutter device, and provided direct evidence that OPEP can reduce the viscoelasticity of sputum.

Oermann and colleagues[28] conducted a prospective randomized crossover study (1) to assess the safety and efficacy of HFCWC and OPEP in maintaining lung function over time, (2) to estimate the magnitude and variability of changes in spirometric measurements resulting from airway clearance, to explore the feasibility of a larger, definitive, comparative study, and (3) to evaluate patient satisfaction with airway-clearance techniques in 29 patients with CF. Spirometry and lung volume measurements were the primary outcome measures. Two validated clinical scores (the modified National Institutes of Health score and the Petty score) were secondary outcome measures. Patient satisfaction was also a secondary measure, assessed via 2 methods. Twenty-four of the 29 subjects completed both therapy types and were included in the final analysis. Self-reported adherence documented in the study diaries indicated higher-than-normal adherence rates for both HFCWC and OPEP (88% and 92%, respectively). There were no significant differences in spirometry or lung volume measures between HFCWC and OPEP. There were no differences in either the modified National Institutes of Health score or the Petty score. The patient-satisfaction survey data were divided into 3 components: treatment efficacy, convenience, and patient comfort. The HFCWC efficacy score was higher than that of CPT and OPEP, but the difference was only statistically significant for HFCWC versus OPEP. The convenience score for OPEP was significantly higher than that for either conventional CPT or HFCWC. There were no statistically significant differences in the comfort scores between the therapies. Of the 24 subjects who completed both therapy types, 12 (50%) preferred HFCWC, based on belief in efficacy, 9 (37%) preferred OPEP because of convenience, and 3 subjects (13%) preferred postural drainage and percussion because of familiarity with the technique. Oermann and colleagues concluded that the study suggested that HFCWC and OPEP are safe and effective methods of airway clearance and offer acceptable alternatives to conventional CPT. The patients showed better adherence with prescribed airway-clearance regimen than has been generally reported for CPT, and this better adherence may relate to greater patient satisfaction and perception of technique superiority of postural drainage, percussion, and vibration, in terms of efficacy and/or convenience.

Asthma

Girard et al[29] studied OPEP (Flutter VRP1) in 20 patients with asthma, mucus hypersecretion, and hypersensitivity to dust mites as a major allergen. Patients were instructed to use the Flutter a minimum of 5 times a day for at least 5 min per setting, for 30–45 consecutive days. There were significant improvements in FEV_1, FVC, and peak expiratory flow with daily Flutter use. Girard et al concluded that both objective and subjective improvement occurred in 18 of the 20 subjects.

Chronic Bronchitis

Bellone and colleagues[30] conducted a randomized crossover study to compare the short-term effects of improved secretion removal with 3 different techniques with regard to oxygen saturation, pulmonary function, and sputum production during exacerbations of chronic bronchitis in 10 male patients. The patients were assigned to receive one of 3 airway-clearance treatments on 3 consecutive days, in random order: postural drainage, Flutter, or ELTGOL (*expiration lente totale glotte ouverte en infralatéral* [slow expiration with the glottis open during the entire exhalation, with the patient in infralateral decubitus position]). Sputum production increased significantly 30 min after treatment, with all methods. One hour after treatment, sputum was significantly increased with Flutter and ELTGOL. There were no significant differences in pulse-oximetry-measured saturation or FEV_1. Bellone and colleagues concluded that all 3 treatments were effective in removing secretions without causing any undesirable effect on oxygen saturation in patients with chronic bronchitis exacerbation. Because the techniques other than postural drainage allow patients to do their treatment by themselves, they might be valid alternatives to postural drainage and should be considered very attractive first choices of CPT in the treatment of chronic bronchitis exacerbation. Furthermore, Flutter and ELTGOL are more effective than postural drainage in prolonging the secretion-removal effect, which suggests a more homogeneous drainage of the bronchial tree.

Panbronchiolitis

Burioka and colleagues[31] evaluated the clinical effectiveness of OPEP (Flutter) in clearing mucus from the airways of 8 patients with clinically stable diffuse panbronchiolitis. In this crossover study, patients received no therapy in the initial week, followed by 1 week of Flutter, administered 4 times daily. Sputum collected was weighed daily for the 2 weeks of the study. Outcome measures (spirometry, P_{aO_2}, and P_{aCO_2}) were measured prior to therapy and during the last day of the intervention or control week. Patients also completed a symptom score for difficulty of expectoration. There was a significant increase in mean daily sputum weight and peak expiratory flow with the Flutter. The self-reported symptom score also improved significantly during the week of Flutter therapy. One patient developed a pneumothorax while using Flutter. Burioka and colleagues concluded that the Flutter is effective in clearing mucus from the airways, but pneumothorax can complicate its use in some cases.

Bronchiectasis

Thompson and colleagues[32] conducted a randomized crossover study with patients with non-CF bronchiectasis, to compare the Flutter to active cycle of breathing technique. The outcomes included daily weight of sputum, duration of CPT, peak expiratory flow, and breathlessness (Borg scale) before and after each CPT session. Post-bronchodilator spirometry, peak expiratory flow, and health-related quality of life (Chronic Respiratory Disease Questionnaire) were measured at baseline and after each arm. A questionnaire after completion of the study asked the patients which technique they preferred for routine use. Seventeen of the 22 subjects completed both arms. There was no significant difference between the active cycle of breathing technique and Flutter for any outcome, nor was there evidence to suggest any treatment-order or interaction effect. There was a statistically significant improvement in FEV_1 with the Flutter, but this did not achieve a clinically meaningful change. Eleven of the 17 patients preferred the Flutter for routine daily use, 3 preferred active cycle of breathing technique, and 3 had no preference. Thompson et al concluded that the Flutter was as effective as active cycle of breathing technique in the home for non-CF bronchiectasis, and suggested that individuals with bronchiectasis should be offered a trial of the Flutter and, if the patient prefers Flutter, it should be recommended for regular daily use.

Summary of Oscillatory PEP Therapy

From the relatively small (total $n = 155$) and few (7) studies of OPEP in patients with CF,[7,23–28] it is somewhat difficult to draw an objective clinical or scientific conclusion. These studies would lead one to believe that OPEP therapy may facilitate mucus secretion removal; however; OPEP is not different than other airway-clearance techniques or devices. The other 4 OPEP studies reported above were conducted in patients with 4 different disease states or conditions: asthma, chronic bronchitis, panbronchiolitis, and bronchiectasis. The studies in patients with asthma or bronchiectasis showed improved lung function, but no change or improvement in mucus production.[29,32] In the 2 studies that involved chronic bronchitis or panbronchiolitis, though the total study sample populations were small (10 and 9, respectively), the outcomes would lead one to speculate that OPEP may improve sputum production in these patient populations.[30,31] However, more robust trials are indeed needed to provide scientific validity.

PEP Versus OPEP

The following section reviews the literature from 1986 through 2006 on head-to-head comparative studies of PEP versus OPEP, and is based on disease pathophysiology. Table 5 summarizes the studies reviewed.

Cystic Fibrosis

Newbold and colleagues[33] conducted a study to compare the effectiveness of the Flutter device to mask PEP therapy in 42 patients with CF. Patients were randomly assigned to one of the airway-clearance methods over 1 year. The outcome measures were pulmonary function test results, the Quality of Well-Being score, and Chronic Respiratory Disease Questionnaire score. There was no difference in FEV_1, Quality of Well-Being score, or Chronic Respiratory Disease Questionnaire score, evaluated by linear regression analysis. Newbold et al concluded that there were no significant differences in pulmonary function or health-related quality of life between the Flutter and PEP mask in the treatment of adults with CF over a 13-month period.

A crossover study to evaluate the immediate effects of PEP and OPEP treatment on blood gas tensions in 15 patients with CF was conducted by Lagerkvist et al.[34] Patients were randomized to receive PEP or OPEP on 2 separate occasions, 8 weeks apart, in connection with an ambulatory visit. The immediate results with PEP showed

Table 5. Studies That Compared PEP and Oscillating PEP: 1986 Through 2006

First Author	Population	n	Study design	Outcome Variables Measures	Major findings
Newbold[33]	Cystic fibrosis	42	Prospective randomized trial of: · PEP · Flutter	Pulmonary function Quality of life Symptom scores	No difference in any measured outcome
Lagerkvist[34]	Cystic fibrosis	15	Prospective randomized crossover trial of: · PEP · Flutter	Pulmonary function Transcutaneous blood gas values	Significant decrease in P_{tcCO_2} ($p < 0.05$) with Flutter during and immediately after sessions. Immediate transcutaneous results after oscillating PEP demonstrated significantly higher P_{tcO_2} ($p < 0.05$) and significantly lower P_{tcCO_2} ($p < 0.001$) compared to PEP. All differences between methods disappeared after therapy. No differences in spirometry values.
McIlwaine[35]	Cystic fibrosis	40	Prospective randomized trial of: · PEP · Flutter	Pulmonary function Hospitalization rates Huang score Schwachman score Chest radiograph Sputum culture Patient adherence rate	No difference in Schwachman scores, chest radiographs, or changes in sputum bacteriologic cultures. Significant difference in FVC ($p < 0.05$), hospitalization rate ($p = 0.03$), and Huang scores ($p < 0.05$) in favor of PEP. No difference in patient adherence rate.
van Winden[36]	Cystic fibrosis	22	Prospective randomized crossover trial of: · PEP · Flutter	Pulmonary function S_{pO_2} Symptom score Cough frequency Sputum production Shortness of breath	No difference in any measured outcome.
Valente[37]	Bronchiectasis	8	Prospective, randomized, crossover trial of: · Flutter · PEP	Sputum production Sputum viscoelasticity	No difference in any measured outcome.

PEP = positive expiratory pressure
P_{tcCO_2} = transcutaneously measured partial pressure of carbon dioxide
P_{tcO_2} = transcutaneously measured partial pressure of oxygen
FVC = forced vital capacity
S_{pO_2} = blood oxygen saturation measured via pulse oximetry

a significant reduction in P_{tcCO_2}, but there was no difference in P_{tcO_2}. Immediate results with OPEP showed a significant reduction in P_{tcCO_2} and a significant increase in P_{tcO_2}. After 5 min of airway-clearance therapy with either PEP or OPEP, there were no differences in P_{tcO_2} or P_{tcCO_2}. There was no difference in pulmonary function status (spirometry values) after PEP or OPEP therapy.

A significant change in P_{tcCO_2} occurred during OPEP within intra-individual sessions. A significant reduction in P_{tcCO_2} also was recorded during and immediately after OPEP, compared to PEP. Immediate transcutaneous results after OPEP showed significantly higher P_{tcO_2} and a significantly lower P_{tcCO_2}, compared to PEP. However, after a period of steady state, all differences between methods disappeared and there was no sustained effect on blood gases. There were no differences in the spirometry values after treatment. Lagerkvist and colleagues concluded that PEP and OPEP cause short-lived changes in blood gases in patients with CF. OPEP caused greater immediate blood gas changes than did PEP, but the changes subside rather quickly (in < 10 min). Spirometry values appear to not be affected by PEP or OPEP.

In a long-term study, McIlwaine et al[35] randomized 40 patients with CF to receive airway clearance twice daily with Flutter or PEP. Patients were asked to maintain a daily treatment adherence record and complete a monthly questionnaire that assessed physical activity, how the patient was feeling, cough, sputum production, the patient's impression of the airway-clearance technique, adverse reactions to therapy, and adherence or reasons for nonadherence with the airway-clearance regimen. An adherence recording of < 85% for a 1-month period was considered nonadherence, and the patient was removed from the study. Thirty-two patients completed the 1-year study period.

There was no significant change in pulmonary function status in the PEP patients over the course of the year. There was a mean annual rate of decline in three of the pulmonary function variables assessed (FEV_1, FVC, and $FEF_{25–75}$), which resulted in a significant difference in FVC compared to PEP therapy. A statistically significant difference in hospitalizations favored PEP therapy, compared to those assigned to receive airway clearance with the Flutter device. There was a significant difference in Huang scores between the PEP group and the Flutter group, but there were no significant differences in Shwachman scores, chest radiographs, or changes in sputum bacteriologic cultures. McIlwaine and colleagues concluded that the Flutter was not as effective as PEP in maintaining pulmonary function in patients with CF, and that Flutter was more costly because of the greater number of hospitalizations and greater antibiotic use.

Van Winden and colleagues[36] conducted a randomized crossover study to compare Flutter to PEP mask in 22 clinically stable children with CF. Before and after airway-clearance therapy, peak flow readings were measured daily, in the morning, and a symptom questionnaire for daytime and nighttime cough, sputum production and shortness of breath (each was scored on a 3-point scale) was completed daily. Cumulative symptoms during the 2-week study period were taken as the symptom score. All 22 patients completed the study. There was no significant difference in morning peak flow between the 2 groups. There were no significant differences in mean lung function values after one session or after 2 weeks of the airway-clearance methods. There also were no differences in arterial oxygen saturation values before, during, or 30 min after their airway-clearance sessions. There were no differences in symptom scores with either therapy. Subjective improvement, preference, time needed, and effect on sputum production were similar for both treatments. Ten patients preferred the PEP mask, 11 patients preferred the Flutter, and one patient had no preference. Van Winden et al concluded that there was no difference between Flutter and PEP in the variables they measured in children with CF. Long-term studies may reveal effects that are not apparent after 2 weeks. The best airway-clearance tactic ultimately may be to choose the method that matches the patient's abilities and preference, to improve adherence to the CPT regimen.

Bronchiectasis

Valente and colleagues[37] conducted a pilot study to examine the effects on mobilization of tracheobronchial mucus in 8 out-patients with bronchiectasis for 3 consecutive days. The comparison was designed also to determine which of the Flutter effects (the oscillating waves or the positive expiratory pressure) would most alter the mucus properties. All study participants had daily expectoration of more than one tablespoon of yellow sputum, with greater expectoration in the morning, and they used medicinal therapy according to their needs. None had any previous experience with Flutter or PEP techniques. There was no significant difference in expectorated sputum samples between Flutter and PEP therapy at 20 min or 40 min after airway clearance, compared to the baseline values. Evaluation of the mucus adhesive forces (as measured by the contact angle) demonstrated a consistent reduction in the contact angle after 40 min of airway clearance, with both interventions, and also in the control condition. Valente et al concluded that, in patients with bronchiectasis, airway clearance with the Flutter VRP1, carried out for 40 min in a single session, did not appear to alter the ciliary or cough clearance of mucus or the mucus contact angle. Nevertheless, the trend of reduced contact angle and increased velocity through the cough mechanism, and the patients' subjective report of greater facility in expectoration deserve further investigation.

Summary of PEP Versus OPEP

Five studies have compared PEP to OPEP, four of which were in patients with CF. Those 4 studies included roughly 150 participants, and they found no difference in patient outcomes between PEP and OPEP, with the possible exception of transient blood gas changes.[33–36] In the one study of a disease entity (bronchiectasis) other than CF, the sample size ($n = 8$) was too small to draw a scientific opinion or conclusion.[37]

Cochrane Analysis

A Cochrane analysis was performed by Elkins et al[38] to determine the effectiveness and acceptability of PEP devices, compared to other forms of CPT, as a means of improving mucus clearance and other outcomes in randomized controlled studies of patients with CF. A total of 40 studies were discovered, of which 25 met the inclusion criteria, with a total of 507 patients. Twenty of the studies (which included 300 participants) were crossover studies, and 9 of those 20 studies had only been reported in abstract form. The included studies compared PEP to a wide range of therapies and differed in the duration of the intervention period. Because of low study-quality scores, crossover design in 80% of the studies, and the limited outcome data, Elkins et al decided that a meta-analysis could not be conducted. They concluded that there was no clear evidence that PEP therapy improved FEV_1, compared to other methods of airway clearance in studies of $\leq$ 3 months duration. Among studies that were $>$ 3 months duration, the results were either conflicting or showed no difference between the compared therapies.

Three studies found significant differences in expectorated sputum measures when other types of CPT were compared to PEP[39,40] or high-pressure PEP.[13] The Cochrane analysis cautioned that expectorated sputum measurements can be affected by swallowed secretions and expectorated saliva. In studies where these confounding factors were eliminated by measuring mucociliary clearance, the significant differences in favor of PEP therapy were not evident. All were crossover studies.

Many other outcomes did not show a significant difference between PEP and the therapy to which it was compared. In a year-long study with 26 infants,[41] there was no significant difference in the incidence of gastroesophageal reflux between PEP and conventional CPT. Reflux severe enough to cause withdrawal from the study occurred in 3 participants in the conventional CPT group and in no participants in the PEP group, although that difference was not statistically significant.

There is conflicting evidence on whether PEP is preferred to other types of airway clearance by patients with CF. In the studies that had an intervention period < 1 month there was no difference in patient preference about airway-clearance procedures, whereas all the studies with an intervention period ≥ 1 month favored PEP, regardless of the preference measures assessed. However, the Cochrane analysis stated that the studies that reported participant preference were generally of low quality and the tools used to record participant preference were not well described or validated. The Cochrane analysis concluded that there was no clear evidence to verify the hypothesis that PEP is more effective in improving mucus clearance or other outcomes than are other types of CPT.

A Cochrane analysis was performed by Main et al[42] to determine the effects of conventional CPT versus other airway-clearance techniques on respiratory function, individual preference, adherence, quality of life, and other outcomes, in patients with CF. Main et al searched the literature for randomized or quasi-randomized clinical studies, including those with a crossover design. Studies < 7 days duration were excluded. Seventy-eight studies were identified, of which 29 were included, representing 15 data sets and 475 participants. Those that compared conventional CPT to PEP therapy for major outcomes analyzed are briefly discussed below.

A meta-analysis of 6 studies[12,43–47] with pulmonary function data sets (164 participants) that compared conventional CPT to PEP found no differences between the 2 groups in the weighted mean differences in FEV_1, FVC, or FEF_{25-75}. Two studies found significant differences between conventional CPT and PEP, but in opposite directions between the 2 groups. One study (16 participants, 8 weeks duration) found significantly improved FEV_1 and the improvement in FVC approached significance in the conventional CPT group.[46] By contrast, a separate study (36 participants, 12 months duration) showed significant improvements in both FEV_1 and FVC with PEP.[12] Study duration ranged from 4 weeks to 2 years, but the Cochrane review stated that visual examination of the data plots indicated no associated effect of time.

A meta-analysis of 4 (6 total) studies that compared patient airway-clearance preference between PEP and conventional CPT, from self-administered questionnaires, indicated that individuals preferred PEP.[12,43,44,48] The reasons for their preferences were very subjective and included comfort, convenience, independence, ease of use, more control and flexibility over treatment time, and less interruption to daily living. A study by Tyrrell et al did not provide a formal questionnaire about preference but noted that patients' comments about PEP were generally favorable, and at 6 months after completion of the study, 56% used PEP exclusively, 4 used it in addition to conventional CPT, and 3 expressed no benefit from PEP.[46] Costantini et al reported that both infants and their parents "greatly" preferred PEP to conventional CPT.[48] McIlwaine et al stated that 92% adherence to conventional CPT treatment, compared to 96% in the PEP group, indicated a preference for PEP therapy, but they did not report whether that difference was significant.[12] Another study made reference to participants keeping adherence diaries, but those data were not reported in the abstract.[44] None of the other studies commented on adherence.

As an analysis of quality of life, conventional CPT was compared to other methods of airway clearance for frequency of hospitalization. Only one study (36 participants) reported no difference in the number of hospitalizations between the conventional CPT and PEP groups (relative risk 0.85, 95% confidence interval 0.51–1.41).[12]

An assessment of the infection impact of airway clearance was evaluated by days of intravenous antibiotics per year. Costantini et al found more days of antibiotic therapy among infants that used PEP (29.6 d vs 18.2 d) over 12 months, but they did not comment on the significance of that difference or specify whether the antibiotic courses were intravenous or oral.[48]

Another analysis looked at differences in mucociliary transport rate, assessed via radioactive tracer clearance. One study used radioactive tracer (technetium-99m diethylenetriamine penta-acetic acid) clearance to compare the efficacy of conventional CPT to PEP therapy. They found no differences in mucus clearance between the groups.[43]

The Cochrane analysis concluded that no advantage with conventional CPT over other airway-clearance techniques in terms of respiratory function. There was a trend that participants preferred self-administered airway-clearance techniques. Limitations of this review included a paucity of well-designed, adequately-powered, long-term studies.

Table 6. Cost of Airway Clearance Per Treatment and Per Day With Treatments Schedules 4 Times Daily With Time Standards From the American Association for Respiratory Care Uniform Reporting Manual[49]

Population	Airway Clearance Procedure	Cost/Treatment ($)	Cost/Day ($)
Adult	Percussion/vibration and postural drainage ≤ 3 positions	8.40	25.22
Pediatric	Percussion/vibration and postural drainage ≤ 3 positions	8.06	24.18
Adult	Percussion/vibration and postural drainage ≥ 4 positions	12.85	38.55
Pediatric	Percussion/vibration and postural drainage ≥ 4 positions	12.57	37.71
Adult	Autogenic drainage initial	7.56	22.69
Adult	Autogenic drainage subsequent	6.19	18.57
Adult	Intrapulmonary percussion	8.60	25.81
Pediatric	Intrapulmonary percussion	8.43	25.30
Adult	Expiratory pressure valve therapy–initial	7.19	21.58
Pediatric	Expiratory pressure valve therapy–initial	7.11	21.33
Adult	Expiratory pressure valve therapy–subsequent	5.48	16.45
Pediatric	Expiratory pressure valve therapy–subsequent	5.45	16.36
Adult	External chest wall oscillation	8.61	25.83
Pediatric	External chest wall oscillation	8.76	26.28

Cost

Hospital

Compared to other airway-clearance devices, both PEP and OPEP devices are relatively inexpensive. Typical PEP devices cost $25–35 per single-patient device, whereas OPEP devices cost $35–50 per single-patient device.

The more important factor of cost may lie in the human-resource costs of the various airway-clearance procedures in the hospital setting. As an example, at the University Hospitals of Cleveland, as indicated by the Relative Value Unit data from 2006, aerosol therapy was by far the most frequently ordered therapy, as is probably true in most institutions, and airway-clearance therapy was a distant second in ordered therapies. However, a close look at the Relative Value Unit data for labor hours indicated that airway-clearance therapies at University Hospitals of Cleveland encompassed 18% of respiratory therapist time, whereas 15% of the labor hours went to aerosol therapy.

Table 6 shows estimated labor costs, from the American Association for Respiratory Care Uniform Reporting Manual[49] time standards for various airway-clearance therapies, with the assigned labor time from the Uniform Reporting Manual, with an average salary of $25/h. The estimated costs are shown for both per-treatment and per-day rates (based on 4 treatments per day, every 6 hours). Though the cost difference is not astronomical for a single treatment or on a daily basis provided every 6 hours, the differences increase greatly over multiple days and hundreds or thousands of patients, or when prescribed at greater frequencies. This leads to the consideration that, if the therapies are equivalent, based on a scientific review, then other factors, such as treatment cost or patient preference, may need to be factored into airway-clearance regimen decisions.

Ambulatory/Out-Patient

Patients with CF probably account for the majority of airway-clearance therapies outside the hospital setting. In an epidemiology study of almost 13,000 patients with CF, Konstan et al[50] found that 88.2% of the patients in that study were prescribed daily airway-clearance therapies, and bronchodilators were the second most prescribed therapy, ordered for approximately 80% of those patients.

In a survey by Carr and colleagues[51] of 52 (out of 96 surveys sent out) patients with CF, the information return provided an overview of particular airway-clearance therapies prescribed, the amount of time generally spent on airway clearance, and potential explanations for adherence issues in the ambulatory setting. Less than 10% of the patients in the survey received airway clearance via PEP or OPEP, whereas the majority of the rest of the respondents received their airway clearance by some form of breathing maneuver or CPT. Sixty-seven percent of the patients reported spending 10–30 min per airway-clearance session, whereas 21% of the respondents reported spending greater than 30 min per airway-clearance session. Another interesting result was that 79% of the patients reported a preference for self-administered airway-clearance therapy (46% all the time, and 34% when feeling well). A lack of time was the most common reason cited for nonadherence. Nonadherence because of lack of time to conduct multiple prolonged airway-clearance sessions supports the findings of Currie et al[52] in patients with bronchiectasis and Fong et al[53] in patients with CF.

In a study of 3 airway-clearance therapies (HFCWC versus OPEP versus postural drainage, percussion, and vibration) by Oermann and colleagues,[28] in 24 patients with CF, a portion of the study assessed 3 domains of patient satisfaction with the prescribed therapies: efficacy, convenience, and comfort. There were no significant differences in patient comfort scores between the 3 therapy types. The HFCWC efficacy score (4.1) was higher than that of OPEP (3.28) or postural drainage, percussion, and vibration (3.59), but was significantly higher only when compared to OPEP ($p < 0.02$). The convenience score for OPEP (4.26) was significantly higher ($p < 0.02$) than that of HFCWC (2.88) and postural drainage, percussion, and vibration (2.58).

So it is easy to see that, again, the cost of therapy in regard to time spent performing airway clearance in the ambulatory setting can be high, and CPT can greatly interfere with the patient's and the caregivers' activities. The "cost" in this setting is not in Relative Value Units or labor adherence, but in failure to adhere to the prescribed airway-clearance regimens and frequencies, which could result in more infections and exacerbations that require hospitalizations of patients with CF and bronchiectasis.

Summary

In a review of the published literature on airway clearance strategies, Hess[54] summarized that PEP therapy may be as effective as conventional CPT. Hess did note that the majority of the studies of PEP have been performed in patients with CF, a few have been in patients with chronic bronchitis or postoperative patients, and the role of PEP therapy in airway clearance for other disease populations is virtually unknown. Hess finished his review of PEP therapy by adding that one recurrent theme in these studies is a reported patient preference for PEP, compared to CPT, most likely because PEP is more convenient and less time-consuming. Hess also provided the following summary of the literature on OPEP, which mainly consists of studies of the Flutter device. From a methods standpoint, most of these studies are limited by crossover designs and small sample sizes. Hess concluded the review of OPEP by stating that the best that can be concluded from these studies is that Flutter therapy may have similar effects on sputum production and pulmonary function as conventional secretion-clearance therapies.

The present review, 6 years after Hess's, makes many of the same conclusions on PEP and OPEP therapies, from an evidence-based perspective. However, while PEP and OPEP do not definitively have proven superiority to other airway-clearance strategies, there is no clear evidence that they are inferior either. In fact, PEP and OPEP appear to be at least equivalent to other airway-clearance strategies, where they have been compared and contrasted. Ultimately the correct choice of airway-clearance strategy may be the one that is clinically effective, cost-effective, and preferred by the patient and therefore supports adherence.

Maybe the secret to airway clearance comes from the literature a century ago; Booker commented:

> I have had good results in these cases from pouring a small quantity of whiskey and water into the [child's] throat, some of which passed into the trachea and brought on coughing, which was soon followed by good breathing.

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Discussion

Rubin: That was a very nice summarized section. It's interesting how little things have changed. I did want to make a brief comment about the viscoelastic measurements, particularly Ernst App's study.[1] At the time that study was done the best way of measuring viscoelasticity in very small quantities—we're talking only about 2 microliters of secretions—was using an oscillating sphere microrheometer. It has since been shown that these studies may be invalid,[2] that there were significant edge effects, and the measurement is done in a nonlinear portion. Viscoelasticity isn't done in a single measurement, but it's dynamic, so those studies, all of the old ones, including stuff that I did in my lab in those times are probably invalid and nonreproducible. That being said, it may be that some of these will affect rheology, but only rheology of what is expectorated, as opposed to what may be in the lungs. So it is nice to know this information, but I would caution over-interpretation of this being not only a good thing, but whether it really exists at all within the lungs.

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Myers: Point well made.

Fink: Great presentation, Tim. A question about use of PEP with high pressure and use of PEP with FET. What type of evidence do we really have that supports using the high-pressure PEP with an FET maneuver?

Myers: You know, it was interesting. There were 2 papers, I believe one in 1986[1] and one in 1992[2] that really studied the use of high-pressure PEP therapy with FET afterward, and actually those studies, if my memory stands correctly, showed short-term benefits in things like oxygen saturation, which would be expected, because they were probably at a lower lung volume and they took them to a higher lung volume; and there actually were some benefits in pulmonary function, but if I remember correctly there was not additional mucus production or sputum production in either of those studies of significant difference compared to their comparator, which I think in that case were all postural drainage and percussion.

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Fink: So this was a PEP followed by FET?

Myers: Correct.

Fink: Is there any documentation of PEP with the FET maneuver being done into the PEP device or Flutter valve?

Myers: None that I can think of in the review of the papers that I've looked at.

Fink: People talk about high pressures and FET and doing the maneuvers together, but I'm not sure of the genesis of that approach.

Myers: Right. That is correct, and I think most of the studies, the two that were out there that looked at high pressure PEP also used FET with PEP and compared it to FET, I think, alone, with FET and postural drainage. So, again, there was nothing that looked at those 2 components as separate entities or compared them against one another.

Fink: Thank you.

Hess: A technique that we use increasingly in patients with COPD exacerbation is noninvasive ventilation. From what you know about PEP, would you expect that the expiratory pressure, the PEEP, or the CPAP that we set to have a benefit as far as airway clearance? Or just mask CPAP therapy that we use sometimes in patients with atelectasis?

Myers: It is interesting, because, although I did not spend a lot of time reading the papers, as I was looking for the PEP therapy papers, a lot of the therapies in the 1970s started off with noninvasive ventilation or mainly CPAP at that point in time; and actually the reported benefits of the end-expiratory pressure from those CPAP trials, potentially in sputum production, actually led them to thinking that potentially this would be a benefit to use PEP therapy, either in those same simultaneous patients who were on CPAP or potentially patients who may not necessarily *need* CPAP or noninvasive ventilation might benefit and have mucus production if they used the concepts of the CPAP and got therapy. And so that's kind of where PEP therapy originated, and it appeared out of the 1970s, but I didn't spend a lot of time looking at the literature on CPAP therapies as they related to airway clearance.

Restrepo: In 2006, Placidi et al[1] conducted a study in 17 patients with CF. They compared sputum weight, dry and wet, with the use of positive pressure as an adjunctive therapy to CPT. They found that PEP therapy was associated with a significantly higher wet sputum weight. CPAP came in second, and noninvasive positive pressure was third. However, there were no differences in sputum clearance or pulmonary function between the 3 therapies tested.

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