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APPLICATION OF POSITIVE EXPIRATORY PRESSURE (PEP) IN CYSTIC FIBROSIS PATIENT INHALATIONS

ZASTOSOWANIE PODWYŻSZONEGO CIŚNIENIA WYDECHOWEGO (PEP), W INHALACJACH U CHORYCH NA MUKOWISCYDOZĘ

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Abstract

Inhalations, whose aim is the liquefaction of dense viscous secretions and preparing them for evacuation from the bronchial tree by means of drainage techniques, are standard treatment procedures in cystic fibrosis. Numerous studies showed that during inhalation only a small percentage of the drug was deposited in the bronchi. The use of the so-called elevated positive expiratory pressure, or PEP system, can improve the drug deposition in the lungs and consequently have the effect of increasing the effects of physiotherapy and delay the progression of the disease.

***The aim** of the study was a retrospective evaluation of the applicability of the PEP system in mucolytic drug inhalations in CF patients.*

***Material and Methods:** Analysis of the variation of selected spirometry indicators over time: FEV1, FVC, MEF75%, 50%, 25%, performed in two groups of patients with cystic fibrosis: group I using PEP (n 29), group II without PEP (n 38). The analysis of parameter variance in time, as well as of the course taken by the changes and the difference in this respect regarding the PEP and no PEP group of patients was made by means of the analysis of linear regression for correlated data (generalized estimating equation).*

***Results:** The use of the PEP system for inhalation in patients with cystic fibrosis had the greatest impact on improving the values of MEF75%, 50%, 25%. After 18 months, observations indicated the improvement of the values by 8.1%, 10.4% and 13% respectively in the group of PEP and reduction by 6%, 4.6% and 4.5% in the group without PEP. The differences in the level of change observed between the two groups proved to be statistically significant (p=0.033, p = 0.019, p=0.006). After 18 months compared to the initial visit, the analysis of variation over time in the PEP group showed significant improvement only in the case of MEF 25% (p=0.024).*

***Conclusions:** 1) The PEP system may be applied in inhalations of mucolytic drugs in cystic fibrosis patients. 2) the application of the PEP system for inhalations in cystic fibrosis patients showed the greatest improvement in the values of MEF75%50%25% 3) the use of PEP for inhalation of mucolytic drugs in patients with cystic fibrosis may be one of the factors affecting the delay of progression of functional changes in the lungs. 4) Long-term randomized observation should be carried out in order to confirm the retrospective study results.*

Key words: PEP, aerosol distribution in the lungs, physiotherapy

Streszczenie

***Wstęp:** Zabiegi inhalacyjne, których celem jest upłynnienie gęstej, lepkiej wydzieliny i przygotowanie jej do ewakuacji z drzewa oskrzelowego przy pomocy technik drenażowych stanowią standardowe leczenie mukowiscydozy. Liczne badania pokazują, że w czasie inhalacji tylko niewielki procent leku deponuje się w oskrzelach. Zastosowanie podwyższonego ciśnienia wydechowego tzw. systemu PEP może zwiększyć depozycję leku w płucach i w konsekwencji mieć wpływ na zwiększenie efektów leczenia fizjoterapeutycznego i opóźnienie progresji choroby.*

***Celem pracy** była retrospektywna ocena przydatności systemu PEP w inhalacjach z leków mukolitycznych u chorych na mukowiscydozę.*

Materiał i metody: *Przeprowadzono analizę zmienności w czasie wybranych wskaźników spirometrycznych: FEV1, FVC, MEF75%,50%,25%, w dwóch grupach chorych na mukowiscydozę: grupa I (n 29) – chorzy, którzy stosowali system PEP, grupa II (n 38) – kontrolna. Analizę zmienności badanych parametrów w czasie oraz różnic w przebiegu zmienności pomiędzy grupami pacjentów stosujących PEP i bez PEP zbadano przy pomocy analizy regresji liniowej dla danych powiązanych (uogólnione równanie estymujące, ang. generalized estimating equation).*

Wyniki: *Zastosowanie systemu PEP w inhalacji u chorych na mukowiscydozę miało największy wpływ na poprawę wartości MEF75%,50%,25%. Po 18 miesiącach stwierdzono poprawę wartości wskaźników MEF75%,50%,25% odpowiednio o 8,1%, 10,4% i 13% w grupie z PEP i obniżenie o 6%, 4,6% i 4,5% w grupie dzieci inhalowanych bez PEP. Różnice w poziomie zmian zaobserwowane między grupami okazały się istotne statystycznie (p=0,033, p=0,019, p=0,006). Analiza zmienności w czasie w grupie stosującej PEP wykazała istotną statystycznie poprawę tylko w przypadku MEF25% po 18 miesiącach w stosunku do badania wyjściowego, (p=0,024).*

Wnioski: *1) System PEP może mieć zastosowanie w inhalacjach z leków mukolitycznych u chorych na mukowiscydozę. 2) Zastosowanie systemu PEP do inhalacji u chorych na mukowiscydozę miało największy wpływ na poprawę wartości MEF75%,50%,25%. 3) Zastosowanie PEP w inhalacji z leków mukolitycznych u chorych na mukowiscydozę może być jednym z czynników mających wpływ na opóźnienie progresji zmian czynnościowych w płucach. 4) Wymagane jest przeprowadzenie badania randominizowanego, długofalowego, które potwierdziłoby wyniki uzyskane w badaniu retrospektywnym.*

Słowa kluczowe: PEP, dystrybucja aerozolu w płucach, fizjoterapia chorych na mukowiscydozę

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INTRODUCTION

Cystic fibrosis is the most common, genetically conditioned, inherited autosomal recessive disease. It is characterised by bronchial mucous periciliary membrane dehydration, thick and sticky mucous stagnation, common infections of the respiratory tract and pathogenic bacterial early infection. This chronic and progressive disease results in pulmonary tissue destruction in the form of fibrosis, bronchiectasis, disturbances of breathing mechanics leading to chronic pulmonary insufficiency and the patient's death.

Inhalations of mucolytic drugs aiming at liquefaction of the thick and sticky secretion and its evacuation from the bronchial tree by means of drainage techniques constitute standard treatment of cystic fibrosis. Numerous surveys demonstrate that during inhalations, only a small a amount of the drug is deposited in the bronchi [1, 2, 3]. The application of positive expiratory pressure (PEP) may improve the drug depositing in the lungs [4, 5].

PEP is a mono-valve appliance increasing resistance on expiration. The resistance results in the increase of expiratory pressure in the bronchi up to 15-25 cm/H2O. The PEP system was found to activate collateral canals in the bronchi. It momentarily dilates bronchioles, reduces the air trap symptom and as a consequence improves lung ventilation [6, 7, 8].

Since 1982, the PEP system has been applied in cystic fibrosis as a drainage method [9, 10, 11]. In recent years, many centres of cystic fibrosis treatment in Europe, including the Institute of Mother and Child, have recommended the application of the PEP system in inhalations as a method improving drug deposition in the lungs and the efficacy of physiotherapy.

Available literature does not provide results of short or long-term studies which would prove the advantageous influence of the PEP system on the functioning of lungs in cystic fibrosis patients. The scarce surveys that were done in this domain were carried out mainly in COPD and bronchial asthma patients and were short-term observations [11, 12, 13].

The aim of the study was retrospective assessment of the applicability of the PEP system in mucolytic drug inhalations in cystic fibrosis patients.

PATIENTS

On the basis of their case histories, 29 cystic fibrosis patients aged 8-20 years (11 boys and 18 girls) were selected. The average age of the group of patients applying PEP was 11.9 years (10.54 – boys: 12.72 – girls). They applied the PEP system in inhalations with hypertonic saline (n 23) or saline (n 5) and additionally rhDNase (n 15), 1 patient used PEP with rhDNase only. The control group consisted of 38 CF patients (10 boys and 28 girls) aged 8-17 years who did not use the PEP system for inhalation. The average age in the control group was 11.26 years (10.3 – boys and 12.18 – girls).

Patient characteristics

The patients were in differential clinical conditions assessed on the basis of spirometry essential indices, as well as the bacteriologic sputum test (Tables II and III). Administration of the PEP system for patients suffering

from the acute course of the disease was conducted on the assumption that the PEP system would effectively support daily physiotherapy and could delay the progress of the disease.

The bacteriologic sputum test in both groups revealed the presence of pathogenic bacterial strains characteristic for cystic fibrosis: Staphylococcus aureus and Pseudomonas aeruginosa [Table III].

METHODS

The applicability of the PEP system in CF patient inhalations was assessed on the basis of the retrospective analysis of the variance of selected spirometric indices in two groups of CF patients 1) group I – patients who applied the PEP system for mucolytic drugs inhalations, 2) group II – patients who did not apply the PEP system for inhalations. Forced expiratory volume in the first second (FEV_1), and forced vital capacity (FVC), maximum expiratory flow at forced expiration during the particular stages (MEF75,50,25%) were determined over 5 successive follow-ups in the Cystic Fibrosis Outpatient Clinic of the Institute of Mother and Child in the years 2008-2013. Due to different intervals between successive follow ups and therefore the small number of studies carried out in the coming months, observations were grouped into 6-month periods. (Table I).

Table I. Number of spirometric tests performed at various time intervals.

Tabela I. Liczba badań spirometrycznych wykonanych w poszczególnych przedziałach czasowych.

Group *Grupa*	Time/*Czas**				
	0	6m	12m	18m	>18m
I	29	33	35	25	19
II	38	26	50	44	31

*0 – the initial visit, 6m – observation up to 6 months, 12m – 6-12 months, 18m – 12-18 months, >18m – over 18 months after visit 0.

**0 – wizyta początkowa, 6m – czas do 6 miesięcy, 12m – czas między 6-12 miesięcy, 18m – czas między 12-18 miesięcy, >18 – czas powyżej 18 miesięcy.*

The test group comprised patients who started PEP application over the age of 7 and continued the procedure for at least 12 months.

Physiotherapy

Inhalations were carried out with the use of PARI PEP. All the patients performed inhalations with PARI air-compressors and nebulizers type LC PLUS or LC Sprint. In all the patients, standard physiotherapy was applied. Patients used Acapella® or Flutter® as well as Aided Autogenous Drainage and the choice was relative to their age. Additionally, in some patients tapping and succussion of the thorax in lateral position were administered. The duration of a physiotherapy session performed immediately after inhalations varied from 15 to 25 minutes and was relative to the patient's age.

Protocol

The PEP system requires an individually selected valve for each patient, so that even during small active expiration, bronchial pressure amounts to 15-25 cm H_2O. The pressure head was controlled using a manometer. Valves were selected by an experienced physiotherapist during the physiotherapeutic consultation visit. Parents and patients were instructed how to install the PEP system in the nebulizer, breathe correctly during inhalation and control pressure on the manometer. Inhalations were carried out with the use of a mouthpiece, in sitting position, with elbows leaning against a table.

Mode of respiration during inhalation

Patients were instructed to take slow and deep inspirations with inferior thorax distension in the frontal plane, arrest the aerosol for 2 seconds at the peak inhalation moment and to exhale while controlling the pressure in the bronchi and on the manometer.

Statistical methods

The analysis of parameter variance in time, as well as of the course taken by the changes and the difference in these between the PEP and no-PEP groups of patients was made with the use of the analysis of linear regression for correlated data (genera estimating equation – GEE). The models conserved the identifier of the group examined

Table II. The values of spirometry recorded at baseline.

Tabela II. Wartości wskaźników spirometrycznych zarejestrowane w badaniu wyjściowym.

	Spirometry at baseline *Spirometria, badanie wyjściowe*									
	FEV1%P		FVC %P		MEF75% %P		MEF50% %P		MEF25% %P	
	PEP	no-PEP	PEP	no-PEP	PEP	no-PEP	PEP	no-PEP	PEP	no-PEP
x	76.1	85.61	85.59	91.39	70.03	83.95	57.9	69	41.1	53.68
SD	20.46	16.73	16.34	15.11	22.46	25.64	23.93	19.91	21.42	22.61
Min-max	36-99	49-112	53-104	66-116	21-112	34-138	16-88	22-99	6-78	14-99
p	0.040*		0.133		0.029*		0.018*		0.019*	

Table III. Bacteriological examination of sputum.

Tabela III. Badanie bakteriologiczne plwociny.

	Bacteriological examination of sputum *Badanie bakteriologiczne plwociny*									
	P. aeruginosa		**Staph. aureus**		**MRSA + P.a**		**P.a. + S.a**		**Normal flora** *Flora fizjologiczna*	
	PEP	**no-PEP**	**PEP**	**no-PEP**	**PEP**	**no-PEP**	**PEP**	**no-PEP**	**PEP**	**no-PEP**
Male (n)/ Chłopcy (n)		1	5	5			6	4		
%	-	10%	45.4%	50%	-	-	54.5%	40%	-	-
Female (n) Dziewczęta (n)	2	2	8	16	2		5	9	1	1
%	11.1%	7.1%	44.4%	57.1%	11.1%	-	27.7%	32.1%	5.5%	3.5 %
Total (n) Ogółem (n)	2	3	13	21	2	-	11	13	1	1
%	6.9%	7.9%	44.8%	55.3%	6.9%		37.9%	34.2%	3.4%	2.6%

(PEP, no PEP), identifier measurement period (W0, i.e. Visit 0, observation up to 6 months, 6-12 months, 12-18 months and 18 months after W0) as well as interactions between the group identifier and the measurement period identifier. The significance level was defined as p=/<0.05. The results of the test of interaction of statistical significance reveal the presence or absence of a significant difference in the variability of the parameters examined between the PEP and no-PEP patients. The analysis was made with the use Stata v.10.0 [ref].

RESULTS

The course of variation over time in the case of the spirometric indices examined was not homogenous in either group. The variations in spirometric indices results are characteristic for cystic fibrosis patients and are connected with frequent infections and bronchopulmonary disease exacerbations (Fig. 1, 2, 3, 4, 5).

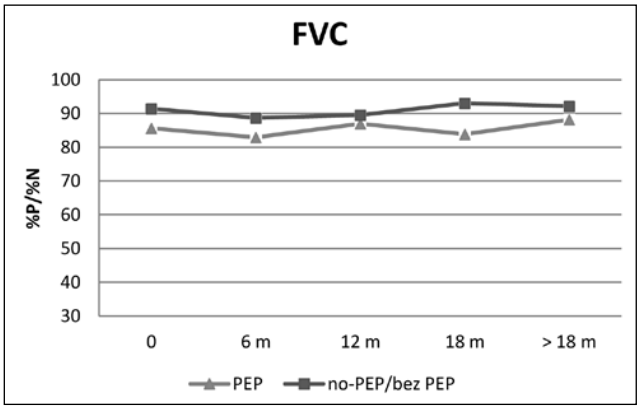

Fig. 2. The variation in time of FVC in patients with cystic ibrosis.

Ryc. 2. Przebieg zmienności w czasie wartości FVC u chorych na mukowiscydozę.

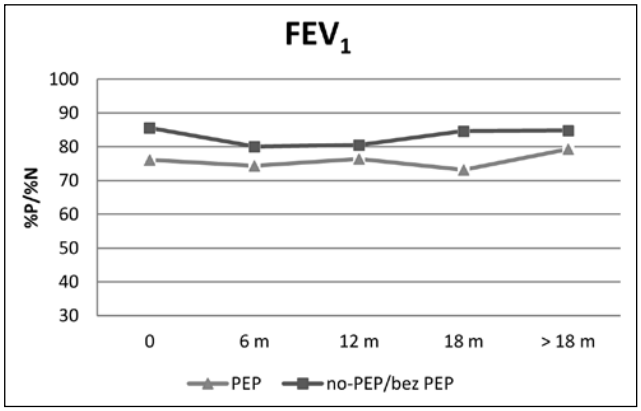

Fig. 1. The variation in time of FEV1 in patients with cystic fibrosis.

Ryc 1. Przebieg zmienności w czasie wartości FEV1 u chorych na mukowiscydozę.

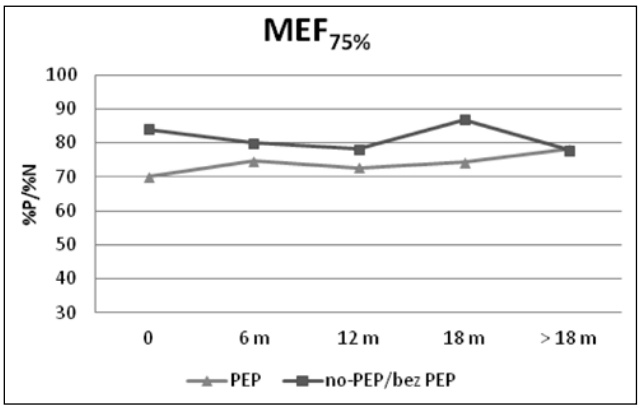

Fig. 3. The variation in time of MEF75% in patients with cystic fibrosis.

Ryc. 3. Przebieg zmienności w czasie wartości MEF75% u chorych na mukowiscydozę.

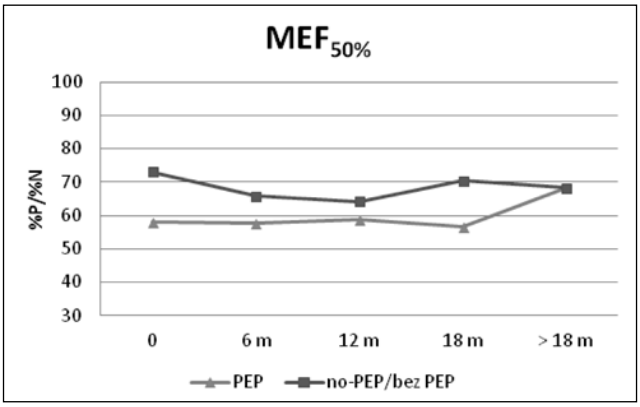

Fig. 4. The variation in time of MEF50% in patients with cystic fibrosis.

Ryc. 4. Przebieg zmienności w czasie wartości MEF50% u chorych na mukowiscydozę.

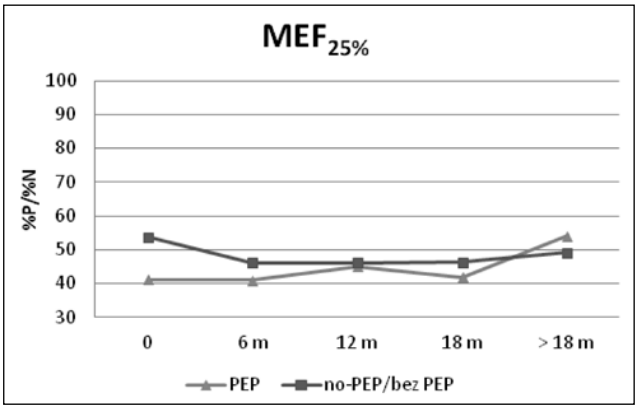

Fig. 5. The variation in time of MEF25% in patients with cystic fibrosis.

Ryc. 5. Przebieg zmienności w czasie wartości MEF25% u chorych na mukowiscydozę.

Table IV. Comparison of variability of FEV1 in time and between the group using PEP, as compared to the control group, nonuser of PEP.

Tabela IV. Porównanie zmienności FEV1 w czasie pomiędzy grupą stosującą PEP w stosunku do grupy kontrolnej niestosującej PEP.

FEV1	**β**	**95% CI dla β**		**P**	**P Time+time*PEP** *β Czas+czas*PEP****
Visit 0 no-PEP *Wizyta 0 bez PEP*	85.6	80.3	90.9	0.000	
Visit 0 PEP vs no-PEP *Wizyta 0 PEP vs bez PEP*	-9.5	-18.6	-0.4	0.040	
noPEP for 6 vs visit 0 *bez PEP do 6 vs wizyta 0*	-5.5	-10.2	-0.9	0.019	
6-12 vs visit 0 *6-12 vs wizyta 0*	-5.1	-8.6	-1.5	0.005	
12-18 vs wisit 0 *12-18 vs wizyta 0*	-0.9	-5.3	3.4	0.667	
>18 vs visit 0 *>18 vs wizyta 0*	-0.8	-5.3	3.7	0.729	
PEP additional * change in time *PEP dodatkowa* zmiana w czasie*					
for 6 vs visit 0 *do 6 vs wizyta 0*	3.7	-3.7	11.1	0.323	0.5407
6-12 vs visit 0 *6-12 vs wizyta 0*	5.4	-0.3	11.0	0.061	0.9039
12-18 vs wizyta 0	2.0	-9.2	5.1	0.578	0.3082
>18 vs visit 0 *>18 vs wizyta 0*	4.0	-4.8	12.9	0.374	0.4082

*the difference between the change for the PEP group compared to the change for the no-PEP group.
**różnica pomiędzy zmianą dla grupy z PEP w stosunku do zmiany dla grupy bez PEP.*
**test for total variation in time for the PEP group compared to visit 0
***test dla łącznej zmiany w czasie dla grupy z PEP w stosunku do pomiaru z wizyty 0.*

Table V. Comparison of variability of FVC in time and between the group using PEP, as compared to the control group, nonuser of PEP.

Tabela V. Porównanie zmienności FVC w czasie pomiędzy grupą stosującą PEP w stosunku do grupy kontrolnej niestosującej PEP.

FVC	β	95% CI dla β		P	P Time+time*PEP** *Czas+czas*PEP***
Visit 0 no-PEP *Wizyta 0 bez PEP*	91.4	86.6	96.2	0.000	
Visit O PEP vs no-PEP *Wizyta 0 PEP vs bez PEP*	-5.8	-13.4	1.8	0.133	
noPEP for 6 vs visit 0 *bez PEP do 6 vs wizyta 0*	-2.7	-7.3	1.8	0.234	
6-12 vs visit 0 *6-12 vs wizyta 0*	-1.9	-5.1	1.3	0.240	
12-18 vs wisit 0 *12-18 vs wizyta 0*	1.6	-2.4	5.6	0.427	
>18 vs visit 0 *>18 vs wizyta 0*	0.7	-4.1	5.5	0.776	
PEP additional * change in time *PEP dodatkowa* zmiana w czasie*					
for 6 vs visit 0 *do 6 vs wizyta 0*	0.0	-7.0	7.1	0.993	0.3253
6-12 vs visit 0 *6-12 vs wizyta 0*	3.2	-1.8	8.2	0.204	0.4994
12-18 vs wizyta 0	-3.4	-10.1	3.4	0.332	0.5328
>18 vs visit 0 *>18 vs wizyta 0*	1.9	-6.6	10.3	0.664	0.4668

*the difference between the change for the PEP group compared to the change for the no-PEP group.
**różnica pomiędzy zmianą dla grupy z PEP w stosunku do zmiany dla grupy bez PEP.*
**test for total variation in time for the PEP group compared to visit 0
***test dla łącznej zmiany w czasie dla grupy z PEP w stosunku do pomiaru z wizyty 0.*

In the range of FEV_1, in the PEP group, the average value of the ratio was 9.5% lower than in the no-PEP group on visit 0 (p=0.04). In the no PEP group FEV_1 was lower on subsequent visits in relation to visit 0 by an average of 5.5% on the visit in the first half of the follow-up (p=0.019), similar to the visit in the second half (p=0.005). Then it returned to the values of visit 0. The mean FEV_1 was lower by 0.9% and 0.8% respectively, p=0.667, p=0.729) between 12-18 months and at 18 months. In the PEP group, variations over time were the same as in the no-PEP group. Tests for significance of time and PEP treatment interaction, as well as for the group and time total effect proved statistically non significant [Fig. 1, Table IV].

In the range of FVC, similarly to the one for FEV_1, the groups did not differ from each other in terms of the average value of FVC at any of the visits. Changes in FVC over time in any of the groups were not of statistically significant importance (Fig. 2, Table V].

The average value of MEF75% in the PEP group was 14% lower than in the no-PEP group on visit 0 (p=0.029). In the no-PEP group there were no statistically significant differences in the MEF75% variation in successive intervals compared to visit 0. Changes in the PEP group had a slightly different character than in the no-PEP group. There was a systematic increase in the value of MEF75% in each time interval, however, the results were not statistically significant compared to the value of visit 0. In contrast, the differences in the level of change observed between the two groups showed a statistically significant difference in the last interval (p=0.033). In this interval, patients using PEP improved the rate by 8.13% compared to the baseline examination, whereas in the no-PEP group a 6% reduction of MEF75% was observed (Fig. 3, Table VI).

The average value of MEF50% in the PEP group was 15% lower than in the no-PEP group at visit 0 (p=0.018). In the no-PEP group, the average value of MEF50% was significantly lower between 6 and 12 months than the value on visit 0 (p=0.01). The values of this index for the remaining visits were not significantly different from the

Table VI. Comparison of variability of MEF75% in the time and between the group using PEP, as compared to the control group, nonuser of PEP.

Tabela VI. Porównanie zmienności MEF75% w czasie pomiędzy grupą stosującą PEP w stosunku do grupy kontrolnej niestosującej PEP.

MEF75%	β	95% CI dla β		P	P Time+time*PEP** *Czas+czas*PEP***
Visit 0 no-PEP *Wizyta 0 bez PEP*	83.9	75.8	92.1	0.000	
Visit O PEP vs no-PEP *Wizyta 0 PEP vs bez PEP*	-13.9	-26.4	-1.4	0.029	
noPEP for 6 vs visit 0 *bez PEP do 6 vs wizyta 0*	-4.1	-11.6	3.4	0.285	
6-12 vs visit 0 *6-12 vs wizyta 0*	-5.8	-11.7	0.1	0.053	
12-18 vs visit 0 *12-18 vs wizyta 0*	2.9	-3.6	9.5	0.384	
>18 vs visit 0 *>18 vs wizyta 0*	-6.0	-13.8	1.7	0.127	
PEP additional * change in time *PEP dodatkowa* zmiana w czasie*					
for 6 vs visit 0 *do 6 vs wizyta 0*	8.7	-1.6	19.0	0.096	0.1964
6-12 vs visit 0 *6-12 vs wizyta 0*	8.5	-0.1	17.2	0.054	0.4034
12-18 vs wizyta 0	1.4	-9.9	12.6	0.811	0.3574
>18 vs visit 0 *>18 vs wizyta 0*	14.2	1.2	27.2	0.033	0.1274

*the difference between the change for the PEP group compared to the change for the no-PEP group.
**różnica pomiędzy zmianą dla grupy z PEP w stosunku do zmiany dla grupy bez PEP.*
**test for total variation in time for the PEP group compared to visit 0
***test dla łącznej zmiany w czasie dla grupy z PEP w stosunku do pomiaru z wizyty 0.*

value on visit 0. In the PEP group MEF50% remained at a similar level in the observation periods up to 6 months, between 6-12 months and between 12-18 months. Only after 18 months, was there an increase of the test ratio 10.42% relative to baseline examination. The result, however, was not statistically significant (p=0.056). Comparison of the differences in the changes observed between the two groups showed a statistically significant difference in the last interval (p=0.019) (Fig. 4, Table VII).

The average value of MEF25% in the PEP group was nearly 13% lower than in the no PEP group on visit 0 (p=0.019). In the no PEP group for three consecutive visits (for up to 6 months, between 6-12 months, and between 12-18 months), the average value of MEF25% was significantly lower than the value on visit 0 (p=0.046, p=0.013 and p=0.009). On the visit after 18 months, the average value of MEF25% approached the value of visit 0 (p=0.107). In the PEP group, the course of MEF25% changes was slightly different than in the no-PEP group. On visits undertaken in the first 6 months and between 12-18 months, the average values of MEF25% were similar to those of visit 0. In the intervals between 6-12 months and after 18 months, the average value of MEF25% was 3.9% and 12.9% higher compared to visit 0 respectively. After 18 months, the value of this index was higher than the value on visit 0 (p=0.022) in a statistically significant way. The comparison of differences in the level of change observed between the two groups showed statistically significant differences between 6-12 months and in the last interval (p=0.034, p=0.019) (Fig. 5, Table VIII).

DISCUSSION

A long-term evaluation of the test results is difficult in cystic fibrosis, because of the progressive and diverse character of the disease and frequent bronchopulmonary exacerbations, which periodically result in significantly lower values of spirometry and affect the unstable curves showing the variation in spirometric indices in time. Nevertheless, results obtained on the basis of a retrospective study, indicate

Table VII. Comparison of variability of FEV1 in time and between the group using PEP, as compared to the control group, nonuser of PEP.

Tabela VII. Porównanie zmienności FEV1 w czasie pomiędzy grupą stosującą PEP w stosunku do grupy kontrolnej niestosującej PEP.

MEF50%	**β**	**95% CI dla β**		**P**	**P Time+time*PEP** *Czas+czas*PEP***
Visit 0 no-PEP *Wizyta 0 bez PEP*	72.9	63.9	82.0	0.000	
Visit O PEP vs no-PEP *Wizyta 0 PEP vs bez PEP*	-15.1	-27.5	-2.6	0.018	
noPEP for 6 vs visit 0 *bez PEP do 6 vs wizyta 0*	-7.1	-15.0	0.8	0.080	
6-12 vs visit 0 *6-12 vs wizyta 0*	-8.7	-15.3	-2.1	0.010	
12-18 vs visit 0 *12-18 vs wizyta 0*	-2.6	-10.0	4.8	0.488	
>18 vs visit 0 *>18 vs wizyta 0*	-4.7	-11.3	2.0	0.168	
PEP additional * change in time *PEP dodatkowa* zmiana w czasie*					
for 6 vs visit 0 *do 6 vs wizyta 0*	6.8	-4.0	17.7	0.216	0.9448
6-12 vs visit 0 *6-12 vs wizyta 0*	9.6	0.2	19.0	0.046	0.8035
12-18 vs wizyta 0	1.3	-9.6	12.3	0.809	0.7601
>18 vs visit 0 *>18 vs wizyta 0*	15.1	2.5	27.6	0.019	0.0557

*the difference between the change for the PEP group compared to the change for the no-PEP group.
**różnica pomiędzy zmianą dla grupy z PEP w stosunku do zmiany dla grupy bez PEP.*
**test for total variation in time for the PEP group compared to visit 0
***test dla łącznej zmiany w czasie dla grupy z PEP w stosunku do pomiaru z wizyty 0.*

a favorable change in the average values of spirometric indices occurring in patients using PEP in inhalation compared with those not applying PEP. Statistically significant differences were observed in the change level of MEF75%,50%,25% between the groups after 18 months and between 6-12 months for MEF25%. The results do not show the whole process of change in patients with cystic fibrosis. Cystic fibrosis is a progressive disease and, although progression is characterized by different dynamics in different patients, a gradual decrease in spirometric values of all patients with CF over the years has been observed. In our study, we observed a tendency to lower the assessed value of spirometric indices in patients not applying PEP at the time when patients using PEP observed an upward trend. Given the worse clinical condition of patients using PEP compared to no PEP patients and the progressive nature of the disease, the results can be considered beneficial.

There is a small number of articles relating to the efficacy of increased expiratory pressure applied on inhalation. The majority of these papers concern cystic fibrosis and COPD patients. Frischknecht-Christensen et al. applied PRP in inhalation with β2-agonists in patients suffering from bronchial asthma. Two two-week periods of terbutaline were administered. In the first period, inhalations with PEP were applied, in the second one, inhalations were carried out without PEP. The surveys demonstrated the increase of values of peak exhalation flow (PEF) after PEP inhalation in comparison with no-PEP inhalation ($p<0.0001$)[13]. Andersen and Klausen applied PEP during the nebulization of a drug dilating bronchioles in 8 patients with acute respiratory insufficiency due to the severe contraction of their bronchioles. Each patient underwent two nebulizations with PEP and two nebulizations without this appliance. The time interval between drug administration amounted to three hours. The statistically significant ($p<0.005$) growth of FEV_1, FVC and PEF was observed after nebulization with the application of PEP [12]. For three months Oisin used

Table VIII. Comparison of variability ofMEF25% in time and between the group using PEP, as compared to the control group, nonuser of PEP.

Tabela VIII. Porównanie zmienności MEF25% w czasie pomiędzy grupą stosującą PEP w stosunku do grupy kontrolnej niestosującej PEP.

MEF25%	**β**	**95% CI dla β**		**P**	**P Time+time*PEP** *Czas+czas*PEP***
Visit 0 no-PEP *Wizyta 0 bez PEP*	53.7	46.5	60.8	0.000	
Visit O PEP vs no-PEP *Wizyta 0 PEP vs bez PEP*	-12.6	-23.1	-2.1	0.019	
noPEP for 6 vs visit 0 *bez PEP do 6 vs wizyta 0*	-7.6	-15.2	-0.1	0.046	
6-12 vs visit 0 *6-12 vs wizyta 0*	-7.5	-13.4	-1.6	0.013	
12-18 vs wisit 0 *12-18 vs wizyta 0*	-7.4	-13.0	-1.9	0.009	
>18 vs visit 0 *>18 vs wizyta 0*	-4.5	-10.0	1.0	0.107	
PEP additional * change in time *PEP dodatkowa* zmiana w czasie*					
for 6 vs visit 0 *do 6 vs wizyta 0*	7.5	-2.8	17.8	0.153	0.9703
6-12 vs visit 0 *6-12 vs wizyta 0*	11.4	0.8	21.9	0.034	0.3858
12-18 vs wizyta 0	8.3	-0.6	17.1	0.068	0.8164
>18 vs visit 0 *>18 vs wizyta 0*	17.4	5.1	29.8	0.006	0.0224

*the difference between the change for the PEP group compared to the change for the no-PEP group.
**różnica pomiędzy zmianą dla grupy z PEP w stosunku do zmiany dla grupy bez PEP.*
**test for total variation in time for the PEP group compared to visit 0
***test dla łącznej zmiany w czasie dla grupy z PEP w stosunku do pomiaru z wizyty 0.*

PEP during inhalations with 6% hypertonic saline in 4 cystic fibrosis patients at the advanced stage of the disease. These patients did not tolerate hypertonic saline administered with a Jet nebulizer. Before inhalations, they administered albuterol by inhalation (100g/inhalation). The author observed their absolute tolerance of hypertonic saline during the whole observation period and 137 after the test completion. Also the periods between bronchopulmonary exacerbations were 3.6 times longer in comparison with the pre-examination period and the cough, thoracic pressure sensation, as well as sore throat symptoms became less intensive [15]. In turn, Laube et.al, applied PEP for inhalation with saline and technetium 99m medical radioisotope in 8 cystic fibrosis patients. Then, with the use of a gamma camera, they followed the aerosol's decomposition in the lungs. They demonstrated that during PEP supported inhalation, a significantly smaller amount of aerosol was deposited in the lungs in comparison with the procedure without this appliance [4, 13]. In their paper, Laube et al. suggested that on application of PEP, a better distribution of aerosol in peripheral bronchioles depends on the kind of drug administered and the severity of the disease.

It seems that in our study, maximum expiratory flow (MEF) improvement in cystic fibrosis patients in whom PEP was applied in mucolytic drug inhalation procedures, could have been influenced by the recovery of peripheral bronchiole ventilation and consequently the aerosol's better distribution in worse-ventilated, diseased, pulmonary areas. MEF75%,50%,25% is a factor evaluating the peripheral bronchi and bronchioles. In cystic fibrosis patients, abnormalities in peripheral bronchioles appear early with FEV1 and FVC normal values. This was regularly observed in our survey as well [Table II].

It is too early to recommend PEP standard application in cystic fibrosis patients, as it would call for long-term randomized observations, which could confirm retrospective study results.

CONCLUSIONS

1. The PEP system may be applied in mucolytic drug inhalations in cystic fibrosis patients.
2. The application of the PEP system in inhalations in cystic fibrosis patients mostly influenced the improvement of MEF75%50%25% values.
3. The application of the PEP system in mucolytic drug inhalations in cystic fibrosis patients may be one of the factors inhibiting the progress of pulmonary functional lesions.
4. Long-term randomized observations should be carried out in order to confirm retrospective study results

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Conflicts of interest/Konflikt interesu
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