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# Effectiveness of positive expiratory pressure on patients over 16 years of age with cystic fibrosis: systematic review and meta-analysis

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***Abstract***

**Introduction:** Cystic fibrosis (CF) is an autosomal recessive disease that involves the cells that produce mucus and sweat, affecting many organs, especially the lungs. Positive expiratory pressure (PEP) devices generate a pressure opposite to that exerted by the airways during expiration, thus improving mucociliary clearance.

**Objectives:** To evaluate the efficacy of PEP devices as a resource to facilitate the mucus removal and other outcomes in people with CF, as well as the possible adverse effects derived from their use.

**Material and Method:** A systematic review and meta-analysis was conducted according to PRISMA standards. The descriptors were 'cystic fibrosis', 'PEP', and 'physiotherapy and/or physical therapy'. The search was performed in four databases: PubMed, PEDro, and Web of Science and Scopus, in July 2021. The inclusion criteria were randomized controlled trials (RCTs) over the last 10 years. The methodological quality of the studies was analyzed and meta-analysis was performed with Review Manager software.

**Results:** Ten RCTs met the objectives and criteria, with a total of 274 participants. The trials score a moderate methodological quality on the PEDro scale. No clear results were obtained on whether PEP provides better lung function than other breathing techniques (such as airway clearance); but it does achieve a higher rate of lung clearance than physical exercise.

**Conclusions:** PEP is more effective than usual care or no intervention, although there is not enough evidence to confirm that PEP achieves improvements in forced expiratory volume in the first second ($FEV_1$) compared with other techniques. It is a safe technique, without adverse effects.

***Keywords:*** adverse effects, cystic fibrosis, mucociliary clearance, physical therapy, positive expiratory pressure (PEP)

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## Introduction

Cystic fibrosis (CF) is an autosomal recessive disease that involves the cells that produce mucus and sweat, affecting many vital organs, particularly the lungs. It causes a decrease in quality and life expectancy, causing death in 90% of patients.[1–3]

CF is usually caused by a mutation in the CFTR gene. As it is a recessive hereditary disease, it is necessary that both parents have a copy of the defective gene. Thus, the disease only manifests itself when the child inherits both altered genes.[4] It usually manifests with thick and sticky mucus that obstructs the airways, which can lead to serious lung infections, especially *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which cause chronic and systemic inflammation of the airways and destruction of tissues.[2,5]

CF is classified as a rare or infrequent disease due to its low prevalence, affecting one in every 2000 to 4000 newborns. It is more common in the Caucasian population, although it depends on ethnicity and region of origin.[2,3]

According to a recent study[6] in the United States, it has been estimated that the average life expectancy for patients born in 2010 would be 37 years for women and 40 years for men. However, it is expected that this age could exceed 50 years if the mortality rate continues to decrease at a rate of 1.8% per year. CF transmembrane conductance regulator (CFTR) modulator therapies, which targets the protein defective in CF and boosts its function, can be considered the newest development in CF care.[7] With the first modulator approved in 2012, latest generation of these drugs offers promise of effective CFTR modulator therapy for nearly 90% of CF patients. In terms of life expectancy, this implies a quantum leap for the vast majority of the CF population.[7] CF is an important cause of suffering, both for patients and their families, because it sometimes entails long-term hospitalizations and a significant decrease in the quality and life expectancy of those affected and can cause the death of even the youngest.[3]

CF represents a significant health expense, due to the continuous respiratory infections that lead to chronic respiratory failure, requiring long-term treatments such as intravenous antibiotic therapy, which makes its financing a major problem.[3,8–10]

Treatment of the infection is multifaceted, including antibiotics, respiratory physiotherapy, inhaled medications to facilitate clearance of secretions, and anti-inflammatory drugs. Better use of antibiotics has resulted in increased survival in individuals with CF.[5,11]

Treatments that promote the elimination of mucus are essential to improve respiratory status and slow the progression of the disease. Physical methods are used, such as airway clearance techniques (ACT)[12–14] or physical exercise;[15] along with chemical methods, such as inhaled medications.[12]

Within Physiotherapy, there are many ACTs for CF patients, such as: active cycle of breathing techniques (ACBT), postural drainage combined with percussion (PD&P), autogenous drainage (AD), forced expirations (huffing and coughing), breathing deep, positive expiratory pressure (PEP), and oscillatory PEP devices and high-frequency chest wall oscillation (HFCWO).[12–14]

PEP devices generate a pressure contrary to that produced by the airways during expiration (expiratory flow resistance), improving mucociliary clearance due to the formation of gas accumulated behind mucus through collateral ventilation, increasing airway diameter and due to the temporary increase in functional residual capacity.[12] There are the PEP devices themselves as well as oscillatory PEP devices (Flutter, Cornet, and Acapella).[16] Oscillatory PEP devices generate repeated occlusions that are known to reduce mucus viscosity.[17]

In 2019, McIlwaine *et al.*[12] conducted a review on the effectiveness of PEP devices compared with other secretion clearance techniques for mucociliary clearance in patients of any age with cystic fibrosis, excluding oscillatory PEPs. The review ultimately recommended PEP as the most effective long-term intervention compared with other forms of physiotherapy. It also highlighted the need for ACTs to be individualized for the patient according to their stage of development, preference, lung function, and symptoms.

The present review aims to show the effectiveness found in this variety of PEP devices, including the oscillatory type, in CF patients over 16 years of age. Focusing on this age group is justified by the progressive increase in life expectancy of these patients, and the exacerbation of symptoms as they get older.

The objective of this systematic review is to evaluate the efficacy of PEP devices as a resource to facilitate the expulsion of mucus as well as other positive effects, namely the improvement of quality of life among people with CF. In turn, the review will also describe any adverse effects derived from their use.

## Material and method

A systematic review was carried out in July 2021 taking into account the Preferred Reporting Items for Systematic Reviews (PRISMA) recommendations.[18] It was registered in the international prospective register of systematic reviews PROSPERO database (CRD42021250470).

Articles were searched electronically in four databases (PubMed, PEDro, Web of Science and

Scopus), without restrictions on the state of publication or language, using the following descriptors: cystic fibrosis, PEP, physiotherapy, and physical therapy. In addition, a fan search was performed.

The following PICOS eligibility criteria were used for the selection of the articles (participants, intervention, comparator, outcomes, and study design):

Participants were people with CF with a confirmed diagnosis based on clinical criteria, genetic tests and/or sweat tests, and with an age greater than or equal to 16 years. Regarding intervention, studies that used PEP as a treatment method for people with CF, either PEP or oscillatory PEP (Flutter or Acapella) were selected.

Comparator corresponded to studies comparing the PEP with other interventions or no intervention (control group), such as PEP versus exercise (e.g. PEP versus treadmill exercise); PEP versus other respiratory therapy (e.g. PEP versus ACBT); PEP versus no therapy (e.g. resting breathing).

Outcomes were measures of pulmonary function: $FEV_1$ measured by spirometry, amount of sputum expectorated, or wet weight of sputum, among other measures.

Adverse effects were situations in which the disease worsened or unexpected events that worsen the participant's health condition, such as an exacerbation, pneumothorax, haemoptysis, other adverse changes in condition from baseline or even death.[12]

They had to be randomized controlled trials (RCTs) in regards to the study type.

*Inclusion criteria*: RCTs between 2010 and 2021, in any language. Studies presenting co-interventions were accepted as long as they were comparable between the intervention groups (e.g. administration of drugs to thin mucus to the two groups).

*Exclusion criteria*: Quasi-randomized clinical trials were not considered. Studies excluded were those that did not address CF, were not related to the objectives, or had a score $< 5$ on the PEDro scale, due to low methodological quality and high risk of bias.

*Study selection, data extraction, and management.* Two independent authors (MJBI and PRP) selected the titles and abstracts of the articles that met the inclusion and exclusion criteria. When there were discrepancies between researchers, a third party (RLL) was consulted. Finally, the characteristics of each study were extracted independently.

The quality assessment of the included articles was carried out using the PEDro scale.[19] In addition to the Cochrane Collaboration Risk of Bias scale, the risk of bias of the articles included in the meta-analysis was determined.[20]

Finally, a meta-analysis was performed with the Review Manager software (RevMan version 5.4.1), which was limited due to the clinical heterogeneity of the included studies, including six of the 10 clinical trials. The I2 statistic was used to determine the degree of heterogeneity: 25% = low, 50% = medium, and 75% = high heterogeneity. Using this scale, if I2 was 50%, a random effects model was used. All the results included were the data collected on $FEV_1$, calculating the difference of means with a confidence interval of 95%. Effects plots (forest plots) were generated to illustrate the overall effect of the interventions on $FEV_1$.

## Results

A total of 394 records were obtained as a result of the search. After eliminating duplicate articles, 282 were found, of which 273 were excluded according to the inclusion and exclusion criteria. In addition, an article was added as a result of the fan search conducted. Finally, 10 articles fulfilled the objective of the study and the criteria indicated (Figure 1), with a total of 274 participants.

The most relevant information for each RCT regarding the population, interventions, duration, and results of the different studies is presented in Table 1.

In addition, each of the main variables was subjected to qualitative analysis.

### *Participant characteristics*

The age was between 17 and 48 years, with the exception of Radtke *et al.*,[21] between 22 and 25 years, and Pryor *et al.*,[23] up to 63 years.

**Table 1.** Summary of the characteristics of the selected studies.

| RCTs | Participants | PEP intervention(s) | Comparison intervention(s) | Restricted co-interventions | Treatment duration | Results |
|---|---|---|---|---|---|---|
| Radtke *et al.*[21] | *N* = 15<br>Average age 23 years; minimum and maximum (22–25 years)<br>56.2% Women<br>43.7% Men | EG 'B': 1 session of cycling at moderate intensity (75% HR max.) + Flutter®. 6 to 10 breathing maneuvers (slightly deep inspiration, 2–3'pause, 5' forced expiration, sitting on the cycle ergometer without pedaling), during each 2' rest period without FET. | • CG 'A': Single session of continuous cycling exercise at moderate intensity without Flutter®. | No fatty foods, caffeine, vigorous physical exercise 24 hours before sessions. No regular inhalation therapy and airway clearance days of sessions. | 1 day: data recording.<br>1 day: single treatment session. | • Group A:> easy sputum expectoration; > Goes post-exercise.<br>• Adverse effects: 1 patient required antibiotic therapy for pulmonary exacerbation. |
| Dwyer *et al.*[22] | *N* = 24<br>30 middle age (19–48)<br>37.5% Women<br>62.5% Men | Flutter therapy intervention for 15 breaths, followed by deep, relaxed breathing, huffing, and coughing, according to the FET. 6 times for 20'. | • Intervention: exercise on a treadmill with a constant load at 60% $VO_2$.<br>• Resting breathing (CG). | For 1 week discontinue routine mucolytic therapy, airway clearance, and exercise on the test morning. | 3 days with 20' sessions, 1 week period. | • PEF > in Flutter and Exercise groups. Only Flutter submitted PEF: PIF.<br>• Viscoelasticity of sputum: Flutter and exercise groups > reduction after intervention and after 20'.<br>• Cough:> in Flutter group (FET). After 20' there were no differences between groups.<br>• Ease of expectoration:> exercise group after 20'.<br>• All treatments were well tolerated with no occurrence of adverse effects. |
| Pryor *et al.*[23] | *N* = 53<br>28 middle age (17–63)<br>37.3% Women<br>62.6% Men | •PEP Group.<br>•Oscillatory PEP group with Flutter.<br>Oscillatory PEP group with Cornet. | • ACBT group.<br>• AD group. | Treatment while sitting independently. | 12 months.<br>The number of ACT sessions per day and the duration of treatment was individualized. | • FEV1: global decline (Flutter and Cornet the least).<br>• Quality of life: With the CRQ for dyspnea there was an improvement in 4 groups (ACBT, AD, PEP and Flutter), > Flutter.<br>• The study did not inform about adverse events or exacerbation. |
| Dwyer *et al.*[24] | *N* = 14<br>27 middle age (18–48)<br>28.6% Women<br>71.4% Men | PEP therapy intervention: performing 15 mouthpiece breaths, followed by huffing and coughing according to FET. | • EG: exercise on a treadmill for 20' with a constant load at 60% of their $VO_2$.<br>• CG: sit quietly for 20'. | Not clearing the airways or exercising. Stop the medication for at least 8 hours before. | 3 days with 20' interventions, separated by at least 48 hours, in a period of 2 weeks. | • Mucus clearance: > in EG than CG in the right lung and the middle and peripheral regions of both lungs. 60' post-exercise the same, but CG > in the central region. PEP group > mucus clearance in all regions of the lung than CG. PEP group cleared more mucus than EG in the right lung and the central area of both lungs.<br>• Cough: > tendency to cough in EG than CG during the intervention, but not in the 60' post-intervention. PEP group > number of coughs than CG and EG during the intervention.<br>• All treatments were well tolerated with no occurrence of adverse effects. |

*(Continued)*

**Table 1.** (Continued)

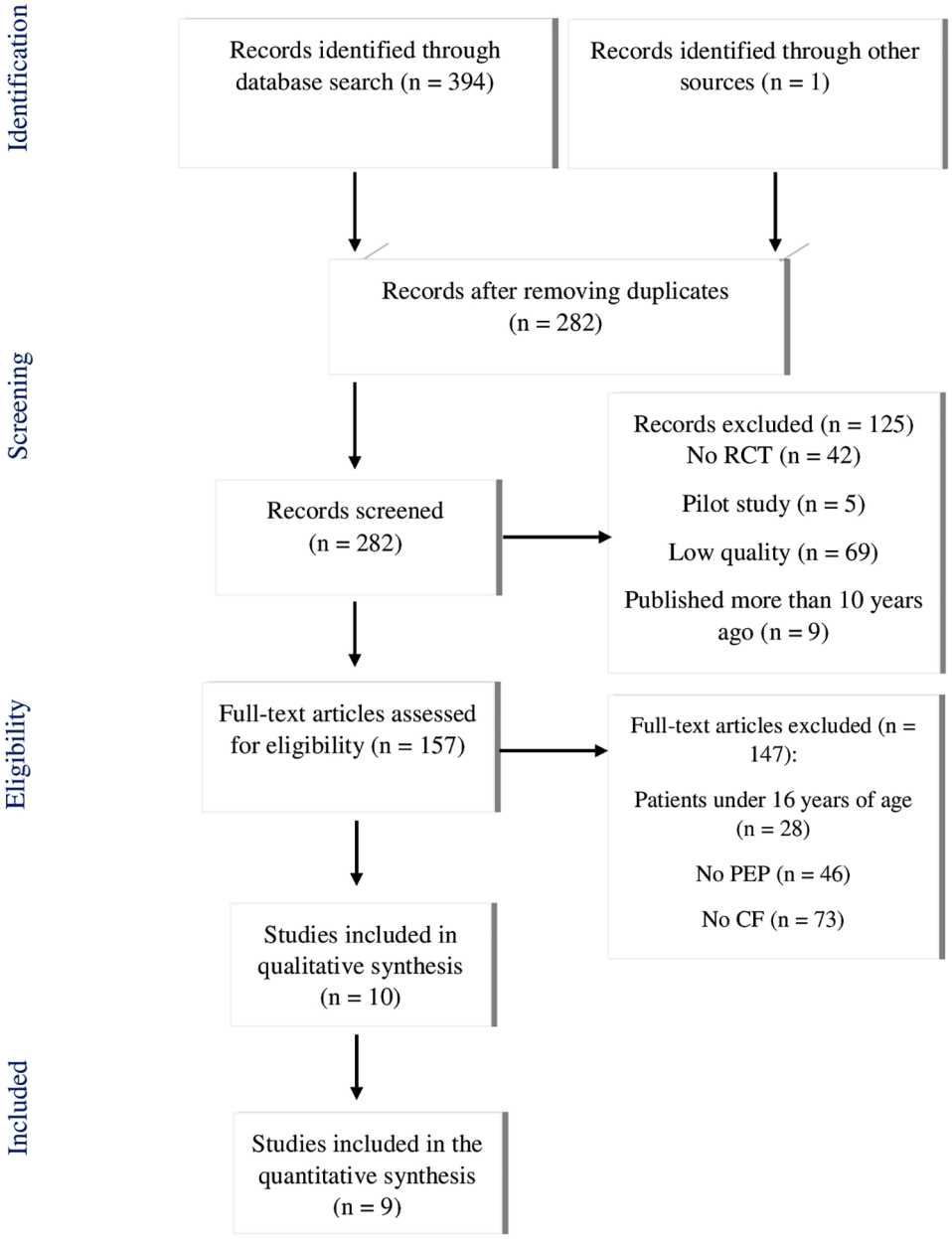
| RCTs | Participants | PEP intervention(s) | Comparison intervention(s) | Restricted co-interventions | Treatment duration | Results |
|---|---|---|---|---|---|---|
| Osman *et al.*[25] | *N* = 29<br>29 middle age (21–37)<br>28% Women<br>72% Male<br>Patients were admitted to hospital with an acute exacerbation of pulmonary infection. | Usual ACT group: 12 ACBT participants with PDyP, 2 with PD only, 8 AD, 2 AD with PD, 2 PEP and 3 Flutter. | • HFCWO group: it was applied for 8' at each frequency in sequence (10, 13 and 15 Hz), each followed by 2' of rest. During HFCWO and rest, patients could cough if they felt necessary to expel bronchial secretions. | Not included or provided. | 30', 2 times a day, 4 days.<br>HFCWO therapy on days 1 and 3, days 2 and 4 received their usual ACT, and vice versa. | • Sputum wet weight: > in ACT group for 24 hours.<br>• Efficacy: > in ACT group.<br>• Preference: 17 out of 29 chose ACT.<br>• Not HFCWO or any of the usual ACTs were associated with any clinical adverse effects. |
| Rodríguez Hortal *et al.*[26] | *N* = 32<br>31 middle age (18–42)<br>50% Women<br>50% Men | Intervention with PEP (Mask): (1) inhalation of bronchodilators and hypertonic saline solution at 7% 10'. (2) AD while inhaling 15' hypertonic saline combined with Huff (forced expiration and cough maneuver). (3) 10 breaths through a PEP mask. (4) Huffing (or FET). Cycle repeat 60'. | • Intervention with NIV as bilevel PAP: (1) inhalation of bronchodilators and hypertonic saline solution at 7% 10'. (2) AD while inhaling 15' hypertonic saline combined with Huff (forced expiration and cough maneuver). (3) NIV by 2' bilevel PAP. (4) Huffing (or FET).<br>• Cycle repeat 60'. | Not included or provided. | 2 sessions of 60', 2 times a day, 3 months. | • Bi-level PAP group < the LCI.<br>• No adverse effects were reported regarding the use of NIV in this study. |
| Ward *et al.*[27] | *N* = 13<br>24 middle age (18–29)<br>53.85% Women<br>46.15% Male | Daily PEP QA + exercise: 6 cycles of 15 breaths + 30' of exercise (walking, jogging or step-ups) of moderate to strong intensity (3–5 Borg scale). After each PEP cycle, or every 5' exercise, take 2–3 inhalations. | • Exercise intervention group with FET: 6 cycles of 15 breaths + 30' of exercise (walking, jogging or step-ups) of moderate to strong intensity (3–5 Borg scale). After every 5' exercise, take 2–3 inhalations. | Only if any participant in the FET exercise group experienced a respiratory exacerbation during the intervention could another form of airway clearance be started. | 4-week washout period followed by a 3-month intervention period. | • No. of exacerbations: in the washout period there were 4, these being the ones that showed atypical values. In the intervention period there were 7 exacerbations, 3 in the PEP group and 4 in the exercise group.<br>• CFQ-R and LCQ: > PEP group score.<br>• Intention of future treatment: 5/6 participants in the PEP group with the intention of continuing with its use. 6/7 participants in the exercise group with the intention of continuing exercise, and 4 of them had the intention of resuming the use of PEP.<br>• Both groups showed similar respiratory exacerbation rates. |

*(Continued)*

**Table 1.** (Continued)

| RCTs | Participants | PEP intervention(s) | Comparison intervention(s) | Restricted co-interventions | Treatment duration | Results |
|---|---|---|---|---|---|---|
| San Miguel-Pagola *et al.*[28] | *N* = 22<br>25 middle age (17–32)<br>45.46% Women<br>54.54% Male | Combined therapy group: hyaluronic acid (HA) + hypertonic saline (HS) with oscillatory PEP (10') with Acapella device with mouthpiece in sitting position, slow and deep inspirations, including 2–3' post-inspiratory pause, and exhale until residual capacity functional lower and then AD (20') seated. If they expectorated during nebulization, they had to pause the nebulizer, so as not to lose medication. | • Usual care group: HA + HS (10') with mouthpiece in a sitting position with slow and deep inspirations, including 2–3' post-expiratory apnea, and exhale to a lower functional residual capacity and, after that, AD (20') sitting.<br>• If they expectorated during nebulization, they had to pause the nebulizer, so as not to lose medication. | Not included or provided. | 5 days in a row, with 1 previous week of washing. Every day, at the same time, 30' of self-administered airway clearance (10' nebulization and 20' AD). | • Expectoration: > during nebulization for combination therapy.<br>• Symptoms of cough and sputum: for CASA-Q there were improvements in both interventions.<br>• Combined therapy promoted greater sputum expectoration than usual care during the nebulization period, reducing both symptoms related to sputum and HA + HS adverse effects.<br>• Both interventions were well tolerated, reporting no serious adverse events. |
| Dwyer *et al.*[29] | *N* = 38<br>30 average age (21–39)<br>35% Women<br>65% Men<br>Patients were admitted with an acute pulmonary exacerbation. | EG: standard comprehensive hospital care + NIV during chest physiotherapy. ACBT consisting of cycles of deep, relaxed breathing, huffing and coughing + additional technique (percussion, vibration, PD, AD, PEP and oscillating PEP). 6 participants used PEP and 1 used oscillating PEP. | • CG: standard comprehensive hospital care for the CF team. ACBT consisting of deep, relaxed breathing, huffing, and coughing cycles.<br>• + 16 participants used PEP, 1 oscillatory PEP and 2 AD. | Not included or provided. | Daily (mean of 65') from day 2 of admission to hospital discharge (mean of 14 days) | • Spirometry: EG with a tendency to improve. Upon discharge, he obtained > values.<br>• $PI_{max}$ and $PE_{max}$: on the 2nd day, CG worsened and EG improved.<br>• Schwartz fatigue scale: SG < fatigue on discharge.<br>• Sputum microbiology: on admission, all samples, except 1, presented *Pseudomonas aeruginosa*. At week one, EG < colonies than GC. At discharge, the EG < colonies.<br>• No adverse events occurred in either group. |
| Fainardi *et al.*[30] | *N* = 34<br>26 middle age (19–32)<br>58.8% Women<br>41.2% Men<br>Participants were admitted for management of an acute exacerbation of respiratory symptoms. | PEP group (mask): 15 breaths followed by FET. | • HFCWO group: Breathe actively and cough 3 to 5 times to achieve expectoration of bronchial secretions. | Routine medication was continued during the study. | 2 days of treatment, 3 times a day, 30' per session.<br>1st day HFCWO, 2nd day PEP therapy, and vice versa. | • $SaO_2$: PEP group had minimal decrease.<br>• Modified Borg scale: > after both interventions.<br>• Comfort: 41% had no preferences. 50% preference for PEP and 9% preference for HFCWO.<br>• The study did not inform about adverse effects. |

ACBT, Active Cycle of Breathing Techniques; ACT, Airway Cleaning Techniques; AD, Autogenous Drainage; BMI, Body Mass Index; CASA-Q, Cough and sputum evaluation questionnaire; CFQ-R, Revised CF Questionnaire; CG, Control Group; CPET, Cardiopulmonary Exercise Test; CRQ, Chronic Respiratory Questionnaire; DLCO, Diffusion capacity of the alveolar-capillary membrane of carbon monoxide; DLNO, Diffusion capacity of the alveolar-capillary membrane of nitric oxide; EG, Experimental Group; $FEF_{25-75}$, Forced Expiratory Flow 25–75%; FET, Forced Expiratory Technique; FEV1, Forced Expiratory Volume in the First Second; FVC, Forced Vital Capacity; HA, Hyaluronic Acid; HFCWO, High Frequency Chest Wall Oscillation; HR, Heart Rate; HRQL, Health-Related Quality of Life; HS, Hypertonic Saline Solution; LCI, Pulmonary Clearance Index; LCQ, Leicester Cough Questionnaire; MEF25, Maximum Expiratory Flow at 25%; N, sample; NIV, Non-Invasive Ventilation; Nº, Number; PAP, Positive Airway Pressure; PDyP, Postural Drainage and Percussion; PEF, expiratory flow; PEF, PIF, Risk of airflow bias; $PE_{max}$, Maximum Expiratory Pressure; PEP, Positive Expiratory Pressure; PIF, Inspiratory flow; $PI_{max}$, Maximum Inspiratory Pressure; RCT, Randomized Clinical Trial; RV% CPT, Residual Volume as a percentage of Total Lung Capacity; $SaO_2$, Oxygen Saturation; SF-36, Short Form 36; VAS, Visual Analog Scale; $VO_2$, Volume of Oxygen.




RCT: Randomized Clinical Trial; PEP: Positive Expiratory Pressure; CF: Cystic Fibrosis.

**Figure 1.** Flow Chart of the selection of articles.

Regarding gender, in most studies the proportion of men is higher, except for Rodríguez Hortal *et al.*,[26] with equivalent percentages of women and men participating, and Radtke *et al.*,[21] Ward *et al.*[27] and Fainardi *et al.*,[30] with a slightly higher proportion of women.

### *Variables or outcome measures*

Seven of the 10 studies included assessed lung function through $FEV_1$.[23,25–30] Five of the studies also examined other types of lung function measures.[22,23,26,29,30] Sputum viscoelasticity, sputum solids content, and ease of expectoration were examined in two studies.[21,22] Four studies evaluated the amount of sputum.[25,28–30] LCI was measured in two other clinical trials.[24,26] The feeling of congestion in the chest was analyzed in three trials[22,24,29] and two of these recorded the number of coughs.[22,24] Half of the studies evaluated the well-being of the participants using different instruments: SF-36,[23] CRQ,[23] VAS scale,[25] CFQ-R,[27,29]

LCQ,[27,28] and CASA-Q.[28] Four trials measured tolerance to therapy.[23,26,28,29] Blood oxygen was recorded in three studies.[25,26,30] Participants' preference for the techniques to which they were subjected was examined in four articles.[25,27,28,30] Seven trials registered the presence or not of adverse effects during the study.[21,22,24–26,28,29] Most studies reported that the treatment was well tolerated and with no adverse effects in any group, except for Radtke *et al.*,[21] since during this study, one female patient required oral antibiotic therapy for the treatment of a pulmonary exacerbation and was excluded from the analyses.

### Type of intervention

In all studies, there were two main comparison arms: PEP technique (either PEP or oscillatory PEP) with a control group (whatever the technique used in this control group). In turn, for the different studies, within the experimental group there may be subgroups, and in some cases, also within the control group.

Three studies had two comparison groups,[22–24] of which two had a control group in which only breaths were taken,[22,24] while the rest had a single comparison group.[21,25–30] Two trials presented a comparison group that only received usual hospital care.[28,29] The different comparison groups included: physical exercise,[21,22,24,27] AD or ACBT,[23] HFCWO,[25,30] and bilevel PAP.[26]

Of the 10 trials included, four used only PEP,[24,26,27,30] two used Flutter alone (oscillatory PEP),[21,22] one used Acapella (oscillatory PEP),[28] and three used both types (PEP and oscillatory PEP) in therapy.[23,25,29]

Only four of the studies included specified whether the PEP technique was performed with a mask[26,30] or with a mouthpiece.[24,28]

In terms of duration, two trials analyzed single-session treatments.[21,30] In four trials, the duration was less than 10 days for each treatment group,[22,24,25,28] while in the rest of the studies, the duration varied between 13 days and 12 months.[23,26,29] Two studies carried out a washout period, one before applying the techniques, lasting 4 weeks,[27] and the other between the techniques, lasting one week.[28]

Five trials conducted sessions lasting 20–30 min.[22,24,25,28,30] Two studies conducted sessions lasting 60–65 min[26,29] and three studies did not specify sessions duration.[21,23,27]

### Effect of interventions

*PEP compared to exercise groups.* Four trials compared PEP versus exercise.[21,22,24,27] One study compared interval exercise with Flutter versus continuous cycling at moderate intensity;[21] another Flutter in relation to treadmill exercise;[22] another work compared PEP therapy with a mouthpiece and treadmill exercise;[24] and PEP therapy in relation to forced expiratory techniques (FET).[27]

One study analyzed the efficacy of PEP versus exercise in relation to $FEV_1$, without finding significant differences between the groups in the medium term.[27] Two studies evaluated the viscoelasticity of sputum in the short term,[21,22] agreeing that there are no significant differences between the two treatment groups, showing an improvement in both. However, regarding the ease of expectoration there was controversy, since one determined that exercise was better than PEP,[21] while the other did not find significant differences between the groups.[22]

Another study that evaluated the LCI indicates that PEP therapy eliminated much more mucus than the exercise group in the right lung and the central zone of both lungs, although there were no differences between the groups in the peripheral or intermediate lung zones of both lungs, both at the end of the intervention and 60 min later.[24]

Two studies agreed that the number of coughs was significantly higher during the application of PEP compared to exercise, but after the intervention, there were no notable differences between the groups.[22,24] Regarding the feeling of congestion, one of the studies indicated that there were no differences between both therapies,[22] while the other obtained clinical improvement with PEP.[24]

In relation to well-being measured with the CFQ-R and LCQ questionnaires, the PEP intervention obtained a higher overall score, finding a certain preference of patients to resume the use of PEP therapy.[27]

Three studies evaluated participants admitted for management of an acute exacerbation during the

interventions.[25,29,30] And, in the study conducted by Ward *et al.*,[27] if a participant in the exercise-only group experienced a respiratory exacerbation during the intervention phase, they were permitted to commence another form of airway clearance.

*PEP compared with other types of respiratory therapy.* One study compared PEP with ACBT and AD;[23] two PEP studies with HFCWO;[25,30] and one study compared PEP with NIV, more specifically, with bilevel PAP.[26]

Four studies analyzed the efficacy of PEP versus another breathing technique in relation to $FEV_1$.[23,25,26,30] No study found differences between the interventions, although in the long-term study by Pryor *et al.*,[23] there was an overall decrease in lung function of all treatment groups at 12 months, with Flutter and Cornet interventions being those that obtained a smaller decrease.

Two trials studied the efficacy of PEP compared with other respiratory therapies on the amount of sputum expectorated in the short term,[25,30] finding little difference between the treatment groups, although the group that performed PEP obtained a slightly higher amount.

One study compared PEP with another type of respiratory therapy in relation to LCI, finding significant improvement after the use of bilevel PAP compared with PEP.[26]

Three studies described the efficacy of PEP versus other respiratory therapies on measures of lung function other than $FEV_1$.[23,26,28] The study by Pryor *et al.*[23] reported that in terms of forced vital capacity (FVC), $MEF_{25}$ and residual volume as a percentage of CPT, there were no differences between the intervention groups within 12 months. The study by Rodríguez Hortal *et al.*[23] stated that in terms of FVC, it did not find significant changes between the groups in a period of 3 months. The study by Fainardi *et al.*[30] did not show significant differences between the groups for $FEF_{25–75}$ in a single session.

The efficacy of PEP versus other respiratory therapy in relation to quality of life was analyzed in two articles.[23,25] The long-term study by Pryor *et al.*[23] carried out with CRQ (dyspnea, fatigue, emotion, and mastery of the technique), found an improvement in dyspnea in four of the five groups (Cornet was the only one that did not obtain improvement), among which the group with Flutter therapy obtained greatest improvement. The SF-36 showed an overall tendency for all groups to worsen. The study by Osman *et al.*[25] found no differences to highlight between the groups in the short term.

The effectiveness of PEP versus other long-term respiratory therapy[23,24] was studied using the modified shuttle test over a 12-month period,[23] and the 6-minute walk test over a 3-month period,[26] but neither found significant differences between long-term groups.

Regarding blood oxygenation, two studies coincided in not finding significant differences between the groups,[25,26] one of them being a short-term study measured by pulse oximeter,[25] and the other long-term measured by blood gas.[26] The study by Fainardi *et al.*[30] shows how in a single session, the intervention group with PEP obtained a minimal decrease in SaO2 measured with a pulse oximeter after the intervention, compared with the group that performed HFCWO, in which this decrease did not occur. These trials also reported participants' preference for short-term PEP therapy.[25,30]

*PEP compared with control groups without therapy.* Two studies compared PEP versus the control group[22,24] with breaths at rest.

One trial measured the effects of oscillatory PEP on sputum viscoelasticity, finding a significant reduction both after the intervention and in the 20 min after Flutter therapy in comparison with control group.[22] Furthermore, among the participants who expectorated after 5 min, a smaller amount of solids was found with Flutter therapy.[22] There were no significant differences between the groups when comparing the ease of expectorating sputum.[22]

With respect to LCI, PEP therapy eliminated much more mucus in all lung regions, both during the intervention and after 60 min.[24]

Both trials agreed that PEP therapy obtained a much greater improvement in the feeling of congestion, and a greater number of coughs, both at the end of the intervention and later,[22,24] and there was no presence of adverse effects.[22,24]

**Table 2.** Evaluation of the methodological quality of the articles included with the PEDro Scale.

| PEDro scale items RCTs | Specified selection criteria | Random assignment | Hidden assignment | Similar groups | Blinded subjects | Blinded therapists | Evaluators blinded | Adequate follow-up | Intention to treat analysis | Results of comparisons between groups | Point measures of variability | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Radtke *et al.*[21] | X | X | X | X | N | N | X | N | N | X | X | 7 |
| Dwyer *et al.*[22] | X | X | X | X | N | N | X | X | X | X | X | 8 |
| Pryor *et al.*[23] | X | X | N | X | N | N | X | X | X | X | X | 7 |
| Dwyer *et al.*[24] | X | X | X | N | N | N | X | X | N | X | X | 6 |
| Osman *et al.*[25] | X | X | N | X | N | N | X | X | N | X | X | 6 |
| Rodríguez Hortal *et al.*[26] | X | X | X | X | N | N | X | X | N | X | X | 7 |
| Ward *et al.*[27] | X | X | X | X | N | N | X | X | X | X | X | 8 |
| San Miguel-Pagola *et al.*[28] | X | X | X | X | N | N | X | X | X | X | X | 8 |
| Dwyer *et al.*[29] | X | X | X | X | N | N | N | X | X | X | X | 7 |
| Fainardi *et al.*[30] | X | N | N | X | N | N | X | X | N | X | X | 5 |

*Usual therapy + PEP (nebulization + AD + PEP) versus usual therapy (nebulization + AD).* This study evaluated lung function in the medium term, showing that it remained stable in both treatment groups.[28] The one that included oscillatory PEP increased the number of expectorations during nebulization; however, there were no differences during AD or in the subsequent 24 hours.[28] The CASA-Q questionnaire showed improvements in the score for both interventions, while no intervention using the LCQ questionnaire obtained changes in the scores. In addition, this study showed a greater preference for PEP therapy, as it presented the lowest number of adverse effects.[28]

*Comprehensive hospital care with NIV versus comprehensive hospital care alone.* The influence and/or need for PEP therapy is evaluated in the presence or absence of NIV.[29] In the experimental group, a non-statistically significant improvement was obtained compared with the Control Group (CG), and at discharge, the Experimental Group (EG) values were slightly higher.[29] There were no differences between the groups in the amount of sputum expectoration or wet weight. Furthermore, on the second day, the CG showed a worsening while the EG improved lung function ($PE_{max}$ and $PI_{max}$), although at 1 week and at discharge the groups showed no differences between them.[29] Regarding the quality of life through CFQ, there were no differences at discharge between the groups in the physical, health and respiratory domains, or in terms of adverse effects.[29]

Despite the main results are referred to NIV (it is suggested that the addition of NIV to standard chest physiotherapy is a useful tool to aid airway clearance and improve lung function and fatigue on discharge from the hospital in people with moderate to severe CF[29]), the preference for the inclusion of PEP within the therapeutic arsenal is also shown, although the reason for this is not made explicit, nor its actual need.

### *Meta-analysis and risk of bias of the included studies*

The 10 trials selected have a 'moderate' methodological quality, with scores between 6 and 8 points on the PEDro scale, with the exception of the study by Fainardi *et al.*,[30] which only reached 5 points (Table 2).

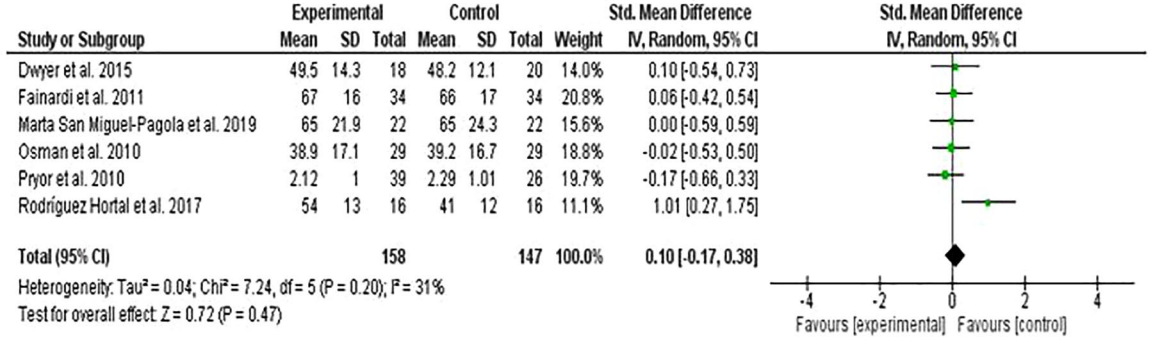



**Figure 2.** Meta-analysis of randomized clinical trials based on $FEV_1$ results.

Finally, a meta-analysis of six clinical trials was carried out whose $FEV_1$ measurement was adequately described (Figure 2). In CF patients, there is not enough evidence to confirm that PEP therapy achieves improvements in $FEV_1$ compared to other therapies or control group (mean difference: 0.10; 95% CI: −0.17 to 0.38; I2: 31%).

The Cochrane Collaboration Risk of Bias scale is described for these RCTs. Some were at high risk of bias in various domains, such as study design, or did not provide enough information to conclude on risk of bias. The randomization process was adequately described in the studies, being low risk in all, except Fainardi *et al.*,[30] which had a high risk of bias. Regarding allocation concealment (selection bias), half of the studies are at lower risk[24,26,29]and the other half are at higher risk.[23,25,30] Due to the nature of the interventions, all studies were at high risk of performance bias. Only the study by Dwyer *et al.*[29] had a high risk of detection bias. Regarding the wear bias, the Pryor *et al.*[23] study had losses to follow up and used intention-to-treat analysis. Many of these biases may have affected the results of clinical trials (Figure 3).

## Discussion

The objective of this review was to evaluate the efficacy of the PEP technique in CF patients over 16 years of age, through secretion clearance, lung function and other measures, such as quality of life or patient preference in relation to the technique used. In the 10 RCTs included, the PEP technique has been compared with physical exercise or other respiratory therapies.

The ACTs used from respiratory physiotherapy are prescribed to help eliminate mucus from the airways and are usually started as soon as CF is diagnosed, improving ventilation, lung mechanics and reducing the impact of infection on the airways.[12,13] In this systematic review, we made comparisons of articles about PEP with exercise groups (such as cycle ergometer, cycling, walking, jogging

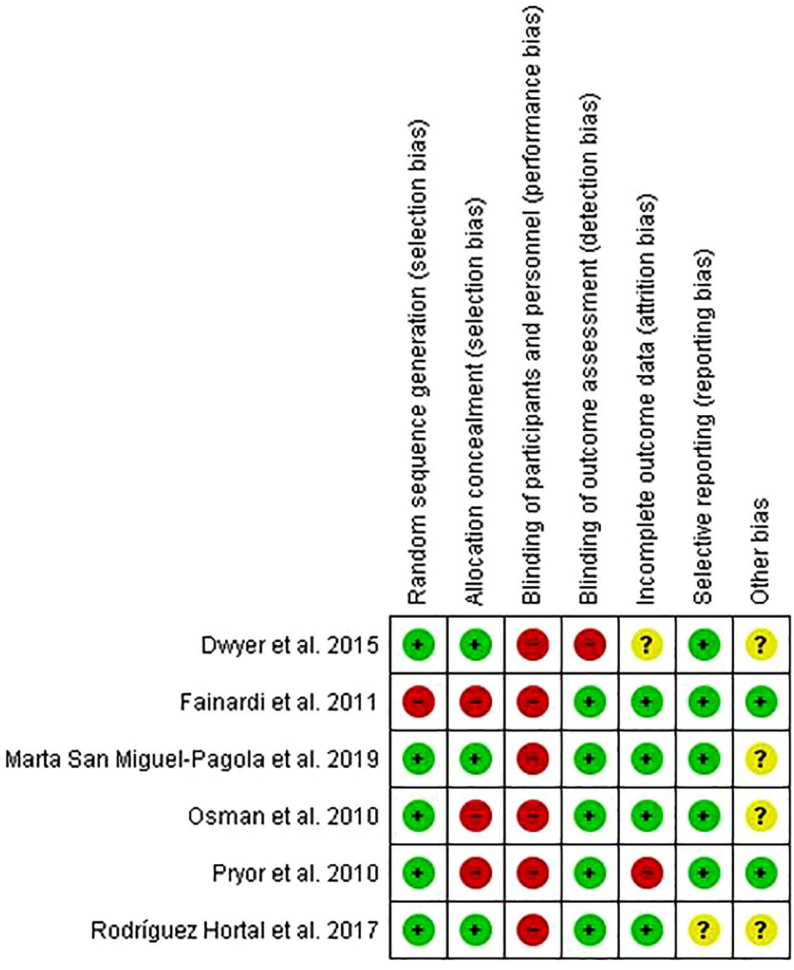



**Figure 3.** Risk of bias of the included studies.

or step-ups),[21,22,24,27] PEP with groups of other types of respiratory therapy (for example, HFCWO, ACBT, AD, bilevel PAP)[23,25,26,30] and PEP with control groups without therapy (such as breath or usual care).[22,24] Also compared was the usual therapy (nebulization + AD) + PEP versus only usual therapy,[28] and comprehensive hospital care with non-invasive ventilation (NIV) versus comprehensive hospital care only.[29]

This review included a total of 274 participants with CF between the ages of 16 and 63, the majority of which were male. The sample size in the different studies ranged from 13 to 53 participants. The technique used ranged from PEP to oscillatory PEP with Flutter, Cornet, or Acapella. There were also different modes of use, with a mouthpiece or with a mask. The PEP compared various therapies and the intervention period ranged from a single treatment session to a 12-month intervention studies. The duration of the sessions ranged from 20 to 65 min. All these factors, together with the small number of studies, the use of different measurement scales to compare the groups and the limited information available from some authors, limited the possibility of performing the meta-analysis with all the studies included.

Lung function, and particularly $FEV_1$, is related to the survival[12,31] of CF patients. This parameter is affected throughout their lives, decreasing life expectancy. Three of the 10 clinical trials[21,22,24] did not collect this outcome measure, which was used in the meta-analysis.

Dwyer *et al.*[29] reported that 85% of the participants in the control group made use of PEP therapy, and 38.9% of the experimental group received treatment with NIV and needed the use of PEP. This shows that the PEP is necessary on many occasions in CF patients, despite receiving other treatments.

Several studies reported patients' preference for PEP therapy.[25,27,30] Another investigation[28] also indicated that with the use of oscillatory PEP, the amount of sputum expelled increased during nebulization, in addition to finding a lower number of adverse events compared with nebulization alone, which led patients to show a certain preference for it use.[28]

Two studies compared PEP with HFCWO[25,30] in patients admitted to hospital with an acute exacerbation, finding differences in the amount of sputum expectorated after the intervention, with a higher amount of wet weight in the PEP group. Neither HFCWO nor any of the usual ACTs were associated with any adverse clinical events.[25] Fainardy *et al.*[30] study showed that HFCWO was comparable to PEP in terms of sputum production and lung function effects, but not in terms of acceptability.[30]

Among the 10 studies included in this review, only seven[21,22,24–26,28,29] reported if there were adverse effects or not, all agreeing on the absence of serious adverse effects during or after the interventions.

The quality of the evidence was moderate in most clinical trials. In all likelihood, by using crossover designs in the studies less evidence was obtained, as it was not possible to blind the participants or the therapists; although blinding the assessors in all studies (except for one[28]) led to a lower risk of bias and a higher quality of evidence. The lack of clear information in certain trials on concealed allocation also increased the risk of bias in this review.[23,25,30] The information provided by the articles included on the primary outcomes was of low to moderate quality and was not analyzed in all comparisons. The lack and imprecision of this information and other outcome measures caused the quality to vary from very low to moderate.

In a review by Morrison *et al.*[16] in 2020 sought to identify the effectiveness of oscillatory devices, both oral and thoracic, in mucociliary clearance in CF patients aged between four and 63 years. The results indicated that there is no evidence that these devices are better than other types of respiratory techniques (low or very low quality of evidence) and the frequency of exacerbations that required treatment with antibiotics was higher with the use of oscillatory devices than with PEP. Previously in 2019, McIlwaine *et al.*[12] had recommended PEP (not including oscillatory PEP) as the most acceptable long-term intervention compared with other techniques. In 2013, McIlwaine *et al.*[32] had compared PEP therapy using a mask versus high-frequency chest wall oscillation (HFCWO) in a long-term multicentre randomized controlled study. Lung function, health-related quality of life, or patient satisfaction showed no significant difference between the two groups, although the time of treatment required using PEP mask therapy was significantly shorter.

With regards to adverse outcomes, there was a significantly higher exacerbation rate in the HFCWO group compared with the PEP group, and significantly fewer days to first exacerbation, indicating that the HFCWO is not as effective as PEP in preventing exacerbations. Both of these aspects highlight the significant superiority of PEP therapy using a mask. This study concluded in favor of PEP use, while not supporting HFCWO use as technique of choice for airway clearance in patients with CF.[32]

Other reviews, such as Moran *et al.*,[33] have analyzed the effectiveness of techniques such as NIV regarding their non-use, for mucociliary clearance during sleep and exercise, in patients with CF. Their findings indicated that NIV is a good complement to other airway clearance techniques for CF patients, highlighting that NIV combined with oxygen therapy improves gas exchange during sleep. However, its effectiveness on exercise, pulmonary exacerbations, and disease progression was not clear.

In 2019, a global review of Cochrane systematic reviews conducted by Wilson *et al.*[34] on the effectiveness and safety of different airway clearance techniques in people with CF, found no evidence that these techniques are better than others, recommending that the choice of these should be based on comfort, convenience, cost or other individual factors, according to the needs of each patient. Similar to the results of our 2021 review, Wilson *et al.*[34] were not able to draw definitive conclusions for comparisons of airway clearance techniques in terms of $FEV_1$, except when it is indicated with moderate evidence that there are no differences between treatment with PEP and oscillation devices after 6 months of treatment.[34] All six reviews included were considered to be at low risk of bias. However, the individual trials included in the reviews often did not reveal enough information to adequately assess this risk of bias.[34]

Among the limitations of our review, it is worth highlighting the fact that there are few studies with high methodological quality and low risk of bias to demonstrate the efficacy of PEP therapy in CF patients, with small samples and different characteristics. Disparity in number of participants, length of sessions, follow-up, or underreporting of some outcome measures increased the risk of bias in this systematic review.

In addition, the use of sputum as a comparator requires the distinction between wet weight versus dry weight of sputum, which is missing in most of the studies. Only Osman *et al.*[25] specified the measure of wet weight sputum, and referred to previous work findings on wet weight and dry weight sputum being proportional.

Future lines of research should carry out trials that compare PEP therapy with other respiratory therapies and/or with long-term exercise, considering the lung function and the amount of sputum (dry/wet weight) expectorated in the results, to objectively verify the efficacy of this technique in elimination of mucus, and thus obtain more solid conclusions. It will also be necessary to consider lung clearance index, well-being or quality of life, tolerance, preferences, and adverse effects as outcome measures in the studies, because the number of studies that include these measures are insufficient to demonstrate the efficacy of the PEP therapy, in this sense.

Among the implications of these studies for clinical practice, this review is aimed to describe the most effective techniques that would achieve an improvement in lung function, fewer respiratory exacerbations in CF, and therefore less need for the use of medicines for the expulsion of mucus, or a probable reduction of hospitalization time – aspects that would result in a reduction in healthcare costs produced by repeated lung infections. The low or moderate evidence presented describes which treatment best affects the quality of life of CF patients, as well as the one that produces better adherence or whether there is a greater preference, for example, in the use of PEP therapy with respect to other therapies.

## Conclusion

In relation to the treatment of people with CF, we found moderate evidence that PEP therapy is more effective than both CG without intervention and usual physiotherapy care, both in-hospital and out-of-hospital (or outpatient) for most of the measures in this study. The number of coughs and the amount of sputum expectorated is greater during PEP therapy than during other respiratory physiotherapy or during exercise. The results suggest that PEP therapy achieves a greater improvement in LCI than exercise, but there is not enough evidence to confirm that PEP therapy improves $FEV_1$ over other therapies.

PEP therapy is not associated with the appearance of adverse effects, which makes it a safe therapy and, therefore, it is often chosen by patients over other alternatives.

## Author contributions

**Patricia Rocamora-Pérez:** Conceptualization; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

**María Jesús Benzo-Iglesias:** Conceptualization; Formal analysis; Investigation; Methodology; Resources; Validation; Visualization; Writing – review & editing.

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