The improving of ventilometric indices using Airway Clearance Techniques Asociated with Inhalation Therapy applied to adolescents with cystic fibrosis

Bogdan Almăjan-Guţă[1], Claudiu Avram[2], Violeta Almăjan-Guţă[3], Lucian D. Hoble[4], Alexandra M. Rusu[3], Ornela O. Cluci[3]

Abstract

Introduction: this study gave particular attention to respiratory damage, lung disease being the main target for developing therapies in MV. *The purpose* of this study was to demonstrate the efficiency of Classical Respiratory clearance techniques combined with Inhalation Therapy and to compare the results of using acetylcysteine with those of using Pulmozyme Therapy. Aerosol (inhalation therapy) is, along with exercise and respiratory clearance techniques, the third component in the physiotherapy of patients with CF. *Material and method:* the study was developed during a period of six months, in The National Center of Cystic Fibrosis, Clinic II of Pediatrics in the Emergency County Hospital, Timisoara. The study group consisted of 12 children with MV . This group was divided into two groups of 6 patients (group 1 and group 2). Group 1 followed inhalation treatment with acetylcysteine, and group 2 with Pulmozyme. *Results:* The evaluation of the results was done after 2 months and 6 months since the study started, by measuring the FEV, and FVC. For the first group, that used acetylcysteine in the inhalation therapy, we observed, after 6 months, an increase of FEV with an average of 2.08% and of FVC with 2.13%.The growth of ventilometric indices were relatively accelerated in the first two months and later there was a slower growth, achieving final value. For the second group, that used Pulmozyme, the growth of ventilometric indices was significantly higher. *Discussion:* considering the two relatively homogeneous groups, in what concerns the values of ventilometric indices and superimposed infection, we believe that inhaled Pulmozyme therapy proved to be superior to acetylcysteine. *Conclusions:* inhalation therapy is an important part of physiotherapy for patients with cystic fibrosis. A consistent physiotherapy is probably the most important element in preventing chronic pulmonary infection and, along with antibiotherapy, improves significantly the prognosis and helps achieving a life quality as close to normal

Key words*: : Pulmozyme, Classical Respiratory clearance techniques, cystic fibrosis, ventilometric indices, inhalation therapy*

Acknowledgement: *This paper work was supported by a research grant from CNCSIS RO, TE/ Code 36.*

[1] Lecturer PhD, Politechnik University of Timişoara, *e-mail: bogdan.almajan@efs.upt.ro*
[2] Assist. Lecturer PhD MD, Physical Education and Sport Faculty, West University from Timişoara
[3] Physical therapist, "Speranţa" Educational Asssitance and Resources Center, Timişoara
[4] Master student, Physical Education and Sport Faculty, West University from Timişoara

Rezumat

Introducere: acest studiu a acordat atenție în special afectării aparatului respirator, boala pulmonară fiind ținta principală pentru dezvoltarea terapiilor în mucoviscidoză (MV). S*copul* acestui studiu a fost de a demonstra eficiența tehnicilor clasice de clearance in combinatie cu aerosoloterapia şi de a comparara rezultatele utilizării acetilcisteinei cu cel al terapiei cu Pulmozyme. Aerosoloterapia reprezintă, alături de exercițiul fizic şi tehnicile de clearance respirator, a treia verigă în fizioterapia bolnavilor cu MV. *Material şi metodă:* studiul s-a derulat pe un interval de 6 luni. Lucrarea a fost efectuată în cadrul Clinicii II Pediatrie şi a Centrului de Mucoviscidoză Timişoara.Lotul de studiu a fost format din 12 copii cu Muciviscidoză. Acest grup a fost împărțit în două subgrupuri a câte 6 bolnavi. Grupul 1 a urmat tratament inhalator cu acetilcisteină, iar grupul 2 Pulmozyme. *Rezultate:* evaluarea rezultatelor s-a realizat la 2 luni şi la 6 luni de la inițierea aerosoloterapiei prin măsurarea VEMS şi CVF (Fig. 2, 3):La primul grup, la care în terapia inhalatorie am utilizat acetilcisteină am observat o creştere a VEMS-ului la 6 luni, în medie de 2,08% şi a CVF de 2,13%. Creşterea indicilor ventilometrici a fost relativ mai accentuată în primele 2 luni, pentru ca ulterior creşterea să fie mai lentă, până la valoarea de final. La bolnavii din grupul 2, care au primit în tratament Pulmozyme, creşterea indicilor ventilometrici a fost semnificativ mai mare. *Discuții* În contextul în care am încercat să avem două loturi relativ omogene, atât ca valori ale indicilor ventilometrici, cât şi a infecției supraadăugate, considerăm că terapia inhalatorie cu Pulmozyme s-a dovedit net superioară terapiei cu acetilcisteină. *Concluzii*: aerosoloterapia reprezintă o componentă importantă în fizioterapia bolnavilor cu muucoviscidoză. O fizioterapie consistentă şi adevărată este probabil cel mai important factor în prevenirea unei infecții pulmonare cronice şi adăugată antibioterapiei ajută la ameliorarea semnificativă a prognosticului şi la menținerea la o perioadă cât mai lungă a unei calități a vieții cât mai apropiată de normal.

***Cuvinte cheie**: Pulmozyme, mucoviscidoza, tehnici clasice de clearence respirator, indici ventilometrici, terapie inhalatorie*

***Finanțare:** Realizarea acestei lucrări a fost susținută financiar cu ajutorul grantului de cercetare CNCSIS RO, TE/cod 36.*

Introduction

Mucoviscidosis (MV) disease or cystic fibrosis is the human chronic diseases most recently recognized as being the most common monogenic disease of the Caucasian population, with fatal potentiality and an incidence of 1:2000 - 1: 2500 new born.
This study gave particular attention to respiratory damage, lung disease being the main target for developing therapies in MV.

The improvement of bronchial secretion clearance using physiotherapy and specific exercise is the primary aim for people with CF due to its efficiency, low cost compared with other components of the therapeutic strategy and is accessible for all socio-economic levels.

The purpose of this study was to demonstrate the efficiency of Classical Respiratory clearance techniques combined with Inhalation Therapy and to compare the results of using acetylcysteine with those of using Pulmozyme Therapy. Aerosol (inhalation therapy) is, along with exercise and respiratory clearance techniques, the third component in the physiotherapy of patients with CF. It is an important way for assimilating anti-inflammatory drugs (anti-inflammatory steroids), bronchodilators, antibiotics and Mucolytics medication in particular**.** (Tabels I and II). Therapy inhalation is, along with exercise and respiratory clearance techniques, the third component in the physiotherapy of patients with MV.

Tabel I. Group 1 – Inhalation Therapy with Acetylcysteine

Initials of Name /First name	Infection	FEV	FVC
Z. F.	Stafilococcus aureus	58%	72%
F. C.	Stafilococcus aureus	59%	84%
H. L.	Stafilococcus aureus	62%	86%
F. A.	Pseudomonas aeruginosa	60%	78%
K. S.	Pseudomonas aeruginosa	59%	84%
S.C.	Pseudomonas aeruginosa	79%	112%

Tabel II. Group 2 – Inhalation Therapy with Pulmozyme

Initials of Name /First name	Infection	FEV	FVC
M.N.	Stafilococcus aureus	63%	76%
G. L.	Stafilococcus aureus	68%	72%
C.A.	Stafilococcus aureus	74%	86%
G.A.	Pseudomonas aeruginosa	55%	78%
N.A.	Pseudomonas aeruginosa	48%	72%
T.G.	Pseudomonas aeruginosa	50%	68%

Aerosol (inhalation therapy) is, along with exercise and respiratory clearance techniques, the third link /component in the physiotherapy of patients with MV. It is an important way for assimilating anti-inflammatory drugs (anti-inflammatory steroids), bronchodilators, antibiotics and Mucolytics medication in particular (1.2). The shown that reduces airway inflammation (10). The airways of patients with CF contain a large amount of inflammation mediators, mucus, cytoplasmic DNA resulted from the destruction of neutrophils in inflammation process and bacteria. Pacient s level of cytoplasmic DNA is 3 to 5 times higher than the level of free subjects and increases with age. The DNA resulted from the destruction of neutrophils increases significantly the sputum viscosity and also determines the hinder of its removal by clearance mechanisms.

Recombinant human Dezoxiribonucleaza (Pulmozyme) is a therapeutic modality in recent MV, targeting at precisely this DNA leukocyte cytoplasmic cleavage (9). This ensures a high degree of sputum fluidity, providing the possibility of achieving its optimum clearance. It was also shown that reduces airway inflammation (10).

Material and Method

The study was developed during a period of six months, in The National Center of Cystic Fibrosis, Clinic II of Pediatrics in the Emergency County Hospital, Timisoara. The study group consisted of 12 children with MV (6 girls and 6 boys). This group was divided into two groups of 6 patients (group 1 and group 2).

Each group consisted of three patients infected with Staphylococcus aureus coagulase positive and 3 patients with Pseudomonas aeruginosa infection.

Inclusion criteria were:

- Stable pacients (outside the periods of exacerbation)
- Age over 12 years
- FEV > 45%

- FVC > 50%
- pacient without mixt infection: Ps aer.+ coagulase positive Staphylococcus aureus.

All pacients followed the same phisiotherapy conditions using Airway Clearance Techniques

1. Active Cycle of Breathing Techniques (ACBT)
2. Autogenic Drainage (AD)
3. Postural drainage

Group 1 followed inhalation treatment with acetyl-cysteine (Fluimucil) and group 2 with recombinant human dezoxiribonucleaza (Pulmozyme). Starting from literature references we initiated a study to prove the efficiency of Inhalation Therapy with Pulmozyme applied on selected group of pacients with MV.

Presentation and administration of Mucolytics:

- Acetylcysteine (Fluimucil or ACC 200,3 ml ampoules of 300 mg) was administered in two sessions, morning and evening, before session of physiotherapy.
- Pulmozyme (ampoules of 2.5 and 2500 IU) was administrated in a single session in the morning before physiotherapy. The treatment was provided by National Health Program No 3, Timisoara Center Cystic fibrosis being the Technical Coordinator on the issue of cystic fibrosis in the country plan.
- For both situation was used as a device a nebulization system “Pary Boy” air jet (figure 1), each patient used a particular nebuliser system. Most instruments were obtained through donation (Charitable Society Deutsche Rote Kreuz "and company Hoffmann La Roche)
- An aerosol session lasted 10 to 15 minutes up to 20 minutes, depending on patient compliance
- Patients were instructed regarding proper drug administration and the maintenance of nebuzation system
- Mucolytics inhalation therapy was performed before clearance techniques, and in case of administration of antibiotics, was made later. Recombinant human dezoxiribonucleza (Pulmozyme®) was used in the inhalatory therapy of selected cases according to standardized criteria.

Figure 1. Aerosol administration with Pari Nebulizer System (Z.F., 18 years, compound heterozygous genotype Δ F508)

Statistical analysis was performed using a specialized program (Statistics ver. 6.0). Considering the small number of subjects (N <30), we used a non-parametric Wilcoxon test for comparison (Wilcoxon matched pairs test).

This test evaluated treatment effectiveness by comparing ventilometric indices (FEF 25% -75%, FEV, and FVC) before and after the treatment.

For the whole group the datas were analyzed using the same test (Wilcoxon matched pairs test) but using another statistical program (Graph PadPrism).

Results

The evaluation of the results was done after 2 months and 6 months since the study started, by measuring the FEV, and FVC (figures 2, 3).

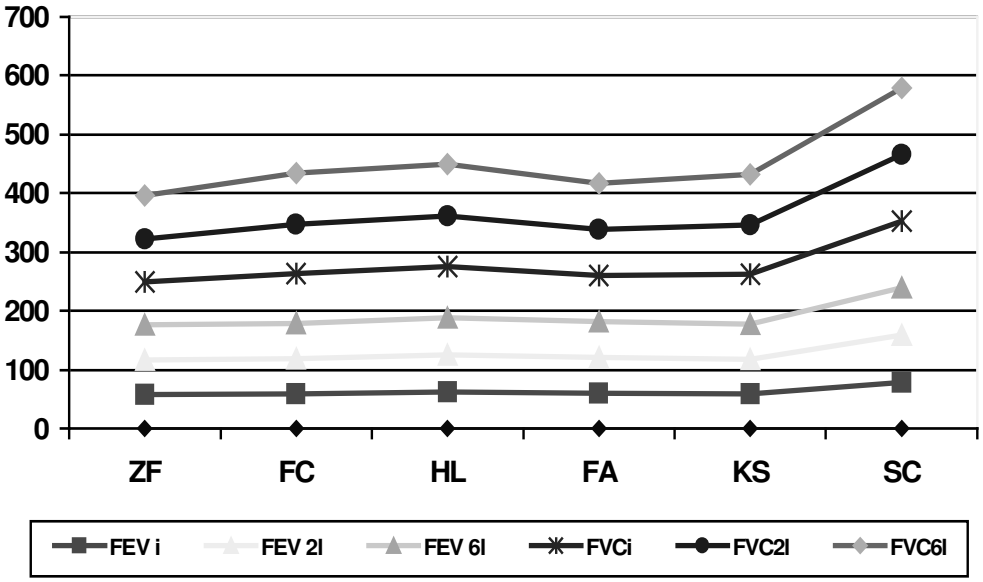

Figure 2. The evolution of ventilometric indices – aerosols with acetylcisteyne

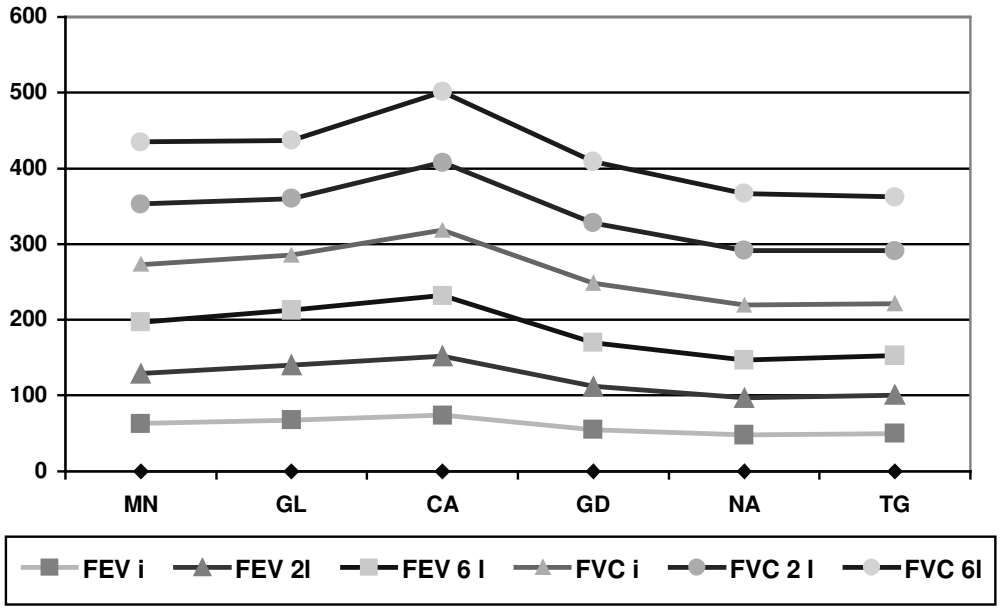

Figure 3. The evolution of ventilometric indices – aerosols with Pulmozyme

For the first group, that used acetylcysteine in the inhalation therapy, we observed, after 6 months, an increase of FEV with an average of 2.08% and of FVC with 2.13%.

The growth of ventilometric indices was relatively accelerated in the first two months, and later there was a slower growth, achieving final value. The answer to inhalation therapy was equally sensitive both for patients infected with Staphylococcus aureus and for those infected with Pseudomonas aeruginosa.

For the second group, that used Pulmozyme, the growth of ventilometric indices was significantly higher.

After six month FEV has grown with an average of 6,1% . Also FVC has grown with an average of 5,8%. It is important that we notice the increase of 4.8% for FEV and 4,1% for FVC in the first two months. Over the next four months the growth of ventilometric indices was much slower (only 3% to FEV 1.7% to FVC).

Another observation is related to higher therapeutic benefit for patients infected with Staphylococcus aureus compared with those infected with Pseudomonas aeruginosa. The difference was 3,3% to FEV and 3,2% to FVC.

For proper comparison we used non-parametric test for independent groups Kolmogorov-Smirnov (figure 4.).

The results were statistically significant (p = 0.03). The results of statistical analysis indicate significant differences (p <0.05) before and after treatment.

- FEF $_{25\%-75\%}$: Z = 4,01, p= 0,02
- FEV: Z= 4,11, p= 0,01
- FVC: Z= 3, 62, p= 0,03

Ventilometric indices showed significant improvements for the whole group, as figures 5, 6 and 7 illustrate. Data are presented as mean ± standard deviation. The results of statistical analysis indicate significant differences (p <0.05) before and after treatment.

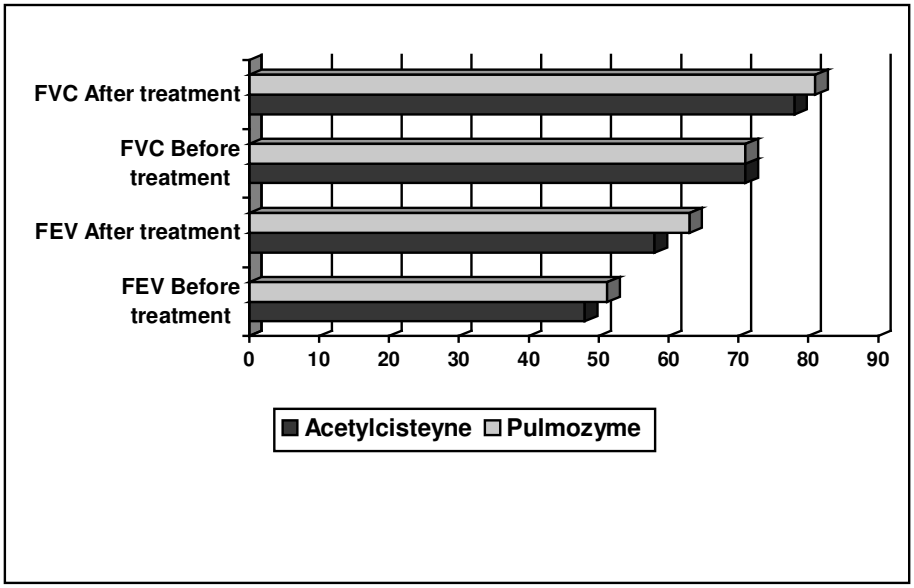

Figure 4. Comparative evolution of the studied groups

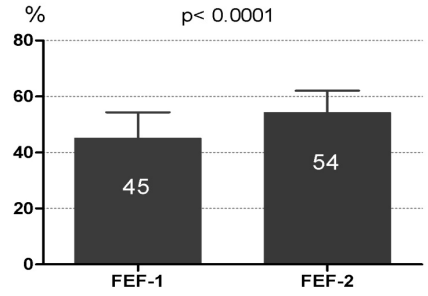

Figure 5. FEF evolution after inhalation therapy

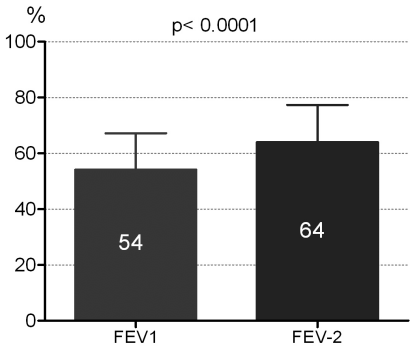

Figure 6. FEV evolution after inhalation therapy

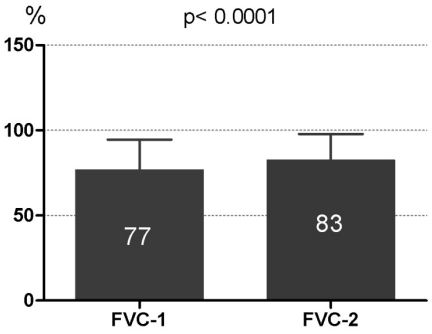

Figure 7. FVC evolution after inhalation therapy

Discussion

Considering the two relatively homogeneous groups, in what concerns the values of ventilometric indices and superimposed infection, we believe that inhaled Pulmozyme therapy proved to be superior to acetylcysteine. However, we can notice that the results of thoese infected with Staphylococcus aureus were better than of those infected with Pseudomonas aeruginosa. It is likely that pacients wich are not infected had better results, which implies the need of Inhalation Therapy since diagnosis, before respiratory infection appeares. The inhalation therapy should be done continuously, as part of physical therapy program, along with exercise and clearance techniques. Studies in this field will indicate whether the current recommendations for using Pulmozyme prior to clearance techniques remain valid, or it will prove that administration is more efficient after these techniques.

Conclusions

Inhalation therapy is an important part of physiotherapy for patients with mucoviscidosis. Inhalation therapy with recombinant human deoxyribonuclease (Pulmozyme), compared with acetylcysteine (Fluimucil), the drug currently most affordable in our country, was clearly superior for improving ventilatory parameters, even for pacients with respiratory infection with Pseudomonas aeruginosa.

Thus, the use of a non-parametric statistical comparison for independent groups showed that differences were significant ($p=0.03$). A consistent physiotherapy is probably the most important element in preventing chronic pulmonary infection and, alog with antibiotherapy, improves significantly the prognosis and helps achieveing a life quality as close to normal.

References

1. Almăjan-Guță B. (2006) *Îmbunătățirea calității vieții copiilor cu mucoviscidoză (fibroză chistică) prin fiziokinetoterapie*, Ed. Mirton, Timişoara;
2. Fitzgerald D.A., Hilton J., Jepson B., Smith L. (2005) *A crossover, randomized, controlled trial of dornase alfa before versus after physiotherapy in cystic fibrosis,* Chest 128: 2327-2335;
3. Button B.M., Heine R.G., Catto-Smith A.G., Phelan P.D. et al (2004) *Chest physiotherapy, gastro-oesophageal reflux, and arousal in infants with cystic fibrosis,* Arch Dis Child, May;89(5):435-9;
4. Ayres S.M., Kozam R.L., Lukas D.S. (1963) *The effects of intermittent positive pressure breathing on intrathoracic pressure, pulmonary mecanics and the work of breathing*, Am Rev. Resp. Dis., 87, 370-379;
5. Barak A., Wexler I.D., Efrati O., Bentur L., Augarten A., Mussaffi H., Avital A., Rivlin J., Aviram M., Yahav Y., Kerem E. (2005) *Trampoline use as physiotherapy for cystic fibrosis patients*, Pediatr Pulmonol 2005 Jan;39(1):70-3;
6. Barker M., Hebestreit A., Gruber W., Hebestreit H. (2004) *Exercise testing and training in German CF centers*, Pediatr Pulmonol, Apr; 37(4):351-5;
7. Borsje P., de Jongste J.C., Mouton J.W., Tiddens H.A. (2000) *Aerosol therapy in Cystic Fibrosis: a survez of 54 centers*. Pediatric-Pulm., 30: 368-378;
8. Băiescu M.L. (2003) *Ghid de explorări funcționale ventilatorii*, Ed. Risoprint, Cluj-Napoca;
9. Kerem P. et al (2005) *Standards of care for patients with cystic fibrosis: a European consensus*, Journal of cystic Fibrosis, 4, 7-26;
10. Popa I., Pop L. (1993) *Aspecte ale mucoviscidozei la adult, capitol in Actualitati in Medicina Interna* (sub red Gh.Gluhovsci) Ed Helicon, Timişoara, 486-508;
11. Popa I., Pop L. (1997) *Mucoviscidoza (fibroza chistică)* , capitol în *Pediatria*, Tratat, editia I, sub redactia, Ciofu E.P., Ciofu. C., Ed.Medicală, 1388-1405;
12. Price J.F., Greally P. (1993) *Corticosteroid treatment in cystic fibrosis*, Arch. Dis. Child., 68, 719-721;
13. Taussig L.M., Kattwwinkel J., Friedwald W.T. and Di Sant Agnese P.A. (1973) *A new prognostic score and clinical evaluation system for cystic fibrosis*, J. Pediatr., 82;
14. Wood J. (1996) *Nebulization, Practical guidelines for the use of nebulizers in cystic fibrosis.* Association of Charted Physiotherapists with an interest in CF and CF Nurse Specialists Group.