8-15-2009

The Most Effective Form of Airway Clearance Therapy to Preserve the Pulmonary Function in Cystic Fibrosis Patients

Van-Minh Nguyen
Pacific University

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The Most Effective Form of Airway Clearance Therapy to Preserve the Pulmonary Function in Cystic Fibrosis Patients

Abstract
OBJECTIVE: To systematically review the evidence comparing the chest physiotherapy (CPT) with other forms of non-pharmacological airway clearance therapy (ACT) in order to determine what is the best intervention which preserves the pulmonary function (PF) in cystic fibrosis (CF) patients.

METHODS: MEDLINE and CINAHL were used to search for randomized studies limited to human, published in English language between 1980 and May 2009. Key terms included "cystic fibrosis," "chest physiotherapy," "chest physical therapy," "postural drainage," "airway clearance therapy," and "pulmonary function". A list of summary tables was developed to assess collected information for the conclusion.

RESULTS: Eight studies met the selection criteria presenting the results or discussion of pulmonary function (PF) in ACT management for the CF patients. The review found no significant changes in pulmonary function compared between chest physiotherapy (CPT) with other airway clearance (ACT) techniques. There were inconsistent and limited clinical evidence to prove neither CPT nor other ACT techniques were an effective method preserving the pulmonary function (PF) among cystic fibrosis (CF) patients.

CONCLUSION: This review did not reveal the most effective ACT form in preserving the PF in CF. Further multi-center, long term, appropriately designed clinical studies are suggested to determine the most effective form of airway clearance therapy that preserves the pulmonary function (PF) in cystic fibrosis (CF) patients.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
cystic fibrosis, pulmonary function, airway clearance therapy, chest physiotherapy

Subject Categories
Medicine and Health Sciences

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THE MOST EFFECTIVE FORM OF AIRWAY CLEARANCE THERAPY TO PRESERVE THE PULMONARY FUNCTION IN CYSTIC FIBROSIS PATIENTS

By:

VAN-MINH NGUYEN

A Clinical Research Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Forest Grove, OR

For the Masters of Science Degree August, 2009

Faculty Advisor: Mark S. Pedemonte M.D
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Van-Minh Nguyen was born in Vietnam. He started his healthcare profession as a respiratory therapist in the Silicon Valley in 1994. Later, Van received his Master of Education at the University of Texas in Arlington where his family has lived. Van likes Jazz, and coastal lifestyle. Besides medicine, Van also appreciates the moments to learn from human and the natural diversities.
Abstract

OBJECTIVE: To systematically review the evidence comparing the chest physiotherapy (CPT) with other forms of non-pharmacological airway clearance therapy (ACT) in order to determine what is the best intervention which preserves the pulmonary function (PF) in cystic fibrosis (CF) patients. METHODS: MEDLINE and CINAHL were used to search for randomized studies limited to human, published in English language between 1980 and May 2009. Key terms included “cystic fibrosis,” “chest physiotherapy,” “chest physical therapy,” “postural drainage,” “airway clearance therapy,” and “pulmonary function”. A list of summary tables was developed to assess collected information for the conclusion. RESULTS: Eight studies met the selection criteria presenting the results or discussion of pulmonary function (PF) in ACT management for the CF patients. The review found no significant changes in pulmonary function compared between chest physiotherapy (CPT) with other airway clearance (ACT) techniques. There were inconsistent and limited clinical evidence to prove neither CPT nor other ACT techniques were an effective method preserving the pulmonary function (PF) among cystic fibrosis (CF) patients. CONCLUSION: This review did not reveal the most effective ACT form in preserving the PF in CF. Further multi-center, long term, appropriately designed clinical studies are suggested to determine the most effective form of airway clearance therapy that preserves the pulmonary function (PF) in cystic fibrosis (CF) patients. KEYWORDS: cystic fibrosis, pulmonary function, airway clearance therapy, chest physiotherapy.
Acknowledgements

To Professors: Mark Pedemonte, M.D, Rob Rosenow PharmD, OD & Annjanette Sommers MS, PA-C who gave me the guidance that works.

To The Saunders, who offered me warm hospitality and accommodation when I did my first clinical rotation with the correctional health system of University of Texas at Medical Branch in Galveston.

To Tuyet Le, Hien Nguyen and their families, who gave me support during this training.

To my parents who lovingly give me their simplicity and encouragement.

To my sons, Andrew and Martin Nguyen, who worked diligently to be excellent students, and enjoyed playing with their piano when I was away for this intensive training.
# Table of Contents

Biography ..................................................................................................................1

Abstract ....................................................................................................................2

Acknowledgements ....................................................................................................3

Table of Contents ......................................................................................................4

List of Tables ..............................................................................................................5

List of Abbreviations ..................................................................................................6

Introduction and Background ....................................................................................7

Materials and Methods ...............................................................................................8

Results .......................................................................................................................9

Discussion ..................................................................................................................13

Conclusion .................................................................................................................15

List of tables ..............................................................................................................16

References .................................................................................................................18
List of Tables

One list of tables summarizing the characteristics of reviewed studies on page 16.
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>Airway clearance therapy</td>
</tr>
<tr>
<td>ACBT</td>
<td>Active cycle of breathing technique</td>
</tr>
<tr>
<td>AD</td>
<td>Autogenic drainage</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>CPT</td>
<td>Chest physical therapy</td>
</tr>
<tr>
<td>FEF</td>
<td>Force expiratory flutter</td>
</tr>
<tr>
<td>FEF\textsubscript{25-75}</td>
<td>Force expiratory flow at 25% and 75% of vital capacity</td>
</tr>
<tr>
<td>FEV\textsubscript{1}</td>
<td>Force expiratory volume at 1 second</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Force vital capacity</td>
</tr>
<tr>
<td>HFCWO</td>
<td>High frequency chest wall oscillation</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>OD</td>
<td>Oscillation device</td>
</tr>
<tr>
<td>PF</td>
<td>Pulmonary function</td>
</tr>
<tr>
<td>PEP</td>
<td>Positive expiratory pressure</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
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</tbody>
</table>
THE MOST EFFECTIVE FORM OF AIRWAY CLEARANCE THERAPY TO PRESERVE THE PULMONARY FUNCTION IN CYSTIC FIBROSIS PATIENTS

Introduction

Cystic fibrosis (CF) is the life limiting genetic disease associated with viscid secretions and gradual deterioration of the pulmonary function (PF) \(^3\). The pulmonary complications account for more than 90% of the mortality rate in cystic fibrosis patients \(^19\).

Therapeutically, both chest physiotherapy (CPT) and other non-pharmacological airway clearance therapy (ACT) techniques all are recommended as first-line intervention to remove the obstructing secretions and to maintain PF of the patients. Chest physiotherapy (CPT) or conventional chest physiotherapy includes postural drainage, chest percussion and vibration either performed manually or mechanically. Non-pharmacological airway clearance therapy (ACT) or airway clearance techniques which include active cycle of breathing technique (ACBT), autogenic drainage (AD), force expiratory flutter (FEF), force expiration technique (FET), Positive Expiratory Pressure (PEP), high frequency chest wall oscillator (HFCWO) or oscillation devices (OD), and non-invasive ventilation (NIV).

Pulmonary function (PF) indexes are used for the assessment of the progress of CF. Specifically these indexes are: Force expiratory volume in one second (FEV\(_1\)), force expiratory flow at 25% and 75% of vital capacity (FEF\(_{25-75}\)), force vital capacity (FVC), functional residual capacity (FRC), and total lung capacity (TLC). The lower the PF indexes, the worse the prognosis. Some studies indicated no correlation between the amount of lung secretions produced in CF and improvement in pulmonary function\(^3\).

Chest physiotherapy or conventional CPT has been considered as the gold standard therapy for CF patients for more than 40 years \(^3, 6, 8, 19\). However, there have been questions about
the rationale and validity of the use of this intervention. There were studies even suggesting that CPT may not improve the cystic fibrosis patients’ pulmonary function and may even cause bronchoconstriction\textsuperscript{3}. Some others studies promoted CPT as a more superior than ACT techniques\textsuperscript{15, 17}. Whereas others stated ACT techniques were more effective than CPT \textsuperscript{7, 11, 16}. More recently, several self-administered alternatives to CPT have been developed in order to provide an effective intervention for ACT competing with CPT. Unfortunately, there are few data from valid clinical studies available on the effect of CPT and other forms of ACT on pulmonary function\textsuperscript{3}. In addition, these studies were short-term, and the participants did not represent large enough population of CF patients. There were mixed results and many disagreements in different studies comparing the benefits between different forms of ACT with chest physiotherapy\textsuperscript{6, 15, 17, 19}. Therefore, there have been many suggestions for further valid studies concerning the role of airway clearance therapy (ACT) forms in managing pulmonary complications in CF patients.

When being a respiratory therapist, the author used to administer CPT, and assisted in the use of other ACT techniques to manage the pulmonary complications in CF patients, and wondered whether the CPT or another airway clearance therapy (ACT) technique deserved to be the gold standard in enhancing the pulmonary function in CF patients. Therefore, the goal of this paper is to review the literature in order to determine the most effective form of ACT that preserves the pulmonary function in cystic fibrosis patients.

**Materials and Methods**

A comprehensive search of the literature using two computer bibliographic search systems: MEDLINE, and CINAHL for randomized trials limited to human subjects, published in the English language between 1980 and May 2009 were conducted. Key terms included “cystic
fibrosis,” “chest physiotherapy,” “chest physical therapy,” “postural drainage,” “airway clearance therapy,” “non-pharmacological airway clearance therapy,” and “pulmonary function.” Articles were excluded if they did not have results or discussions of pulmonary function in relation with cystic fibrosis, airway clearance therapy, and chest physiotherapy. To facilitate the analysis and appraisal, summary tables were developed to organize the validity and central outcomes from the studies.

**Results**

A total of fifteen trials found in which eight trials were selected, and the other seven were excluded. The selected studies had randomized cross-over trials with presentations of pulmonary function results used for the analysis and appraisal of this review. They were organized into three major groups according to the types of comparisons and central outcomes relating to the hypothesis. The evaluations for these three groups are presented respectively in the following:

Group one has four trials which compare improvement and changes in PF between CPT and PEP (Schans 1991, Braggion 1995; Gaskin 1998; and Mcllwaine 2001). Group two includes two trials which compare CPT to NIV (Holland 2003; and Giles 1996). And group three includes two trials which compare effectiveness of CPT and OD in improving the PF (Mark 2004; and Gondor 1999).

To select the trials for review the comparison of pulmonary function changes between CPT and positive expiratory pressure (PEP), Placidini 2006 which compares between PEP and CPT but was excluded for having no data of pulmonary function. In group one, comparing between CPT and PEP, Schans 1991 attempted to determine the effectiveness of preserving pulmonary function by using single intervention with one treatment of CPT and PEP. It was a cross-over randomized trial which involved eight pediatric patients. There was no blinding, and
description of randomization. The results showed no changes in FRC and TLC for the treatment with CPT, and slight improvement in FRC (from 0.1 to 0.3) and TLC (from 0.2 to 0.3) for the treatment with PEP. With the results of this single treatment, Schans 1991 concluded the PEP increased the lung volumes in cystic fibrosis patients. Another trial was Braggion 1995 who had a cross-over randomized trial to compare between CPT and PEP. This trial involved sixteen CF patients with age ranging from fifteen to twenty-seven years old. The trial had two interventions with twice CPT treatments per day to compare with the same treatment frequency of PEP. Baseline pulmonary function was assessed before the trial, and measured thirty minutes after each treatment. There was no statement of blinding and how randomization was achieved. Braggion 1995 found no significant changes in lung function in both interventions, and concluded there were no differences in short-term efficacy of CPT on hospitalized CF patients.

In the same scope of comparing between CPT and PEP, Gaskin 1998 had a randomized parallel design trial. The trial had sixty six (34 males) CF patients within the age ranging from eleven to forty five years old. Gaskin 1998 used the data of hospitalization in two years of these patients to compare. There were no statements or explanation about treatment frequencies, blinding or randomization. There were no follow ups about the four drop-out patients. Gaskin 1998 reported no significant changes in FEV₁ and FVC in both CPT and PEP interventions. Another trial evaluated in this group is of Mcllwaine 2001. The goal of this trial was to compare the results of the positive expiratory pressure to CPT. The method claimed randomized design but there were no clear descriptions on concealment and randomization. The trial involved thirty-six (26 males) CF patients; age ranging from six to seventeen years old. There were two interventions, one for PEP treatment and one for CPT treatment. Both interventions were performed twice daily for one year. FEV₁, FVC, and FEF₂₅₋₇₅ were measured every three months for one year. The results
showed an annual rate of decline of -2.28 percent for FEV$_1$, no changes for FVC and FEF$_{25-75}$ for the group of having CPT. A slight improvement was indicated in the group of using PEP in all PF parameters (FEV$_1$ +6.98%; FVC +6.57%; FEF$_{25-75}$ +3.30%) $^{12}$. McIlwaine 2001 concluded PEP was superior to CPT in maintaining PF in CF patients.

The second group includes two trials comparing CPT and non-invasive ventilation (NIV). Holland 2003 selected twenty six CF patients with ages ranging from twenty to thirty six years old. The trial stated cross-over randomized with single intervention of one treatment with CPT and NIV for comparison. No description of how randomization was achieved. The total outcomes of this trial showed 1.35 percent increase for FEV$_1$, 2.51 percent increase for FVC, and 0.53 percent for FEF$_{25-75}$ in the group given with CPT; and 1.35 percent increase for FEV$_1$, 2.55 percent increase for FVC, and 0.57 percent increase for FEF$_{25-75}$ in the group given with NIV $^2$. The results showed no significant changes or differences on pulmonary function. Another trial found in the group of comparing CPT to NIV presented with PF results was Giles 1996. This trial involved sixteen CF patients with ages between seven to seventeen years old $^{14}$. The trial stated cross-over randomized but there was no detailed description how it was done. It used the data of one month with treatments of CPT and NIV for comparison, but treatment frequency was not mentioned. The results presented with no differences or changes on FEV$_1$, FVC, and FEF$_{25-75}$ for both interventions between CPT and NIV $^{14}$.

The third group in this review has two trials (Marks 2004; and Gondor 1999) found with pulmonary function results compared between CPT and OD (Oscillation devices which include forced flutter valve/ FEF, and high frequency chest wall oscillation/ HFCWO). The review excluded Stites 2006, Hare 2002, Steen 1999, Newhouse 1998, and Desmond 1983 for the reason that they had the assumption of no changes or differences on pulmonary function between
CPT and OD in cystic fibrosis patients but did not actually present factual data from the trials to conclude. The trial of Homnick 1998 compared CPT to FEF, was also excluded for providing inconsistent results. The results reported with thirty-three patients whereas there were only twenty two patients involved. The trial of Marks 2004, as one of its goals, was to compare the effective changes in pulmonary function between CPT and a brand name oscillation device (OD) called the percussive tech high frequency which was made by Votran Medical Tech; Sacramento, California. Marks 2004 did not qualify as a valid randomized control trial as claimed. The trial involved a small group of nine pediatric CF patients with age ranging from ten to twenty-one years old. Marks 2004 received funding from the manufacturer of the device, had only single intervention of two treatments. It failed to describe how patients were randomized and treated during the trial. Most parts of the study explained about how the device was used, how rules and regulation affected it, and the general meaning of PF studies. The collected PF data showed a mean percentage change in PF after single treatments with no significant changes on pulmonary function between CPT and the OD. The conclusion favored the application of OD over CPT in CF patients. However, Marks 2004 went on to call for long-term studies of the effects on pulmonary function. Gondor 1999 attempted to compare the short-term effects of CPT and the FEF, on pulmonary function in patients with cystic fibrosis. The trial had no clear description of design, explanation of randomization, or method of analytical method. It involved a group of twenty CF patients with age ranging from five to twenty-one years old. The presented PF results in both groups showed no improvement or significant difference on FVC or FEV₁. Gondor 1999 admitted having received funding from the manufacturer of the device to conduct the study.
Besides the group above mentioned, there was only one trial (Desmond 1983) found to compare CPT with no chest physiotherapy. But this trial was excluded from the review for the reason that there was no description of how the two interventions were conducted, or the demographic characteristics of involved patients. No explanation of randomization, treatment frequency.

Discussion

Throughout the review of the trials, the results and comparisons of pulmonary function indexes were identified and appraised. The main purpose of this literature review was to determine the most effective form of ACT in preserving the pulmonary function in the CF patients. As it was expected that either CPT would have been superior to any other form of the ACT techniques or vice versa. There was no single study focused mainly on a form of ACT with the ability for pulmonary function preservation in CF patients. Among the studies evaluated, most investigations and results related to the amounts of sputum expectorated, the preference of a certain ACT device due to its cost or convenience but not really the clinical benefit of preserving the PF. Eight trials were examined to address the hypothesis but only small sections addressed pulmonary function. Four trials compared CPT to PEP, and showed no significant improvement or changes in FRC and TLC. Two trials compared CPT to NIV, and indicated no significant differences or changes on FEV₁, FVC, and FEF₂₅₋₇₅. Two trials compared between CPT and OD, HFCWO and FEF, also showed no significant differences or changes in FEV₁ and FVC. Essentially the collected results to determine the most effective ACT form were all over the board and inconclusive. In addition, these trials shared the difficulty of analyzing the data from collected trials due to the mixed and inconsistent results on PF improvement. Even the trials conducted in favor of the manufacturers of devices had to conclude with a call for further intensive and reliable studies.
The seven excluded trials were Placidini 2006; Stites 2006; Hare 2002; Homnick 1998; Newhouse 1998; Steen 1991; and Desmond 1983. These trials did seem to realize the importance of pulmonary function in CF patients but did not directly address their objectives. At times they seemed intent to use the PF results to make points in promoting the role of CPT or other forms of ACT such as FEF or OD using results that were not highly valid and reproducible.

For the completeness and applicability, all the trials had small participants (from five to forty CF patients). All of them were short-term with single interventions of less than four treatments to compare. There was only one long trial (Mellwaine 2001) involved with 36 pediatric CF patients, and lasted one year with one intervention of two treatments in one day a week. None of these study designs were true randomized control trials. All of them had crossover designs, and had difficulty to conceal the treatment forms from the participants and the administrators. There were ethical concerns in using a placebo form in replace of the CPT in CF patients to conduct a valid randomization since chest physiotherapy is firstly prescribed to manage the pulmonary complications as soon as a patient is clinically diagnosed with cystic fibrosis. Besides the limited scale and short-term process, the factors of potential biases were also obvious in most of the reviewed trials, at least three out of eight reviewed trials declared receiving funding from the manufacturers of devices to conduct the trials. The analyzed data between trials were inconsistent, mixed and unreproducible due to the low validity of the study designs and the unclear analytical methods. Consequently, their results did not produce significant data in relative to FEV₁, FEF₂₅₋₇₅, FRC, FVC and TLC to prove which ACT form had the most effect in preserving PF among CF patients.
Conclusion

This review did not reveal the most effective ACT form in preserving the PF in CF patients. More alarmingly, the collected results indicated neither CPT nor any other non-pharmacological ACT techniques effective for that clinical goal. There have been few studies attempting to compare the effectiveness between CPT and other ACT techniques in term of general clinical benefits. Even fewer limited studies were found to evaluate the effectiveness of the ACT techniques on PF among CF patients. And the produced PF data from these limited trials were mixed, unreproducible and inconsistent in determining which ACT form was the most effective method. Still, CPT and other ACT techniques have been regarded as the effective intervention in managing the pulmonary complications in CF patients. Pulmonary function indexes are the criteria needed to evaluate the severity of the CF process. Should it be important to sort out an effective intervention to improve the PF in CF patients, firstly the determination for an effective ACT form is deemed necessary. If one is not found, then it may prompt other medical and scientific specialties such as bio-medicine, bio-engineering, genetics, pulmonology, or endocrinology to develop their research for improving the PF in CF patients. Therefore this paper strongly calls for large-scale, long-term, and valid randomized clinical trials to investigate whether CPT and other non-pharmacological ACT forms are effective in preserving the PF in CF patients, and if they are, which one is most effective.
### SUMMARY TABLES OF CHARACTERISTICS OF REVIEWED STUDIES

#### I. Trials comparing CPT to PEP:

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Mean age</th>
<th>Interventions</th>
<th>Comparisons</th>
<th>Outcomes</th>
<th>Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Braggion 1995</strong></td>
<td>16 CF patients</td>
<td>20.3 (4) years</td>
<td>Cross-over trial. PEP</td>
<td>CPT</td>
<td>No difference or changes between FEV(<em>1), FVC, FEF(</em>{25-75})</td>
<td>Subjective assessment. No concealment. Single interventions</td>
</tr>
<tr>
<td><strong>2. Schans 1996</strong></td>
<td>8 CF patients</td>
<td>16 (3) years</td>
<td>Cross-over trial. Single intervention of one treatment</td>
<td>One treatment of CPT</td>
<td>No difference or changes between TLC, FRC.</td>
<td>No blinding. No randomization or control</td>
</tr>
<tr>
<td><strong>3. Gaskin 1998</strong></td>
<td>66 (34 males) CF patients</td>
<td>11-45 years</td>
<td>Parallel, randomized. No mention of treatment frequency</td>
<td>CPT daily (No mention of treatment frequency)</td>
<td>FEV(_1), FVC decreased non-significantly in both interventions</td>
<td>No details for randomization. No blinding.</td>
</tr>
<tr>
<td><strong>4. McIlwaine 2001</strong></td>
<td>40 CF patients (24 males)</td>
<td>7-17 years. Patients within one month of hospitalization for pulmonary exacerbation.</td>
<td>Randomized, parallel design. Two treatments with FEF daily for 1 year. PF measured every 3 months.</td>
<td>Two treatments with PEP</td>
<td>No significant difference or changes between RV, FEV(<em>1), FVC, FEF(</em>{25-75})</td>
<td>Unclear randomization. No report of drop-outs. Inconsistent final reports.</td>
</tr>
</tbody>
</table>

#### II. Trials comparing CPT to NIV:

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Mean age</th>
<th>Interventions</th>
<th>Comparisons</th>
<th>Outcomes</th>
<th>Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Holland 2003</strong></td>
<td>26 CF patients</td>
<td>27.04 (6.42) years</td>
<td>Cross-over, randomized trial. ACBT, NIV</td>
<td>CPT</td>
<td>No difference or changes between FEV(<em>1), FVC, FEF(</em>{25-75})</td>
<td>No details for randomization. Single interventions.</td>
</tr>
<tr>
<td><strong>2. Giles 1996</strong></td>
<td>16 CF patients</td>
<td>13 (4) years</td>
<td>Cross-over randomized. NIV</td>
<td>CPT. Treatment frequency was not specific.</td>
<td>No difference or changes between FEV(<em>1), FVC, FEF(</em>{25-75})</td>
<td>No randomization. Single interventions. Funded by Scandipharm</td>
</tr>
</tbody>
</table>
### III. Trials comparing CPT to OD:

<table>
<thead>
<tr>
<th></th>
<th>Marks 2004</th>
<th>Gondor 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>10 CF patients. Ages: 10 - 21 years old</td>
<td>20 CF patients (11 males). Ages: 5 - 21 years</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Cross-over randomized design. Single intervention of 2 treatments on 2 different days, one week apart. OD</td>
<td>Parallel design. 2-week interventions. Treatment frequency not mentioned 11 patients given FEF.</td>
</tr>
<tr>
<td><strong>Comparisons</strong></td>
<td>CPT with same intervention</td>
<td>8 patients given CPT</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>No significant difference or changes on FEV&lt;sub&gt;1&lt;/sub&gt;, FVC, FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>No difference or changes between FEV&lt;sub&gt;1&lt;/sub&gt;, FVC.</td>
</tr>
<tr>
<td><strong>Biases</strong></td>
<td>No randomization. No blinding. Funded by Voltran Med. Tech.</td>
<td></td>
</tr>
</tbody>
</table>
References


