MAXIMUM EXERCISE CAPACITY, LUNG FUNCTION AND BODY COMPOSITION IN CHILDREN WITH CYSTIC FIBROSIS

Gabriela Motter[1], Marjane Cardoso[1], Carolina Taffarel[1], Caroline Schmidt[1], Miriam Isabel Simon[2], Luiz Felipe Frohlich[3], Paulo José Marostica[4], and Paula Maria Rovedder[1]

[1]Universidade Federal do Rio Grande do Sul
[2]Hospital de Clínicas de Porto Alegre
[3]UFRGS
[4]Universidade Federal do Rio Grande do Sul; Hospital de Clínicas de Porto Alegre

July 13, 2020

Abstract

Objective: To evaluate the oxygen uptake at peak exercise (VO2 peak) and to correlate with lung volume and capacity and body composition of children and adolescents with cystic fibrosis (CF). Methodology: Cross-sectional study with CF patients treated at the pediatric pulmonology outpatient clinic of a public hospital in Porto Alegre, aged [?] 7 years up to 18 years. Study assessments included: cardiopulmonary stress testing, plethysmography, and body composition assessment using body bioimpedance. Results: Thirty patients were studied, with a mean peak VO2 of 1.511 $\pm$ 0.539 liters in the population studied. Correlation analysis showed a strong correlation between peak VO2 in liters and lean mass ($r = 0.77$ and $p < 0.001$), and strong and inverse correlation with fat percentage ($r = -0.77$ and $p < 0.001$).), a strong correlation with forced vital capacity (FVC) in liters ($r = 0.72$ and $p < 0.001$) and forced expiratory volume in the first second (FEV1) also in liters ($r = 0.69$ and $p < 0.001$). We observed a strong correlation between load (W) and lean mass and during CPET ($r = 0.64$ and $p < 0.001$), and inversely with fat percentage ($r = -0.64$ and $p < 0.001$). This study showed that patients with higher lean body composition have a better performance on cardiopulmonary testing, contributing to greater exercise tolerance.

Introduction

With advances in the treatment of cystic fibrosis (CF) and consequently increased survival and quality of life of these patients, the level of physical activity has been a predictor of morbidity and mortality in this population[1].

Patients with CF often have progressive limitation to physical exercise and reduced activities of daily living. The main causes of exercise intolerance are associated with reduced ventilatory and reserve capacity, loss of peripheral skeletal muscle mass and decreased cardiovascular function. Limiting factors presented by CF patients during exercise include fatigue, dyspnea, bronchospasm, ventilatory limitation, and cardiac dysfunction [2,3].

Regular exercise is important for maintaining functional capacity and pulmonary function in CF patients. Individuals who are more physically active have an oxygen consumption (VO_2) within normal limits during the cardiopulmonary exercise stress test (CPET), presenting better physical fitness, normal lung function and quality of life [4].

Another contributing factor to better physical fitness and quality of life is nutritional status. Studies show that good nutritional status is related to adequate forced expiratory volume in one second (FEV_1) in fibrocystic patients, and those who gain weight may have a concomitant increase in FEV_1 compared to those who have lost weight and consequently decreased lung function[5,6].

Recently, a systematic review and meta-analysis that included six cohort studies, with a total of 551 subjects aged 10 to 30 years old, showed a VO_2 peak below 82% of predicted or a VO_2 peak below 45 ml/kg/min is a predictor of mortality in individuals with CF. Other factors such as FEV_1 and body mass index (BMI) were also significant for longer survival in this population [7]. Hebestreit *et al* .[8], in their ten-year multicenter cohort demonstrated that in addition to VO_2 peak, other findings on CPET variables, a lower than predicted lung function, and a low BMI z-score are predictors of mortality and indication for lung transplantation for these patients. These studies demonstrate that the assessment of VO_2 peak through CPET may be an indicator of disease severity and prognosis beyond FEV_1.

A study by Sovtic *et al.* [9] showed that static hyperinflation assessed by plethysmography is associated with decreased exercise capacity in children with CF, and that the residual volume/total lung capacity ratio may be a predictor of hypoxemia and desaturation during CPET. Alvarez *et al.* [10]studied 32 CF patients in which they assessed fat mass and fat free mass, demonstrating that excess adiposity was inversely associated with lung function. There are few studies correlating pulmonary function and evaluation of lung composition by bioelectrical impedance with CPET in children with CF.

Therefore, the aim of this study was to evaluate oxygen consumption at peak exercise and to correlate with lung volumes and capacities and body composition of children and adolescents with CF.

Materials and Methods

The study design was cross-sectional. The study protocol was approved by the Comitê de Ética e Pesquisa do Hospital de Clínicas de Porto Alegre (HCPA) under number 150635. Free and informed consent was obtained for each child or adolescent and their legal guardians.

Inclusion criteria for the study were diagnoses of CF, established according to the European Consensus [11] criteria, age 7 to 18 years old, clinically stable of respiratory disease in the last 30 days, (defined by the absence of hospitalization and absence of modification in the maintenance regimen in this period). All patients were followed by the Ambulatório de Pneumologia Infantil do HCPA. Those patients and/or guardians who refused to participate in the study, patients with motor impairment or neurological and cardiac diseases not related to lung disease were excluded.

All patients underwent CPET, plethysmography and body composition measurement through bioimpedance.

Cardiopulmonary Stress Test

The CPET was performed on a cycle ergometer following the guidelines published by the American College of Cardiology/American Heart Society[12]. The protocol used was modified Godfrey, with the load (W) ranging from 5W to 15W depending on the height of the child or adolescent [13].

Ventilation measurements during exercise were performed using a flow meter that records the gas exchange measurements at each respiratory cycle. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), ventilatory equivalent of oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) and respiratory quotient (RER) were recorded [14].

The subject was monitored by an electrocardiograph. The Borg scale was presented to the patient in poster format and the patient manually showed the subjective sensation of dyspnea and fatigue in the lower limbs [14].

Body Composition

The bioimpedance test was performed with a Bodystat 1500® device. Two electrodes were placed on the hand and foot unilaterally, with a distal and a proximal electrode positioned on each limb.

Subjects remained fasting for 4 hours, abstaining from caffeine and alcohol for 24 hours, and did not exercise during the 24 hours preceding the exam. The following body composition variables were recorded: fat percentage (% G), lean mass percentage (% MM) and water percentage (% water).

Anthropometric Evaluation

The anthropometric evaluation was performed using Filizola electronic scale, with a maximum load of 150 kg. Height was measured using a Sanny- anthropometer, fixed to the smooth wall and without footer, with movable rod, graduated in centimeters and smaller division in millimeters. To measure the weight and height data, the Z score and percentile were used according to WHO reference values for the Weight/Age (W/A), Stature/Age (S/A), Weight/Height (W/H) and body mass index for age (BMI/A)[15, 16].

Pulmonary Function Tests

Spirometry

Spirometry was performed using a spirometer (MasterScreen, v4.31, Jaeger, Wurzburg, Germany). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded. All parameters were expressed as absolute values and as a percentage of predicted for age, height and gender according to reference data from the Brazilian Society of Pulmonology and Tisiology [17]. The Z-score for FVC and FEV_1 were calculated according to the Global Lung Function Initiative reference values[18].

Plethysmography

Plethysmography was conducted in the sitting position in a hermetically sealed cabin with the subjects using nasal clips and holding their cheeks with their hands. Then, they were asked to breathe normally, followed by the commands of a specialist technician to perform the exam. Total lung capacity (TLC), inspiratory capacity (IC), expiratory residual volume (ERV), residual volume (RV) and effective resistance (Reff) were recorded. All parameters were expressed as absolute values and as a percentage of predicted for age, height and gender according to the guidelines for pulmonary function tests [19].

Clinical Score

The clinical score of Shwachman and Kulczycki [20] was used for clinical evaluation of CF patients. This clinical assessment system considers four different characteristics: general activity, nutrition, physical examination and chest radiological findings. Each one of them was scored on a scale of 5 to 25 points, and a final score of 100 points represents the patient in the best possible clinical condition [20]. The clinical score of each patient was scored by the specialist physician with experience in treating CF patients.

Statistical Analysis

Data were expressed as percentages or means (SD). Categorical variables were compared using the chi-square test with adjusted standardized residuals, followed by Yates' correction or Fisher's exact test when appropriate.

The Kolmogorov-Smirnov test was used to assess the normality of the data. Relationships between variables were determined using Pearson's correlation and Spearman correlation. A linear regression analysis was performed on the independent variables and were associated with the outcomes of interest in ECPT for VO_2 peak. Data were analyzed using SPSS software package, version 20.0. The level of significance was set at $p < 0.05$. All statistical tests were two-tailed.

We calculated the sample size using a correlation coefficient of $r=0.5$ between the VO_2 peak and fat mass index. An adequate sample size in the present study was found to be at least 30 subjects [?]

Student's t test was used for comparison between groups with for data analysis, patients were divided into two groups according to the predicted percentage of peak VO_2; patients with peak VO_2 below 80% of predicted and with peak VO_2 above 80% of predicted[7].

Results

Thirty CF patients were evaluated from March 2016 to June 2018. Table 1 presents patients general characteristics according to peak VO_2 consumption. There was no significant difference between the groups.

Table 2 presents the values of CPET variables in children and adolescents with CF. Peak VO_2 presented an mean of 1.511 +- 0.539 liters, mean RER 1.07 +- 0.08 and maximum load at 103 +- 40.29 watts.

Correlation analysis showed a strong correlation between peak VO_2 in liters and lean mass (r = 0.77 and p < 0.001), and a strong and inverse correlation with fat percentage (r = - 0.77 and p < 0.001), a strong correlation with FVC in liters (r = 0.72 and p < 0.001) and FEV_1 also in liters (r = 0.69 and p < 0.001). Correlating VO_2 ml/kg/min, a moderate correlation was found with lean mass (r = 0.40 and p = 0.031) and a moderate and inverse correlation was found with fat percentage (r = - 0.40 and p = 0.031). With the total lung capacity (TLC), we found a moderate and inverse relationship (r = -0.41 and p = 0.030).

We observed a strong correlation between load (W) and lean mass during CPET, (r=0.64 e p <0.001), and inversely with fat percentage (r= -0.64 e p <0.001), these data suggest that those patients who have reached high loads have better fitness and more lean mass, this is due to good nutritional status and regular physical activity. This study also found a strong correlation between lactate threshold and lean mass (r = 0.67 and p <0.001) and a strong inverse correlation with fat percentage (r = -0.67 and p <0.001), a moderate correlation with FVC in liters (r = 0.53 and p = 0.002) and with FEV_1 in liters (r = 0.50 and p = 0.004).

MV/MVV correlated moderately and inversely with inspiratory capacity (CI) (r = -0.50 and p = 0.008) and lean mass (r = -0.45 and p = 0.015). When comparing the relationship between CPET and pulmonary functions, there were no statistically significant differences. Other correlations between CPET, body composition and pulmonary function are described in table 3.

Figure 1 shows the correlation between lean mass and fat with peak VO_2 and lactate threshold. Figure 2 shows the correlation between pulmonary function and peak VO_2.

Table 4 presents the regression analysis of the variables that were associated with peak VO_2. We observed that lean mass and fat independently associated with peak VO_2 (p <0.05).

Discussion

The present study showed that children and adolescents with CF who had higher peak VO_2 values had better body composition, with higher lean mass index and lower body fat index. A recent study by Charatsi *et al* .[21] evaluated 54 young adults with CF, and showed that those individuals with lean mass depletion had worse pulmonary function, corroborating our findings. Although without statistical difference, those patients with lower lean mass index had a lower lung mass index, more severe lung disease and consequently reduced values of peak VO_2 on CPET.

Fifteen patients had peak VO_2 lower than 80% of predicted. Studies have shown that CF patients present a reduction in peak VO_2, mainly due to the lung disease progression, impacting their quality of life. A study by Nixon *et al.*[4] compared the survival of 109 CF patients over 8 years and divided them into 3 groups according to the physical fitness, using the Godfrey cycle ergometer protocol. They observed that those with the highest survival rate over 8 years were in the group with a high level of physical fitness and a peak VO_2 above or equal to 82% of predicted.

Tomlinson *et al.* [22], evaluated 72 children and adolescents, the CF group had mild and moderate pulmonary disease and the healthy group was matched for age and gender, in order to compare the responses of oxygen uptake during CPET. This study demonstrated CPET may be a predictor of prognosis for these patients, as lower FEV_1 correlated strongly with lower peak VO_2. A cohort of CF patients investigated 28 subjects with age of 10 to 13 years old and demonstrated a decrease in peak VO_2 consumption proportionally to a fall in FEV_1, while those patients with normal FEV_1 remained with stable peak VO_2[23]. This shows that patients with pulmonary function loss have decreased VO_2 consumption. The present study showed CF patients with normal pulmonary function had sufficient ventilatory reserve to achieve a maximum CPET, without physical effort limitation. These findings coincide with the study by Dodd *et al* .[24] ,who showed that CF patients with mild obstructive disorder were able to perform complete CPET, reaching the maximum effort level. No significant correlations were found between CPET and spirometry data.

The current study found mean peak VO_2 values of 1.51 L/min, close to a recent study that showed a peak VO_2 of 1.74 L/min in CF children, with a mean age of 13 years old[22]. In our study, we observed that half of children and adolescents with CF had peak VO_2 values above 80% of predicted. Weir *et al* .[25] found a peak VO_2 of 1.6 L/min, but they observed that those individuals who lost body weight had a peak VO_2 decline of approximately 3.8 mL/kg/min after 18 months.

This study showed that lean mass and fat were independently associated with peak VO_2, being the best predictor of peak VO_2 in children and adolescents with CF. Higher lean mass values predict higher peak VO_2 consumption values, while higher fat values are associated with lower oxygen consumption values in these patients.

Charasti *et al* . [21] validated an equation for the use of bioimpedance in children and adolescents with CF using DXA as a reference for the equation. The study included 54 CF individuals with a median of 12 years old, and they observed that the use of bioimpedance associated with the equation is reliable for body composition assessment. They also observed that those individuals with greater lean mass depletion were older and had worse lung function.

Some limitations were observed in the present study. No control group to compare plethysmography, body composition and VO_2 peak values. We do not use the gold standard to assess body composition, a recent study suggests that bioimpedance may underestimate lean mass and fat-free mass in CF patients and presents DXA as a better predictor for body composition assessment, however biompedance is a valid and of good reproducibility instrument for research and clinical practice use[26].

In our study, we observed that half of children and adolescents with CF had peak VO_2 values above 80% of predicted. This study showed that patients with higher percentage of lean mass and lower percentage of fat had higher oxygen consumption, contributing to greater exercise tolerance. The patients' nutritional status proved to be the best predictor of exercise capacity.

Acknowledgements: Not applicable

Conflict of Interest: None.

References

1. Hulzebos EHJ, Bomhof-Roordink H, Leeuwen PB van de W, Twisk JWR, Arets HGM, van der Ent CK, Takken T. Prediction of Mortality in Adolescents with Cystic Fibrosis. Med Sci Sports Exerc 2014;46(11):2047–2052. doi:10.1249/MSS.0000000000000344
2. Ribeiro JD, Ribeiro MAG de O, Ribeiro AF. Controversias na fibrose cistica: do pediatra ao especialista. J Pediatr 2002 [accessed 2019 Nov 4];78.http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0021-75572002000800008&lng=pt&nrm=iso&tlng=pt. doi:10.1590/S0021-75572002000800008
3. Ziegler B, Rovedder PME, Dalcin P de TR, Menna-Barreto SS. Padroes ventilatorios na espirometria em pacientes adolescentes e adultos com fibrose cistica. J Bras Pneumol 2009;35(9): 854–859. doi:10.1590/S1806-37132009000900006
4. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The Prognostic Value of Exercise Testing in Patients with Cystic Fibrosis. N Engl J Med 1992;327(25):1785–1788. doi:10.1056/NEJM199212173272504
5. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. J Am Diet Assoc 2008;108(5):832–839. doi:10.1016/j.jada.2008.02.020

6. Steinkamp G. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax. 2002;57(7):596–601. doi:10.1136/thorax.57.7.596
7. Vendrusculo FM, Heinzmann-Filho JP, da Silva JS, Perez Ruiz M, Donadio MVF. Peak Oxygen Uptake and Mortality in Cystic Fibrosis: Systematic Review and Meta-Analysis. Respir Care. 2018 Sep 11:respcare.06185. doi:10.4187/respcare.06185
8. Hebestreit H, Hulzebos EH, Schneiderman JE, Karila C, Boas SR, Kriemler S, Dwyer T, Sahlberg M, Urquhart DS, Lands LC, et al. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. Am J of Respir Crit Care Med 2019 Apr 15; 199(8):987-995. doi:10.1164/rccm.201806-1110OC
9. Sovtic AD, Minic PB, Kosutic J, Markovic-Sovtic GP, Gajic MB. Static Hyperinflation Is Associated With Decreased Peak Exercise Performance in Children With Cystic Fibrosis. Respir Care. 2013;58(2):291–297. doi:10.4187/respcare.01946
10. Alvarez JA, Ziegler TR, Millson EC, Stecenko AA. Body composition and lung function in cystic fibrosis and their association with adiposity and normal-weight obesity. Nutrition. 2016;32(4):447–452. doi:10.1016/j.nut.2015.10.012
11. Elborn JS, Hodson M, Bertram C. Implementation of European standards of care for cystic fibrosis — provision of care. J Cyst Fibros 2009;8(5):348–355. doi:10.1016/j.jcf.2009.05.004
12. Rodgers GP, Ayanian JZ, Balady G, Beasley JW, Brown KA, Gervino EV, Paridon S, Quinones M, Schlant RC, Winters WL, et al. American College of Cardiology/American Heart Association Clinical Competence Statement on Stress Testing: A Report of the American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Task Force on Clinical Competence. Circulation 2000;102(14):1726–1738. doi:10.1161/01.CIR.102.14.1726
13. Hebestreit H, Arets HGM, Aurora P, Boas S, Cerny F, Hulzebos EHJ, Karila C, Lands LC, Lowman JD, Swisher A, et al. Statement on Exercise Testing in Cystic Fibrosis. Respiration 2015;90(4):332–351. doi:10.1159/000439057
14. Guimarães JI, Stein R, Vilas-Boas F. Normatização de técnicas e equipamentos para realização de exames em ergometria e ergoespirometria. Arq Bras Cardiol 2003;80(4):457–464. doi:10.1590/S0066-782X2003000400011
15. who. WHO | WHO Child Growth Standards: Methods and development. Geneva: WHO. World Health Organization; 2006.
16. de Onis M. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85(09):660–667. doi:10.2471/BLT.07.043497
17. Pereira, CAC. Espirometria. J Bras Pneumol 2002;28(3):45–51.
18. Cooper BG, Stocks J, Hall GL, Culver B, Steenbruggen I, Carter KW, Thompson BR, Graham BL, Miller MR, Ruppel G, et al. The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. Breathe. 2017;13(3):e56–e64. doi:10.1183/20734735.012717
19. Pereira CAC, Moreira MAF. Pletismografia. J Bras Pneumol 2002;28(3): 139-150.
20. Shwachman H. Long-Term Study of One Hundred Five Patients with Cystic Fibrosis: Studies Made Over a Five- to Fourteen-Year Period. AMA J Dis Child 1958;96(1):6. doi:10.1001/archpedi.1958.02060060008002
21. Charatsi AM, Dusser P, Freund R, Maruani G, Rossin H, Boulier A, Le Bourgeois M, Chedevergne F, de Blic J, Letourneur A, et al. Bioelectrical impedance in young patients with cystic fibrosis: Validation of a specific equation and clinical relevance. J Cyst Fibros 2016;15(6):825–833. doi:10.1016/j.jcf.2016.05.004
22. Tomlinson OW, Barker AR, Chubbock LV, Stevens D, Saynor ZL, Oades PJ, Williams CA. Analysis of oxygen uptake efficiency parameters in young people with cystic fibrosis. Eur J Appl Physiol 2018;118(10):2055–2063. doi:10.1007/s00421-018-3926-8
23. Pianosi P, LeBlanc J, Almudevar A. Relationship between FEV1 and peak oxygen uptake in children with cystic fibrosis. Pediatr Pulmonol 2005;40(4):324–329. doi:10.1002/ppul.20277
24. Dodd JD, Barry SC, Gallagher CG. Respiratory factors do not limit maximal symptom-limited exercise in patients with mild cystic fibrosis lung disease. Respir Physiol Neurobiol 2006;152(2):176–185.

doi:10.1016/j.resp.2005.08.003

25. Weir E, Burns PD, Devenny A, Young D, Paton JY. Cardiopulmonary exercise testing in children with cystic fibrosis: one centre's experience. Arch Dis Child 2017;102(5):440–444. doi:10.1136/archdischild-2016-310651
26. Ziai S, Coriati A, Chabot K, Mailhot M, Richter MV, Rabasa-Lhoret R. Agreement of bioelectric impedance analysis and dual-energy X-ray absorptiometry for body composition evaluation in adults with cystic fibrosis. J Cyst Fibros 2014;13(5):585–588. doi:10.1016/j.jcf.2014.01.006

Hosted file

`Table I.doc` available at https://authorea.com/users/341931/articles/468805-maximum-exercise-capacity-lung-function-and-body-composition-in-children-with-cystic-fibrosis

Hosted file

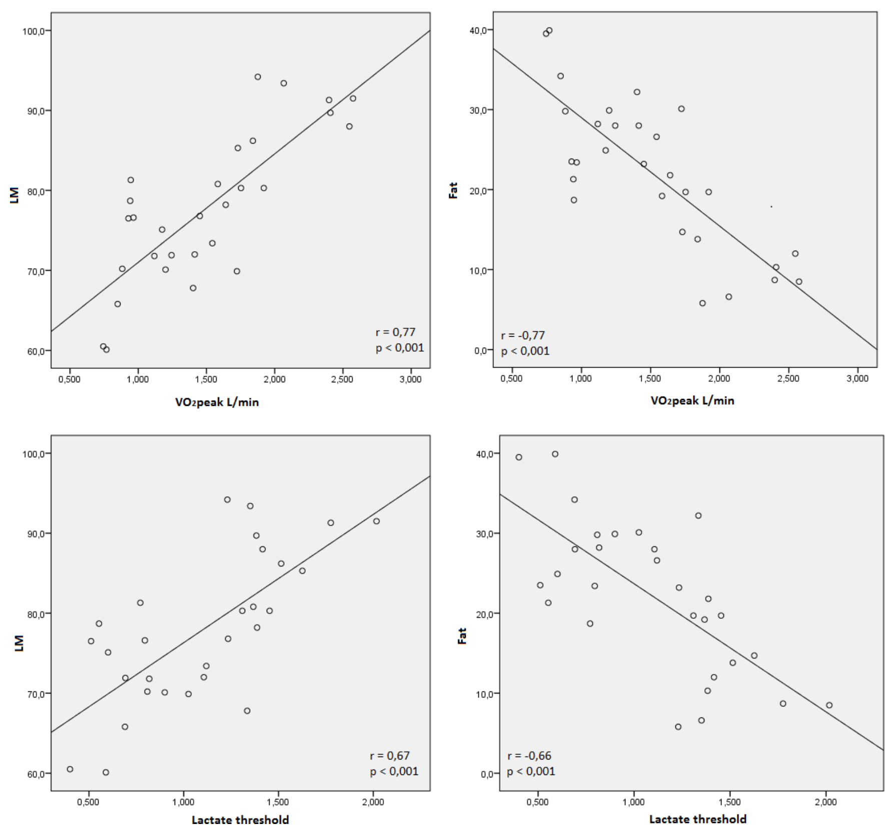
`Table II.doc` available at https://authorea.com/users/341931/articles/468805-maximum-exercise-capacity-lung-function-and-body-composition-in-children-with-cystic-fibrosis

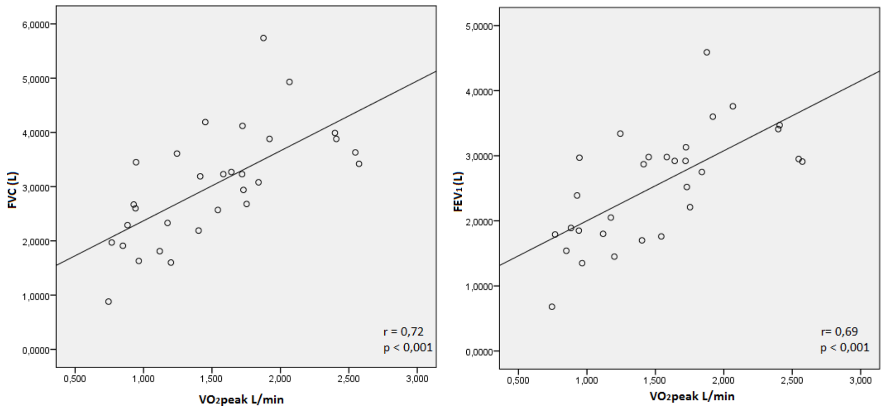
Hosted file

`Table III.doc` available at https://authorea.com/users/341931/articles/468805-maximum-exercise-capacity-lung-function-and-body-composition-in-children-with-cystic-fibrosis

Hosted file

`Table IV.docx` available at https://authorea.com/users/341931/articles/468805-maximum-exercise-capacity-lung-function-and-body-composition-in-children-with-cystic-fibrosis




FVC (L)
6,0000
5,0000
4,0000
3,0000
2,0000
1,0000
0,0000
0,500
1,000
1,500
2,000
2,500
3,000
VO2peak L/min
r = 0,72
p < 0,001
FEV1 (L)
5,0000
4,0000
3,0000
2,0000
1,0000
0,0000
0,500
1,000
1,500
2,000
2,500
3,000
VO2peak L/min
r= 0,69
p < 0,001