Comparison of different levels of positive expiratory pressure on chest wall volumes in healthy children and patients with fibrosis

ABSTRACT | Positive Expiratory Pressure (PEP) improves lung function, however, PEP-induced changes are not fully established. The aim of this study was to assess the acute effects of different PEP levels on chest wall volumes and the breathing pattern in children with Cystic Fibrosis (CF). Anthropometric data, lung function values, and respiratory muscle strength were collected. Chest wall volumes were assessed by Optoelectronic plethysmography at rest and during the use of different PEP levels (10 and 20 cm H2O), randomly chosen. Eight subjects with CF (5M, 11.5±3.2 years, 32±9.5 kilograms) and seven control subjects (4M, 10.7±1.5 years, 38.2±7.8 kilograms) were recruited. The CF group showed significantly lower FEF values 25-75% (CF: 1.8±0.8 vs. CG: 2.3±0.6) and FEV1/FVC ratio (CF: 0.8±0.1 vs. CG: 1±0.01) compared with the control group (p<0.05). Different PEP levels increased the usual volume in chest wall and its compartments in both groups; however, this volume was significantly higher in the control group compared with the CF group during PEP20 (CW: 0.77±0.25 L vs. 0.44±0.16 L; RCp: 0.3±0.13 L vs. 0.18±0.1 L; RCA: 0.21±0.1 L vs. 0.12±0.1 L; AB: 0.25±0.1 L vs. 0.15±0.1 L; p<0.05 for all variables). Minute ventilation was significantly higher during PEP compared with breathing at rest in both groups (p<0.005). End-expiratory volume was also higher during PEP compared with breathing at rest for chest wall and pulmonary rib cage in both groups (p<0.05). Different PEP levels may increase chest wall volumes in CF patients.

Keywords | Cystic Fibrosis; Respiratory Therapy; Respiratory System; Thoracic Wall.

RESUMO | Pressão Expiratória Positiva (PEwP) melhora a função pulmonar, entretanto, as mudanças induzidas pela PEP não estão totalmente estabelecidas. O objetivo do estudo foi avaliar os efeitos agudos de diferentes intensidades de PEP nos volumes da parede torácica (PT) e padrão respiratório em crianças com Fibrose Cística (FC). Dados antropométricos,
Airways clearance techniques are considered of great clinical benefit to reduce lung complications and their prescription is relevant to the clinical course of the disease in these patients. Moreover, airway clearance techniques facilitate bronchial hygiene and, consequently, improve lung function, which is considered essential for optimizing respiratory status and reducing the progression of lung disease. Self-administered therapies as Positive Expiratory Pressure (PEP) are being used to promote greater independence and to improve lung function in patients with Cystic Fibrosis. Studies have shown that the use of PEP induces important benefits in blood gases concentration, aerosol particles deposition, expectoration, airflow, and, consequently, lung function. However, PEP-induced changes on lung volumes are not fully established due to muscular limitations and consequent respiratory muscles asynchronous activity which may be present in children with CF. Besides lung disorders, children with CF frequently show paradoxical or asynchronous
motion between chest wall and abdomen during breathing\textsuperscript{12-14}. This alteration is related to disease severity, increased risk of respiratory failure, and poor prognosis in patients with obstructive disease\textsuperscript{15,16}.

Therefore, the aim of this study was to compare the changes of different intensities of PEP on chest wall volumes and breathing pattern in children with CF and healthy controls. Chest wall volume analysis was performed by Optoelectronic Plethysmography (OEP), which can detect variations in motion and volume of the chest wall and its compartments during breathing, allowing the analysis and evaluation of these changes during rest and/or exercise\textsuperscript{17}.

### METHODOLOGY

#### Subjects

Subjects with CF diagnosis were recruited at the Cystic Fibrosis Multidisciplinary Clinic of a University Hospital. Age-matched healthy controls without previous history of cardiopulmonary disease were recruited in the community. Individuals of both genders, aged 7 years, able to perform acceptable evaluation exams, lung function, and respiratory muscle strength tests and with no postural disorders were included in the study. Subjects who presented disease exacerbation, such as hospitalization three weeks prior to data collection due to respiratory infection, used medication that could interfere in the exam results, such as short-term bronchodilator, and that did not complete all exams, quit or missed an appointment during the evaluation period were excluded from the study. This study was submitted and approved by the Research Ethics Committee of the University Hospital (number 497/10). All participants and their guardians were informed about the study and signed an Informed Consent form in accordance with the principles of the Helsinki declaration\textsuperscript{18}.

#### Study design

This is a cross-sectional study performed in a single day at the Laboratory of PneumoCardioVascular and Respiratory Muscle Performance. Before sample collection, the study was explained to the individuals, who were then interviewed regarding their medical history and medication use. Anthropometric characteristics were assessed before data collection. Next, subjects underwent spirometry and respiratory muscle strength assessment. Lastly, chest wall volumes were assessed by Optoelectronic Plethysmography using two different intensities of PEP (10 and 20 cm \text{H}_2\text{O}). PEP intensity order randomization was performed manually by using a brown paper envelope. Room temperature during data collection was set between 22 and 24°C, with relative air humidity between 50 and 60%.

#### Anthropometric evaluation

Weight and height were determined using an anthropometric scale (Welmy, Santa Bárbara D’Oeste, São Paulo, Brazil). The values obtained were used to calculate Body Mass Index (BMI) (weight (kg)/height\textsuperscript{2} (m)). Percentile values of BMI were used for anthropometric characterization according to the cutoff points recommended by the World Health Organization\textsuperscript{19}.

#### Spirometry

The technical procedure, acceptability and reproducibility criteria, reference and interpretative values, as well as standardization and equipment followed the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS)\textsuperscript{20}. Reference forced expiratory volume in the first second (FEV\textsubscript{1}), forced vital capacity (FVC), and FEV\textsubscript{1}/FVC ratio were obtained by derivations from the pre-established equations\textsuperscript{21}. All procedures were performed in seated position. A DATOSPIR\textsuperscript{®} 120 (Sibelmed, Barcelona, Spain) device, calibrated daily, was used.

#### Respiratory muscle strength

Respiratory muscle strength was assessed by maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using a MVD300 digital manometer (GlobalMed, Porto Alegre, Brazil). Measures were collected according to the recommendations of the American Thoracic Society/European Respiratory Society, using the reference values obtained for children\textsuperscript{22,23}. Briefly, MIP was measured following maximal inspiration from residual volume with nasal nostril closed, while MEP was obtained through maximal expiration from total lung capacity in seated
A nozzle with a hole of approximately 1mm was used to dissipate facial and oropharynx muscles pressure. Five to eight tests were performed until maximal values were reproducible.

Assessment of chest wall volumes and PEP

Optoelectronic pletysmography (OEP) (OEP® system, BTS, Milan, Italy) was used to evaluate chest wall and its compartments (Pulmonary Rib Cage – Rep, Abdominal Rib Cage – Rea and Abdomen – Ab), volumes, and their variations during rest and different levels of PEP in both groups. All individuals were positioned in seated position on a backless bench and centralized in a system of six cameras previously calibrated according to the manufacturer’s recommendations and previously published studies. Subjects were requested to remain motionless breathing freely for 180 seconds. After quiet breathing (QB), chest wall volumes was evaluated using two different PEP intensities (10 and 20 cm H₂O), randomly chosen, using the Threshold PEP® independent flow device (Health Scan Products Inc. Cedar Grove, USA) for the same period of QB (180 seconds). A minimal resting period of 20 minutes between different intensities of PEP was given to subjects. After the data was acquired the most stable period of 30 seconds of each period was analyzed. We considered the following variables for analysis: total tidal volume, percentage contribution of the different chest wall compartments (RCp, RCa and AB) to tidal volume, minute ventilation, respiratory rate, inspiratory time (T_{insp}) and expiratory time (T_{exp}), total respiratory cycle time, total and compartmental chest wall operating volumes, namely end-expiratory (EEV), and end-inspiratory (EIV) volumes. The changes in length of rib cage inspiratory muscle can be estimated by the relationship among Pulmonary Rib Cage volume variation and Inspiratory Time (VT_{tcp}/Ti).

Statistical analysis

Shapiro-Wilk normality test was applied to the variables. Two-way analysis of variance (ANOVA) with Bonferroni post hoc was performed to verify the differences between the variables’ means during quiet breathing and different PEP levels in the study groups. GraphPad Prism 5 software (GraphPad Software Inc. San Diego, California, USA) was used for the analysis, with significance level set at p>0.05. The effect size was calculated using the G*Power software (G*Power 3.1.9.2, Kiel, Germany).

RESULTS

Fourteen subjects with CF and 12 healthy individuals were enrolled. Six subjects from CF group were excluded: three due to disease exacerbation prior to sample recruitment, two due to irregularities and artifacts originated during data collection, and one due to study withdrawal. As for the healthy controls, five were excluded: three due to irregularities and artifacts originated during data collection and two due to study withdrawal.

The mean, standard deviation and standard deviation difference of respiratory rate were considered to calculate the effect size. We found a Cohen’s d of 1.4 considering a α error probability of less than 0.05 (p>0.05) with 0.70 of power. The result found indicated a large effect size. Ideal sample size calculated to the study was eight subjects per group.

Anthropometric characteristics

No significant difference was found regarding anthropometric characteristics between CF group and controls for age, gender, weight, and height (p>0.05). According to body mass index (BMI) percentile cutoff points, two subjects with CF (25%) showed values below those recommended for the age. In contrast, three (43%) controls showed BMI values above those recommended for the age at the moment of sample collection. All anthropometric characteristics are shown in Table 1.

Spirometry and maximal inspiratory/expiratory muscles pressures

CF group showed significantly lower lung function values for FEF_{25-75%} and FEV₁/FVC ratio when compared to the control group (p>0.05). Although CF patients showed slightly lower mean values for MEP compared to controls, neither inspiratory nor expiratory maximal pressures were significantly different between the groups (Table 1).
Table 1. Anthropometric characteristics and lung function values

<table>
<thead>
<tr>
<th>Anthropometric characteristics</th>
<th>Cystic Fibrosis group (n = 8)</th>
<th>Control group (n = 7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>5/3</td>
<td>4/3</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.5 ± 3.2</td>
<td>10.7 ± 1.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>32.1 ± 9.6</td>
<td>38.2 ± 7.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>140 ± 12.8</td>
<td>143 ± 8.5</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>84.3 ± 17.5</td>
<td>82.8 ± 11.9</td>
<td>0.84</td>
</tr>
<tr>
<td>MEP (cm H₂O)</td>
<td>72.7 ± 12.8</td>
<td>84.6 ± 14.4</td>
<td>0.11</td>
</tr>
<tr>
<td>MIP (% pred)</td>
<td>1.8 ± 0.8</td>
<td>2.3 ± 0.6</td>
<td>0.007</td>
</tr>
<tr>
<td>FEV₁,FVC (%)</td>
<td>81.5 ± 5.7</td>
<td>96.9 ± 13.5</td>
<td>0.01</td>
</tr>
<tr>
<td>MIP (cm H₂O)</td>
<td>78.9 ± 25.6</td>
<td>85.3 ± 21.4</td>
<td>0.66</td>
</tr>
<tr>
<td>MEP (cm H₂O)</td>
<td>85.1 ± 25.9</td>
<td>109 ± 21.5</td>
<td>0.05</td>
</tr>
<tr>
<td>MEP (% pred)</td>
<td>84.4 ± 27.9</td>
<td>110.3 ± 24.57</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*absolute values, values expressed in predicted percentage, p-value calculated using Fisher exact test for gender and unpaired t test for the other variables; FVC: Forced Vital Capacity; FEV₁: Forced Expiratory Volume in the first second; FEF25-75%: Forced Expiratory Flow between 25 and 75% of the spirometric curve; VEF₂₀/FVC% ratio expressed in percentage; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure.

Chest wall variations and breathing pattern during QB and PEP

Intragroup analysis showed that tidal volume values in chest wall and its compartments were higher during the use of different PEP levels compared to quiet breathing in both groups (p<0.05). Regarding PEP₁₀, no significant difference was found in intergroup analysis. However, total and compartmental tidal volumes were significantly higher in controls compared to CF patients during PEP₂₀ (CW: 0.77 ± 0.25 L vs. 0.44 ± 0.16 L; RCp: 0.3 ± 0.13 L vs. 0.18 ± 0.1 L; RCa: 0.21 ± 0.1 L vs. 0.12 ± 0.1 L; AB: 0.25 ± 0.1 L vs. 0.15 ± 0.1 L; p>0.05) (Figure 1).

Respiratory rate (RR, breaths/min) was significantly higher in the CF group (36.3±7.33.8±14 and 37.8±14.1 during QB, PEP₁₀, and PEP₂₀, respectively) compared to controls (28.2±5.1, 30.6±17.1 and 24.3±14.6, p<0.005). In both groups, minute ventilation (MV, L/min) was significantly higher during PEP₁₀ (15.6±7.6 vs. 19.5±9.2) and PEP₂₀ (16.6±8.1 vs. 17.8±9.6) in CF patients and controls, when compared to quiet breathing (QB: 10.4±3.3 vs. 8.1±1.2, p<0.005). The increase in minute ventilation when using different intensities of PEP was obtained, however, by adopting different breathing patterns in the two groups (Figure 2A). While controls achieved increased ventilation with higher tidal volume (QB: 0.289 ± 0.062 L; PEP₁₀: 0.719 ± 0.279 L; and PEP₂₀: 0.755 ± 0.259 L) and lower respiratory rate during PEP₂₀, CF children showed an inverse pattern with lower tidal volume (QB: 0.292 ± 0.094 L; PEP₁₀: 0.492 ± 0.169 L; and PEP₂₀: 0.442 ± 0.160 L) and higher respiratory rate (Figure 2A).

Correspondingly, during QB, PEP₁₀ and PEP₂₀ total respiratory cycle time (Ttot, seconds) was lower in CF patients compared to controls (p<0.02, figure 2B). In CF patients, inspiratory time (Tinsp, seconds) was significantly lower than controls during PEP₂₀ (0.74 ± 0.2 vs. 1.16 ± 0.54, p<0.05) and did not change regarding what we observed during spontaneous quiet breathing at rest. Expiratory time (Texp) did not change significantly during PEP compared to QB in both groups. Although there was no significant difference, Texp tended to be higher in controls and lower in CF patients during PEP compared to QB. The increase percentage of total and compartmental tidal volume regarding quiet breathing in resting conditions was slightly higher in controls than CF patients. During PEP₁₀, the increase in CW, RCp, RCa and AB was 60%, 67%, 63%, and 48% in controls and 40%, 52%, 52%, and 13% in CF patients. During PEP₂₀, the increase was 63%, 68%, 67%, and 52% in controls and 34%, 40%, 45%, and 18% in CF patients. The shortening velocity index of rib cage inspiratory muscle showed significant changes during PEP₁₀ and PEP₂₀ in the control group compared to baseline (p<0.05), without changes in intergroup analysis (Figure 2C).
Figure 1. Volumes of chest wall and its compartments during quiet breathing and different levels of PEP in control group and CF

Values represent mean ± standard deviation. QB: quiet breathing; PEP$_{10}$: positive expiratory pressure 10 cm H$_2$O; PEP$_{20}$: positive expiratory pressure 20 cm H$_2$O. *p>0.05 vs. QB (two-way ANOVA).

Figure 2. Breathing pattern and shortening velocity index of the rib cage inspiratory muscle of Values represent mean ± standard deviation. QB: Quiet breathing; PEP$_{10}$: Positive expiratory pressure 10 cm H$_2$O; PEP$_{20}$: Positive expiratory pressure 20 cm H$_2$O; Vtrcp/Ti: relation between pulmonary rib cage volume variation and inspiratory time. *p>0.05 (two-way ANOVA)
Total and compartmental chest wall operating volumes during different intensities of PEP

End-expiratory volume (EEV) of total chest wall and pulmonary rib cage compartment significantly increased during the use of PEP (both intensities) compared to resting conditions (p>0.05) in both groups. Intergroup analysis did not show significant differences regarding EEV. End-inspiratory volume (EIV) was significantly increased in the rib cage pulmonary compartment during PEP compared to QB (p>0.01) (Figure 3).

Figure 3. Operating total and compartmental chest wall volumes during different intensities of PEP

Values represent mean ± standard deviation. A) CF group; B) Control group. QB: quiet breathing; PEP_{10}: Positive expiratory pressure 10 cm H_{2}O; PEP_{20}: Positive expiratory pressure 20 cm H_{2}O; EEV: End-expiratory volume; EIV: End-inspiratory volume. *p>0.05 – PEP_{10} vs. QB; # p>0.01 – PEP_{10} vs. QB; § p>0.01 – PEP_{20} vs. QB; ¥ p>0.05 – PEP_{20} vs. QB. Two-way ANOVA. Bonferroni’s post hoc between moments.
When considering total and compartmental EIVs, intergroup analysis showed significant difference between CF and controls only at PEP \(_{20}\) for abdomen compartment (p>0.01, Figure 4).

![Figure 4](image)

**Figure 4.** End-inspiratory volume (EIV) in abdomen during different intensities of PEP

Values represent mean ± deviation. QB: Quiet breathing; PEP \(_{10}\): Positive expiratory pressure 10 cmH\(_2\)O; PEP \(_{20}\): Positive expiratory pressure 20 cmH\(_2\)O. *p>0.01 (two-way ANOVA). Bonferroni's post hoc between groups

**DISCUSSION**

Results showed that chest wall tidal volume increased during the use of PEP in comparison to quiet breathing. Moreover, the increase was significantly higher in controls compared to CF during PEP \(_{20}\). We also found that, compared to controls, children with CF are characterized by a more rapid and shallow breathing pattern, both during spontaneous quiet breathing at rest and during the use of PEP, as showed in Figure 2A. In addition, we have shown that minute ventilation increases in CF children during the use of PEP due to an increase of tidal volume. End-expiratory volume also increases compared to quiet breathing.

PEP is one of the most common airway clearance techniques used in different countries, such as Canada\(^5\). A recent study with 6,372 CF patients performed in the United Kingdom, showed that PEP was the third most popular technique used to manage patients’ conditions\(^28\). Despite its wide dissemination and use, little is known about its effects in ventilation. This feature is not related only to PEP, but all airway clearance techniques. The lack of knowledge about the physiological responses of airway clearance techniques was observed in the conclusion of five Cochrane systematic reviews that were inconclusive regarding the best airway clearance technique for CF patients\(^5\).

The acute effects of PEP have been previously studied in the literature. However, in the previous studies the possible dynamic changes in ventilation and breathing pattern were not assessed. Van Winden et al. (1998) studied the effects of flutter and PEP mask in symptoms and lung function in 22 CF patients\(^29\). The authors did not find any significant changes in lung function parameters after a single session or 2 weeks of PEP or flutter use. A recent study, by McIlwaine et al.\(^30\), analyzed long-term efficacy of high frequency chest wall oscillation (HFCWO) in comparison to theraPEP in patients with CF\(^30\). The primary outcome was the number of pulmonary exacerbations. The authors found no significant difference in quality of life and lung function between the groups. PEP showed to be more efficient in terms of time of use and number of exacerbations (1.14 for PEP vs 2.0 for HFCWO). A great number of CF studies aim to compare airway clearance techniques. On the other hand, we consider that is more important to first understand the mechanisms and how patients respond to each technique, in this case, PEP.

To our knowledge, this is the first study that evaluated the acute effects of PEP in the volumes of chest wall and its compartments in CF children. For this propose, we have used Optoelectronic Plethysmography, which provides continuous dynamic measurements of volume variations of the chest wall, divided into compartments\(^17\). Our results showed a rapid and shallow breathing pattern at rest and during use of different intensities of PEP in children with CF. Even though minute ventilation was similar between groups, CF patients showed less efficient breathing patterns compared to controls, as observed by the increased respiratory rate (at rest and during PEP use) and a decreased tidal volume during PEP use.

In fact, the use of PEP in Cystic Fibrosis and controls showed an increase in minute ventilation, compared to quiet breathing. The mechanism that leads to this increase, however, differs between groups, at least at the highest level of PEP considered in the study. While in controls the increase in ventilation was due to a significant increase of tidal volume when both PEP \(_{10}\) and PEP \(_{20}\) were applied, in CF subjects the tidal volume significantly increased only during the application of PEP \(_{10}\), while at PEP \(_{20}\) an increase of respiratory rate was observed. A clinical implication of
our findings is, therefore, that high levels of PEP should not be used in children with CF, to avoid overloading respiratory muscles to overcome the load imposed by the use of PEP.

There is still a lack of studies showing respiratory strength impairment in subjects with CF in the literature. Published data in the same topic are also controversial, however, we may speculate that individuals with CF show difficulty in overcoming a pressure load of 20 cmH₂O due to reduction of the strength of expiratory muscles, as shown by the lower values of maximal expiratory pressure (MEP: 83.1 ± 25.9 vs. 109 ± 21.5 for CF and control groups, respectively), compared to controls, found in this study.

We may hypothesize that the increase in end-expiratory volume observed during PEP may be beneficial, particularly in those children in which the restrictive pattern is prevalent. On the other hand, in those children in which the obstructive pattern is prevalent, the EEV increase induced by PEP could not be clinically interesting as these subjects present pulmonary hyperinflation due to air trapping in the lungs, which was maintained.

We believe that the main limitation of our study is the small sample of participants and extrapolation of the results should be done carefully. However, CF is not a common lung disease, therefore, its low prevalence makes the recruitment of individuals even more limited.

CONCLUSION

In conclusion, different levels of PEP induce an increase of chest wall volumes in CF children with different mechanisms compared to controls. Even with the improvement caused by PEP, CF children still show shallow breathing characteristics. PEP levels above 10 cm H₂O should be used with caution in CF children.

REFERENCES


