Spirometry and impulse oscillometry during acute pulmonary exacerbation hospitalization in children with cystic fibrosis

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ABSTRACT

Objective: Evaluate the respiratory system parameters of children with cystic fibrosis (CF) during hospitalization for acute pulmonary exacerbation (APE) treatment. **Methods:** observational study before-after that occurred at the CF reference center. There were included children with cystic fibrosis (CF) between six to 15 years old hospitalized due to APE. The registration of the APE clinical scores, anthropometric data, and respiratory system (IOS and spirometry) evaluation occurred at the beginning (T1), during (T2), and at the end (T3) of the hospitalization. There were registered pathogens, genetic mutation, disease severity (Schwachman-Doershuk Score), and the most recent spirometry when they were clinically stable. The Shapiro-Wilk test was applied to analyze data distribution, and the repeated measure ANOVA, Friedman test, Tpaired test, and Wilcoxon test were performed to compare data, with a significance level set at 5%. **Results:** sixteen children/adolescents participated in the study (68.8% girls, 12.88±1.67 years old). The spirometric parameters, X5 parameter, and anthropometric data increased ($p<0.005$) and the APE scores decreased ($p<0.005$) at T3. **Conclusion:** APE scores, anthropometric data, spirometric parameters, and IOS elastic recoil parameter (X5) improved at the end of hospitalization.

Keywords: Cystic fibrosis, Symptom flare up, Respiratory function tests, Respiratory mechanics.

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https://doi.org/10.11606/issn.2176-7262.rmrp.2022.183755

INTRODUCTION

Inflammation and recurrent infections in individuals with cystic fibrosis (CF) lead to alterations in pulmonary tissue, airway structure, and mechanics.[1,2] Those are associated with acute worsening of respiratory symptoms, also known as acute pulmonary exacerbation (APE).[1,2] This condition is characterized by an increase in coughing and sputum, superficial breathing, weight loss, exercise intolerance, and a decrease in pulmonary function.[3] The treatment consists of antibiotics administration, physiotherapy, osmotic and mucolytic agents inhalation, and increased nutritional support.[3,4]

Forced expiratory volume in one second (FEV_1) measured by spirometry is an important clinical marker and indicator of therapeutic response as long as to identify APE in CF follow-up.[4] Complementary to spirometry, the impulse oscillometry system (IOS) evaluates airway resistance and compliance and could analyze these elements' behavior during APE.[5,6] Some studies analyzed spirometric and oscillometric parameters, although they have shown controversial results, especially the X5 parameter.[5,7,8]

Despite improvement in FEV_1 during APE treatment being well established in scientific literature, in clinical practice, this parameter is not used to evaluate therapeutic response. Therefore, it is important to assess this spirometric parameter and the IOS parameters, foregrounding the X5. This variable may indicate impairment in the peripheral pulmonary region, one of the most affected during APE.

Facing the exposed, this study aimed to evaluate respiratory system parameters behavior during intravenous antibiotic therapy (IAT) as APE treatment in children with CF.

METHOD

Before-after observational analytical study (before and after IAT) performed in CF reference center in Florianópolis, Santa Catarina – Brazil between September 2017 to July 2019. It was approved by the reference center´s Ethics Committee in Research (research and ethics committee) (CAEE: 80800217.4.0000.5361). All children and their parents signed the Informed Consent Term and Informed Assent. This study was also approved by The Brazilian Clinical Trials Registry (REBEC), under the number RBR-489ww6.

Schoolchildren between six to 15 years old with CF[4] participated in this study. Those children that were in the first 72 hours of hospitalization, using IAT, showed a score $\geq$ 25 in Cystic Fibrosis Clinical Score (CFCS) [9] and a score $\geq$ 4 in Cystic Fibrosis Foundation Score (CFFS) [10] were eligible.

The data collection occurred in three moments: at the beginning (T1), during (T2), and at the end (T3) of hospitalization lasting about 14 days. In every moment it has been established 72 hours to collect data. There was register the CFCS, CFFS, and anthropometric data. Then there was performed the respiratory system evaluation through pneumatograph Master Screen IOS (Erich Jaeger, Würtzburg, Germany®) according to the ATS recommendation for IOS[11] and spirometry,[12] in this order. Also, at the medical record was register the most recent spirometry parameters when children were clinically stable (T0), pathogens, genotype, and disease severity according to Schwachman-Doershuk score (SDS).[13]

The oscillometric parameters analyzed were: the impedance at 5Hz (Z5), total (R5) and central (R5) airway resistance, and reactance at 5Hz (X5), which are presented in absolute and predicted percentage values, the last one according to Assumpção et al.[14] The spirometric parameters analyzed were: FVC, FEV_1, peak expiratory flow (PEF) and FEF_{25-75} presented in absolute and predicted percentage values (%), according to Polgar et al.[15] and Knudson et al.[16]

Collected data were analyzed through *IBM SPSS*-20.0© software, and at first, it was performed the Shapiro-Wilk test. In order to analyze FVC% and FEV_1% between the moments T0, T1, and T3 there was applied the repeated measures ANOVA with Bonferroni post-hoc, and the Friedman test. Also, there was applied the paired T-test and Wilcoxon between T1 and T3 moments for other parameters. The significance level was set at 5%. The sample power was analyzed through the FEV_1% parameter in G*Power software. A sample of 16 individuals with an effect size of 0.88 in a two-tailed and paired means comparison test calculated a sample power of 0.93.

RESULTS

Twenty children were considered eligible to participate in the study; however, it was not possible to collect data at the end of the hospitalization from four of them, then they were excluded. Therefore, sixteen children participated in the evaluation protocol. Also, there were registered IOS parameters from eleven children. The sample characteristics are in table 1. At the end of the hospitalization the spirometric parameters decreased, on the other hand, the oscillometric parameters showed no statistical difference despite numerically presented improvement between T1 and T3 (Table 2).

The anthropometric data and APE scores (T1xT3) also showed a positive response to the treatment ($p<0.005$), data are presented in table 3.

Table 1. Sample characteristics

Variables	Sample (N=16)
Age (years)	12.88±1.67 13.0[3.0]
Days of hospitalization	13.63±0.81 14.0[0.0]
FEV_1% in T0	29.36±13.58 25.65[14.16]
Female N(%)	11 (68.8)
SDS classification N(%)	
Excellent	1 (6.3)
Good	3 (18.8)
Average	4 (25.0)
Poor	8 (50.0)
Genotype N(%)	
F508del homozygous	0 (0.0)
F508del heterozygote	6 (37.5)
Other mutations	10 (62.5)
Pathogens N(%)	
Pseudomonas aeruginosa	10 (62.5)
Staphylococcus aureus	5 (31.3)
Burkholderia cepacia	10 (62.5)

Legend: Data are presented in mean±standard deviation and median[interquartile range]; N: sample number; %: sample percentage; FEV_1%: forced expiratory flow in one second percentage; T0: clinically stable; SDS: Schwachman-Doershuk score; F508del: genetic mutation.

Table 2. Spirometric and oscillometric parameters during hospitalization to treat APE.

Spirometry	*FVC (L)^F*	*FVC%^{A}*	*FEV_1 (L)^F*	*FEV_1%^{F}*	*PEF (L)^W*	*PEF%^{T}*	*FEF_{25-75} (L)^W*	*FEF_{25-75}%^{W}*
T0 (N=16)	1.04±0.46*# 0.86[043]	40.92±15.18^I 38.58[18.0]	0.69±0.35# 0.57[0.26]	29.36±13.58# 25.65[14.16]	--	--	--	--
T1 (N=16)	1.0±0.30$ 0.89[0.47]	39.12±8.34^{II} 36.81[13.60]	0.61±0.23$ 0.54[0.36]	25.46±8.0$ 24.96[15.68]	1.56±0.83 1.45[1.03]	28.08±14.07 28.25[17.82]	0.34±0.22 0.25[0.37]	11.85±8.51 9.35[10.43]
T2 (N=12)	1.10±0.31 0.97[0.52]	44.94±11.31 41.65[21.35]	0.62±0.23 0.56[0.22]	28.23±11.18 26.30[13.57]	1.48±0.67 1.30[0.49]	28.86±14.12 26.70[11.73]	0.31±0.31 0.15[0.32]	11.47±11.38 5.55[13.20]
T3 (N=16)	1.28±0.47 1.15[0.73]	50.02±13.33 50.85[28.13]	0.84±0.39 0.71[0.53]	35.72±13.34 33.50[20.13]	2.23±1.13 1.74[1.14]	40.44±16.80 33.60[27.23]	0.53±0.44 0.29[0.62]	18.04±14.75 11.85[17.36]
p-value	0.001	0.001	0.001	0.002	0.013	0.008	0.034	0.044
IOS	***Z5^T***	***Z5%^{T}***	***R5^T***	***R5%^{W}***	***R20^T***	***R20%^{T}***	***X5^T***	***X5%^{W}***
T1 (N=11)	1.03±0.31 0.91[0.52]	256.69±72.66 250.0[146.78]	0.91±0.26 0.88[0.43]	161.78±43.0 157.14[59.61]	0.51±0.10 0.48[0.18]	111.24±24.92 100.0[45.20]	-0.48±0.20 -0.50[0.33]	370.52±135.25 414.28[189.01]
T2 (N=9)	1.02±0.33 1.03[0.34]	173.18±54.88 169.64[49.09]	0.90±0.31 0.83[0.36]	151.67±50.71 148.21[45.09]	0.50±0.07 0.49[0.05]	106.68±21.08 106.98[23.61]	-0.48±0.16 -0.54[0.26]	327.02±108.63 300.0[190.66]
T3 (N=11)	0.90±0.37 0.88[0.75]	216.66±68.55 189.65[138.25]	0.82±0.34 0.82[0.65]	145.10±55.45 134.43[104.0]	0.50±0.10 0.52[0.17]	109.75±25.79 105.66[54.52]	-0.36±0.15 -0.33[0.21]	263.69±84.66 242.10[71.43]
p-value	0.084	0.052	0.198	0.103	0.610	0.675	0.025	0.013

Legend: Data are presented in mean±standard deviation and median[interquartile range]; T0: clinically stable; T1: at the beginning of hospitalization; T2: during hospitalization; T3: at the end of the hospitalization; FVC: forced vital capacity; FEV_1: forced expiratory flow in one second; PEF: peak expiratory flow; $FEF_{25-75\%}$: forced expiratory flow at 25% to 75% of FVC; %: predicted percentage; I: difference between T0 and T3; II: difference between T1 and T3. Wilcoxon and paired t test to FVC and FEV_1: *: difference between T0 and T1; #: difference between T0 and T3; $: difference between T1 and T3; Z5: impedance at 5Hz; R5: total airway resistance; R20: central airway resistance; X5: reactance at 5Hz; T: paired T test; W: Wilcoxon test; p-value: statistic significance value.

Table 3. Weight, BMI and APE scores parameters.

	Weight (kg)	BMI (kg/m²)	CFCS (points)	CFFS (points)
T1 (N=16)	33.17±8.73	15.54±2.55	30.44±5.25	4.94±1.06
T3 (N=16)	34.29±8.57	16.06±2.33	18.63±2.16	0.25±0.45
p-value	0.006	0.008	< 0.001	< 0.001

Legend: T1: beginning of hospitalization; T3: end of hospitalization; BMI: body mass index; CFCS: Cystic Fibrosis Clinical Score; CFFS: Cystic Fibrosis Foundation Score.

DISCUSSION

The children presented FEV_1 mean less than 30% of predicted when they were clinically stable, which indicates pulmonary function impairment, and half of them presented SDS classified as moderate. This pattern may justify the fact there was no statistical difference between T0 and T1 moments to FVC% and FEV_1% parameters. Also, these children showed compromised IOS parameters in T1, probably indicating therapeutic measures. At the end of the hospitalization period, there was an improvement in all spirometric parameters pointing to a positive response to the treatment, despite the FEV_1% mean continued less than 80% of predicted.

During APE occurs obstruction of medium and small airways,[7] therefore, an increase in airway resistance may happen, once a study already correlation between airway mechanics and inflammatory markers in children with CF.[18] In addition, it is expected airway mechanics improvement with the treatment, which was observed in the present investigation, showing a statistical difference in X5 between T1 and T3.

Z5 and X5 parameters represent the total load imposed by the respiratory system and the airway elastic recoil, respectively,[6] and they showed values superior to 50% of predicted in T1. At the end of the treatment, these parameters values decreased 40% for Z5 and 100% for X5. These findings indicate the peripheral airway is the respiratory system region most impaired during APE leading to elastic recoil alteration.

Ren et al., corroborating with the present study, evaluated 14 individuals with CF hospitalized with APE and evidenced improvement in FVC, FEV_1, and FEF_{25-75} as well as R5 and X5 parameters after two weeks of treatment. The changes in FEV_1 correlated positively with changes in X5 indicating the respiratory mechanic's assessment identifies treatment response.[7] These findings were also reported by Buchs et al.,[8] after evaluation of 34 children with CF receiving IAT for APE (most of the sample were at home). The authors declared that spirometry and IOS were able to detect changes in pulmonary function after APE treatment and, X5 was the oscillometric parameter most sensitive to identify this improvement.

Sakarya et al.[5] also investigated oscillometric parameters in 16 children with CF during APE treatment and observed that all parameters showed significant improvement at the end of the treatment, except X5. It was identified abnormalities in some IOS parameters (X10-15 and Z5) at the beginning of IAT compared to baseline values. After treatment, these parameters numerically returned to baseline. However, there were no changes in the X5 parameter, which was not explained by the authors,[5] and did not corroborate to Ren et al. and Buchs et al. findings. Despite some controversial results, the authors of these three studies conclude IOS could detect changes in respiratory mechanics during APE and APE treatment.[5,7,8]

It is necessary to highlight that the current investigation presents a sample with a different clinical condition than showed in previously quoted studies. The individuals evaluated in this study showed respiratory impairment with FEV_1% mean, at the beginning of the hospitalization, numerically lower than the values presented by Ren et al.,[7] Buchs et al.[8] e Sakarya et al.[5] Some oscillometric parameters follow this pattern showing mean values inferior to those observed by Buchs et al.[8]

The pediatric CF patients' analysis with important pulmonary impairment, and receiving treatment for APE as well the findings here discussed, are not commonly evidenced in papers. Articles with this theme frequently disclose the behavior of individuals with better pulmonary function.

Therefore, the current study results indicate that children with CF presenting more severe clinical conditions benefit from APE therapeutic measures, and these interventions' responses may be monitored through spirometry and IOS.

This study stands out as a limitation the preclusion to control and isolate the effect of each item of the therapeutic measures.[3] Also, there was a small sample, mainly the IOS data, which compromises the generalization of the result. Nevertheless, it is important to note that a test power of 93% was found, considering the FEV_1 parameter, which was investigated in 16 children.

Also, there was a significant increase in weight, BMI, and a decrease in APE scores, indicating signs and symptoms improved. According to nutritional CF recommendations, the nutritional status positively correlates to pulmonary function.[19] In this context, Barr et al. found that a larger gain in body mass during hospitalization for APE treatment is associated with a greater time interval between APE episodes, in a study that included 59 adults with CF.[20]

CONCLUSION

The APE treatment included several therapeutic measures and improved the clinical condition of children with CF. There was an improvement in nutritional status, APE scores, and pulmonary function parameters with an increment above baseline values when in clinical stability.

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Authors' Contributions:
1. Contribuição substancial no esboço do estudo ou na interpretação dos dados: TC; RMGW; CISS
2. Participação na redação da versão preliminar: TC; RMGW; CISS
3. Participação na revisão e aprovação da versão final: TC; RMGW; CISS
4. Conformidade em ser responsável pela exatidão ou integridade de qualquer parte do estudo: TC; RMGW; CISS

Institutions where the research was carried out: Centro de Ciências da Saúde e do Esporte (CEFID) da Universidade do Estado de Santa Catarina (UDESC) e Hospital Infantil Joana de Gusmão (HIJG)- Florianópolis, Santa Catarina, Brazil.

Financing: Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina, FAPESC/Brazil (PAP UDESC, Chamada Pública N° 04/2018, Termo de Outorga 2019TR658).
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Conflict of interest: não.

O resumo com resultados parciais desta pesquisa foi premiado no VII Congresso Brasileiro Multidisciplinar de Fibrose Cística, que aconteceu entre os dias 01 e 04/05/2019, na cidade de Campinas/SP – Brasil.

acknowledgment: Agradecemos à equipe de Fibrose Cística do Hospital Infantil Joana de Gusmão, em especial ao Norberto Ludwig Neto e Ana Carolina da Silva Almeida.

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Editor:
Prof. Dr. Felipe Villela Gomes

Received: apr 04, 2021
Approved: dec 06, 2021
