

Reduction of Exercise Capacity, Respiratory and Peripheral Muscle Strength in Severe Asthma

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Abstract

Background: Patients with severe asthma need to be studied separately due to differences from less severe asthma. This is the first study to carry out a wide physical evaluation of children and adolescents with severe asthma. The objective was to evaluate maximal and submaximal exercise capacity, respiratory and peripheral muscle strength in children and adolescents with severe asthma.

Methods: The study included children and adolescents (6 to 18 years) diagnosed with severe asthma, controlled in the last 4 weeks. The maximal exercise capacity was measured by the modified shuttle test (MST) and submaximal by the 6-min walk test. Respiratory muscle strength was evaluated by measuring maximal respiratory pressures and the peripheral strength through a handgrip.

Results: Thirty patients were included, with mean age of 10.3 years, 63% female and 46.7% overweight or obese. Patients underperformed but reached more than 80% of expected in all evaluations. There was a moderate correlation between age and body mass index (BMI) with MST, maximal expiratory pressure and peripheral muscle strength. The correlation between MST and BMI was negative. There was a strong correlation between peripheral muscle strength and age. Peripheral muscle strength also correlated moderately with respiratory muscle strength and lung function.

Conclusion: Children and adolescents with severe asthma had lower maximal and submaximal exercise capacity and reduced peripheral and respiratory muscle strength. These results are slightly below normal and very similar to patients with less severe asthma, allowing us

to infer that patients with severe asthma have a good functional condition when the disease is controlled.

Keywords: Asthma; Exercise tolerance; Respiratory muscles; Muscle strength; Pediatrics; Child; Adolescent

Introduction

Asthma is characterized by chronic airway inflammation and a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, cough, and expiratory airflow limitation. A good symptom control and exacerbations can be achieved in most asthma patients with low to moderate doses of inhaled corticosteroids. However, some patients need moderate to high doses of inhaled corticosteroids associated with long-acting beta₂-agonist, even after maximum control of comorbidities, environmental exposures, psychosocial factors, adherence to treatment, and correct inhalation technique [1]. These patients have severe asthma, which accounts for approximately 5-10% of all patients with this disease, and 50-60% of the asthma's medical costs, resulting in a very significant economic impact [2, 3].

Children and adolescents with severe asthma are at increased risk of adverse events, including medication-related side effects and recurrent exacerbations that negatively impact on the quality of life and can be life-threatening [2]. Symptoms and activity limitations [4], as well as greater severity and number of exacerbations [5] are associated with reduction of quality of life. Added to this, the fact that children with asthma have a sedentary lifestyle [6, 7], and limitation for aerobic exercise [8, 9], showing poorer performance than healthy children on maximal [6] or submaximal [7] exercise capacity tests, being the physical limitation directly associated with disease severity [8].

Reduction in peripheral muscle strength has been described in patients with chronic lung disease, predisposing patients to have a more sedentary lifestyle and in a long-term exercise intolerance [8]. However, there is little evidence in muscle strength and peripheral muscle endurance in pediatric severe asthma. In two studies, peripheral muscle strength was normal and was not influenced by disease severity [6, 8]. In another study, the results showed handgrip strength was significantly lower in children with moderate asthma compared with

Manuscript submitted January 22, 2022, accepted October 14, 2022
Published online October 31, 2022

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doi: <https://doi.org/10.14740/ijcp477>

the healthy group and those with mild asthma, demonstrating the influence of asthma severity on muscle strength [10].

Respiratory muscles have been studied more often than peripheral muscles in asthma, but not in severe asthma. In addition, the available evidence on respiratory muscle strength in pediatric asthma is limited and contradictory, given that some studies found no differences between asthmatics and healthy subjects [11-13], and others found a decrease in only one inspiratory or expiratory strength [14, 15].

This study is justified because severe asthma differs from less severe asthma, due to the risk of complications, by the need of higher doses of medications, the increased demand for health services and costs. Therefore, the current study aimed to assess maximal and submaximal exercise capacity, respiratory and peripheral muscle strength and quality of life in children and adolescents with severe asthma. Secondarily, evaluate possible associations between these variables, lung function, demographic and anthropometric data.

Materials and Methods

Participants

This was a cross-sectional observational study that evaluated patients with severe asthma, with a consecutively selected sample, in two pediatric referral hospitals in Porto Alegre-RS. We included children and adolescents aged 6 to 18 years diagnosed with severe asthma by an experienced pediatric pulmonologist (steps 4 or 5 of the Global Initiative for Asthma (GINA)) [1]. Patients who had uncontrolled or partially controlled asthma (according to GINA assessment of adults, adolescents and children 6 - 11 years - Box 2-2) [1], who were taking preventive medication irregularly, with musculoskeletal and/or neurological disorders that prevented the comprehension and performance of the tests, diagnosed with pulmonary or systemic arterial hypertension, heart disease and other chronic pulmonary disorders were excluded. Patients who refused (or their guardians refused) to participate also were excluded.

This research was approved by the Research Ethics Committees of the participating institutions: Hospital da Criança Santo Antonio (2.348.759), Universidade Federal de Ciências da Saúde de Porto Alegre (2.387.650) and Hospital Materno Infantil Presidente Vargas (2.474.352). The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. Participants (7 years of age or older) and their legal guardians read, agreed and signed the consent forms.

Logistics

Patients were assessed on the same day of routine appointment with the pulmonologist. The evaluations were performed in the following order: 1) Appointment with a pediatric pulmonologist; 2) Presentation of the research, invitation and signature of consent forms; 3) Completion of the data collection form;

4) 6-min walk test (6MWT); 5) Quality of life questionnaire - asthma module; 6) Manovacuometry; 7) International physical activity questionnaire (IPAQ); 8) Handgrip dynamometry; 9) Modified shuttle test (MST). All evaluations were performed by two trained researchers, and there was a rest time between them.

Maximal exercise capacity

Maximal exercise capacity was performed using the MST [16] and according to European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations [17]. The test has 15 levels in a course of 10 m, delimited by two cones with an inset of 0.5 m from either end. This test requires the patient to walk/run with increasing speeds controlled by a series of pre-recorded signals, ranging from 1.8 to 10.2 km/h and may be interrupted if the patient experiences fatigue or dyspnea and does not reach the distance to the cone two consecutive times [17]. At the beginning of each level, a standardized verbal incentive was offered.

The heart rate, peripheral oxygen saturation and respiratory rate were evaluated at the beginning and end of the test, as the modified Borg scale [18], used to assess the subjective sensation of dyspnea and fatigue of the lower limbs. Total distance walked in meters was measured by counting the total number of shuttles at the end of the test and expressed in meters and compared to the values predicted by the national reference equation [19].

Submaximal exercise capacity

The 6MWT was performed according to the guidelines of the ATS/ERS [17]. The subjects were instructed to walk as far as possible, for 6 min in a 30-m corridor, marked at every 3 m. Interruption or slowing down the rhythm were allowed, if necessary. Standardized phrases of encouragement were reproduced every minute of the course. At the end of the test, the total distance covered in meters was measured and compared to the values predicted by the reference equation [20]. The heart rate, peripheral oxygen saturation and respiratory rate were evaluated at the beginning and end of the test, as the modified Borg scale [18], used to assess the subjective sensation of dyspnea and fatigue of the lower limbs.

Respiratory muscle strength

Evaluation of respiratory muscle strength was performed with a digital manovacuometer (MVD 300[®], GlobalMed, Brazil) with variation of ± 300 cm H₂O. The maximal expiratory pressure (MEP) was measured from the total lung capacity and the maximal inspiratory pressure (MIP) from the residual volume. The measurements were performed in a seated posture, upright trunk, and with the use of a nose clip.

The test was conducted following the recommendations from the ERS [21]. All guidelines relative to the reproducibil-

ity and acceptability of the maneuvers were followed. A minimum of five and a maximum of 10 maneuvers were performed for each type of measured respiratory pressure, containing at least three acceptable (without air leak) and reproducible (that vary by less than 10%) maneuvers. The maneuvers were performed with maximum respiratory efforts, with 1-min intervals and sustained by at least 1 s. For this study, we used the maneuver of the highest value and the results were compared to values predicted by the reference equation [22].

Peripheral muscle strength

To measure the handgrip strength (HS), a hand hydraulic dynamometer (JAMAR[®], USA) was used and the measurements were performed following the American Society of Hand Therapists guidelines [23]. The patient was positioned in a chair with feet flat on the floor, shoulder adducted, elbow flexed at 90°, forearm in neutral position and wrist positioned between 0° and 30° extension and between 0° and 15° of ulnar deviation.

The researcher explained the assessment and demonstrated the test's position, as well as providing verbal encouragement to exercise maximum strength during each measurement. The maneuver was repeated three consecutive times with the dominant hand, and the average of the three measurements was used to compare to the normal values [23].

Lung function

Spirometry was performed by a pediatric pulmonologist using the KoKo spirometer (KoKo[®] PFT System, United Kingdom) following ATS guidelines acceptability and reproducibility criteria [24]. These data were collected from patients' medical records when the test had been performed less than 6 months from the day of the evaluation. When there was no spirometry or before 6 months, a new lung function test was scheduled. Lung function was measured without bronchodilator use.

Questionnaires of physical activity and quality of life

The level of physical activity was measured in patients aged 12 years or more using the short version of the IPAQ [25]. The questionnaire contains eight questions related to frequency (days per week) and duration (minutes per day) of physical, vigorous and moderate, activity and walking, categorizing the patient as "very active", "active", "irregularly active A", "irregularly active B" or "sedentary".

Quality of life was assessed using the Brazilian version of the Pediatric Quality of Life Inventory[™] (PedsQL[™]) 3.0 Asthma Module [26, 27] which contains 28 questions related to asthma in the following domains: asthma symptoms, treatment problems, worry and communication. The questions were answered on a Likert scale from 0 to 4 and, subsequently, the items are linearly inverted and transformed on a scale from 0

to 100, where the highest scores reflected better quality of life. This questionnaire can be answered by the population from 5 to 18 years old and has three versions adapted for each age.

Data analysis

Variables were described by frequency and percentage or mean and standard deviation when normally distributed and median and interquartile range when asymmetric, with normality being verified by the Shapiro-Wilk test. Categorical variables were presented in absolute and relative frequency. For comparisons between observed and predicted values, Student's *t*-test was used for parametric domains and Wilcoxon's *W* test for nonparametric domains. Pearson and Spearman correlation coefficients were used to measure the correlations between parametric and nonparametric variables, respectively. As an associated analysis, we used the classification of patients into two groups according to the 6MWT and MST performance: those with performance above the 75th percentile (> Q3) versus those with performance below the 75th percentile (< Q3). Comparisons between the two groups were performed using the Mann-Whitney U test.

According to Andrade et al, 2014 [7], the average estimate of the distance covered in the 6MWT of children and adolescents with severe asthma was 433.7 ± 124.2 m. With a maximum error of 45 m from this estimate, a significance level of 5% and a test power of 80%, the sample was estimated at 29 participants. Data were analyzed using the SPSS software (IBM SPSS Statistics for Windows, version 25., NY, USA) and the significance level was 5% ($P < 0.05$).

Results

We identified 391 patients aged 6 to 18 years old with a diagnosis of asthma. Of these, 78 (20.0%) were classified in step 4 and none reached step 5. Of the 78 patients with severe asthma, 20 were excluded because they had some associated disease, 17 had an uncontrolled disease or were misusing preventive medication, seven did not attend on the day of evaluation and four refused (or their guardians refused) to participate. Thus, 30 patients were recruited, and their demographic, anthropometric and pulmonary function data are described in Table 1.

Of these 30 patients, 28 (93.3%) were of adequate height and two (6.7%) had short stature. In the terms of body mass index (BMI), 16 (53.3%) patients were eutrophic, five (16.7%) were overweight, eight (26.7%) were obese, and one (3.3%) had severe obesity [28]. The lung function was performed in 23 patients because the others could not perform an adequate curve or missed the exam day. Regarding comorbidities, 26 (86.7%) of the subjects had a clinical diagnosis of rhinitis (all with controlled symptoms), 11 (36.7%) of atopic dermatitis, four (14.3%) of food allergy and two (6.7%) of gastroesophageal reflux. Passive smoking was observed in 11 (36.7%) patients, and none of the patients were active smokers. Eleven patients were 12 years old or older and answered the IPAQ, most of them (54.3%) being active.

Table 1. Clinical Characteristics of Patients With Severe Asthma

Variables	N = 30
Female	19 (63.3)
Age, years	10.8 ± 2.88
Anthropometry	
Weight, kg	42.8 ± 1.44
Height, m	1.44 ± 0.15
Height, z score	-0.03 ± 1.37
BMI, kg/m ²	20.34 ± 3.22
BMI, z score	0.99 ± 1.20
Lung function	
FVC, L (%) ^a	2.4 ± 0.8 (104.0 ± 10.6)
FEV ₁ , L (%) ^a	2.1 ± 0.7 (101.5 ± 13.5)
FEV ₁ /FVC ^a	87.7 ± 8.3
FEF ₂₅₋₇₅ , L (%) ^b	2.5 ± 1.1 (100.8 ± 37.4)
PEF, L (%) ^b	5.7 ± 2.2 (104.9 ± 18.5)
Physical activity (IPAQ) ^c	
Very active	0 (0.0)
Active	6 (54.5)
Insufficiently active A	4 (36.4)
Insufficiently active B	1 (9.1)
Sedentary	0 (0.0)
Quality of life (PedsQL asthma)	
Asthma symptoms	69.7 ± 18.0
Treatment problems	84.3 ± 13.3
Worry	70.8 ± 25.6
Communication	83.1 ± 16.1

Data are presented as mean ± SD or n (%). ^an = 23; ^bn = 17; ^c≥ 12 years, n = 11. BMI: body mass index; FEF₂₅₋₇₅: forced expiratory flow at 25-75% of FVC; FEV₁: forced expiratory volume at first second of FVC; FVC: forced vital capacity; PEF: peak expiratory flow; IPAQ: International Physical Activity Questionnaire; PedsQL: Pediatric Quality of Life Inventory Asthma Module.

Table 2 shows the performance in the maximal and submaximal exercise capacity, and respiratory and peripheral muscle strength tests, compared to the values predicted by ref-

Table 2. Comparison Between Predicted and Measured Values of the Tests

Test	Obtained	Predict	% of predict	P value
6MWT (m)	538.0 ± 63.7	640.0 ± 44.1	84.4 ± 11.3 ^a	< 0.001
MST (m)	748.3 ± 201.4	918.2 ± 134.2	81.5 ± 18.1 ^a	< 0.001
MIP (cm H ₂ O)	77.9 ± 24.8	93.4 ± 10.6	83.4 ± 24.6 ^a	0.002
MEP (cm H ₂ O)	82.1 ± 17.2	98.4 ± 7.8	83.9 ± 18.2 ^a	< 0.001
HS (kg)	16.5 ± 5.4	19.1 ± 6.2	88.8 ± 19.3 ^b	0.003

^aPredicted by reference equation. ^bPredicted by normative values. Data are presented as mean ± SD. 6MWT: 6-min walk test; HS: handgrip strength; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MST: modified shuttle test; PedsQL: Pediatric Quality of Life Inventory Asthma Module.

erence equations or normal values. Patients underperformed but reached more than 80% of what was expected in all evaluations. No adverse events occurred during or at the end of either exercise test, except for two patients who presented wheezing after MST, requiring the use of bronchodilators.

Figure 1 shows the correlations between MST, age, BMI, lung function, respiratory and peripheral muscle strength. There was a moderate correlation between MST and both age and BMI, the latter being negative, meaning that the higher the BMI, the worse the performance on the maximal exercise test.

A moderate correlation was found between peripheral muscle strength and MIP (r = 0.487; P = 0.010) and MEP (r = 0.498; P = 0.008). Moreover, there was a strong correlation between peripheral muscle strength and age (r = 0.777; P < 0.001) and moderate with BMI (r = 0.513; P = 0.005), forced vital capacity (FVC) (r = 0.506; P = 0.016) and forced expiratory volume at first second of FVC (FEV₁) (r = 0.484; P = 0.022). Finally, MEP correlated moderately with age (r = 0.425; P = 0.024), BMI (r = 0.432; P = 0.022) and MIP (r = 0.393; P = 0.038).

In the subgroup analysis, patients were classified into two distinct groups according to performance on the 6MWT and MST: those with performance above the 75th percentile (> Q3) versus those with performance up to the 75th percentile (< Q3). In the 6MWT, patients > Q3 achieved a result ≥ 94% of the predicted distance traveled. This group showed significantly higher values of FVC (118% versus 103.9%; P = 0.018) and FEV₁ (120% versus 96%; P = 0.008) compared to < Q3 (Fig. 2). The same analysis was performed for MST: group > Q3 had a performance ≥ 93% of the predicted, but there was no difference about the other percentiles in any evaluated variable.

Regarding quality of life, all significant correlations were negative, indicating that older patients with higher BMI, MEP, and greater peripheral muscle strength had less quality of life. The correlations are described in Table 3.

Discussion

Children and adolescents with severe asthma showed a lower maximal and submaximal exercise capacity and reduced peripheral and respiratory muscle strength. Pulmonary function was normal and quality of life was worse in older patients.

The results of the present study demonstrate a reduction in the maximal exercise capacity evaluated by the MST. Similar

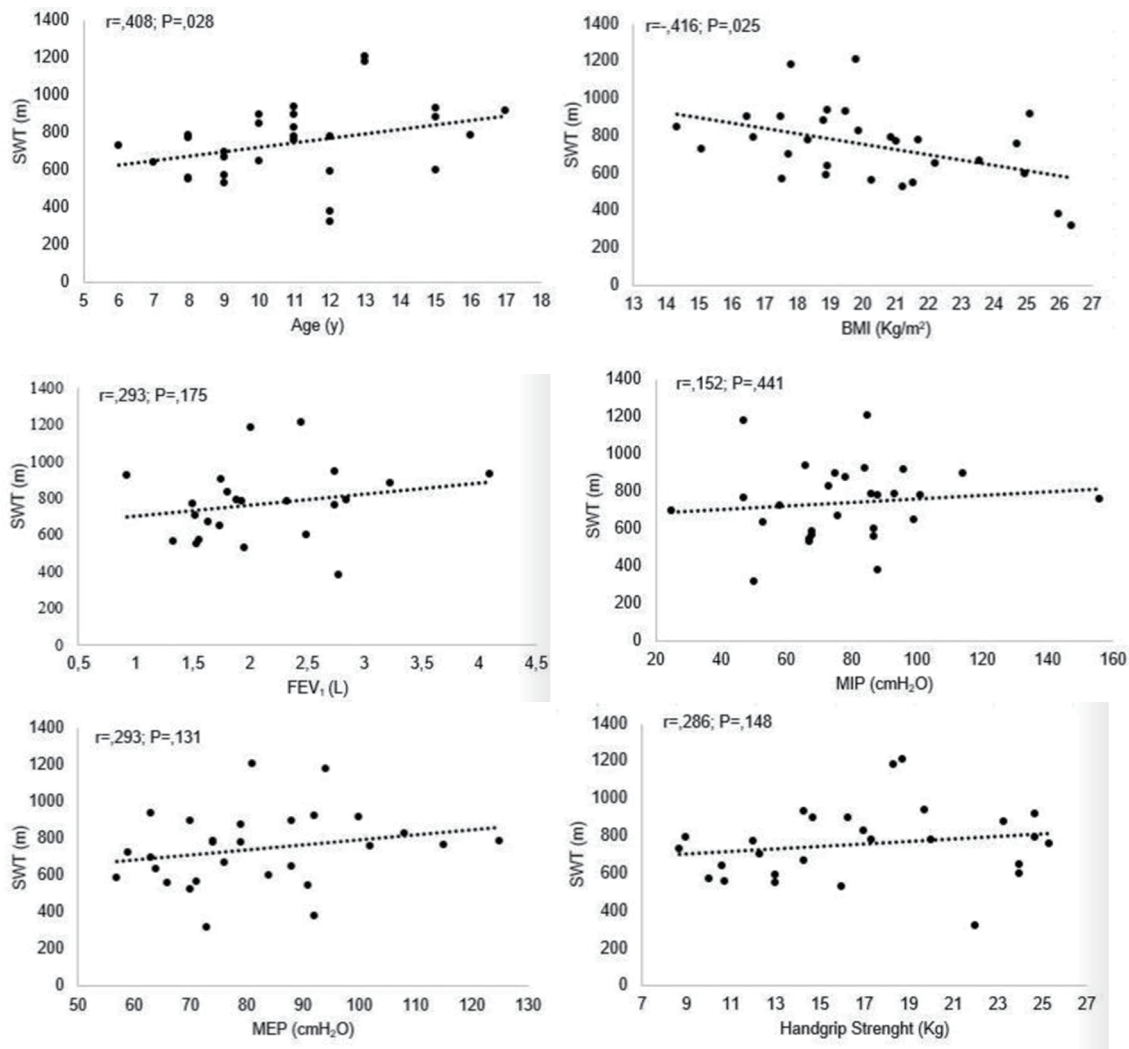


Figure 1. Correlation between MST and age, BMI, pulmonary function test, respiratory and peripheral muscle strength. MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MST: modified shuttle test; BMI: body mass index.

to our results, Reimberg et al, 2018 [6] also found that children and adolescents who had asthma with different severities covered 82% of the predicted distance. Thus, our results suggest that patients with severe asthma had reduced maximal exercise capacity, similar to patients with general asthma.

The MST has been used as an alternative test to evaluate the maximal exercise capacity because it is an easily accessible test, safe for the clinical environment, and has an important correlation with peak oxygen uptake (VO_{2peak}) in children and adolescents with asthma [29, 30]. In the study by Lanza et al, 2018 [29], the MST achieved higher VO_{2peak} and heart rate values than cardiopulmonary exercise testing (CPET), with a strong correlation between the VO_{2peak} predicted by the MST equation and the VO_{2peak} measured by CPET. Similarly, a strong correlation was found between the MST and VO_{2peak} measured through CPET in children and adolescents with severe therapy-resistant asthma in the study by Schiwe et al, 2019 [30].

In the 6MWT, children and adolescents in this study performed better than patients with severe asthma evaluated by An-

drade et al, 2014 [7]. However, the result was lower when compared to patients with mild [14] or all severities of asthma [31].

In subgroup analysis, patients with better results in the 6MWT (above the 75th percentile), had significantly better FVC and FEV₁ values. Despite being an important finding, its clinical relevance needs to be questioned because the patients in this study had normal lung function. However, in the future, a group of patients with impaired lung function may be studied to verify the hypothesis that FVC and FEV₁ could account for worse performance in the 6MWT and even in the maximal test.

Studies [32-34] have shown that children with asthma participate less frequently in physical activity because of the fear of both parents and children that exercise may trigger an asthma attack. Dyspnea during exercise may be mistakenly attributed to asthma when it is a normal consequence of exertion or the result of a lack of physical fitness. Thus, children with asthma do not participate in physical exercise, leading to a reduction in cardiorespiratory conditioning [35]. In our study, more than half of the patients aged 12 years and older

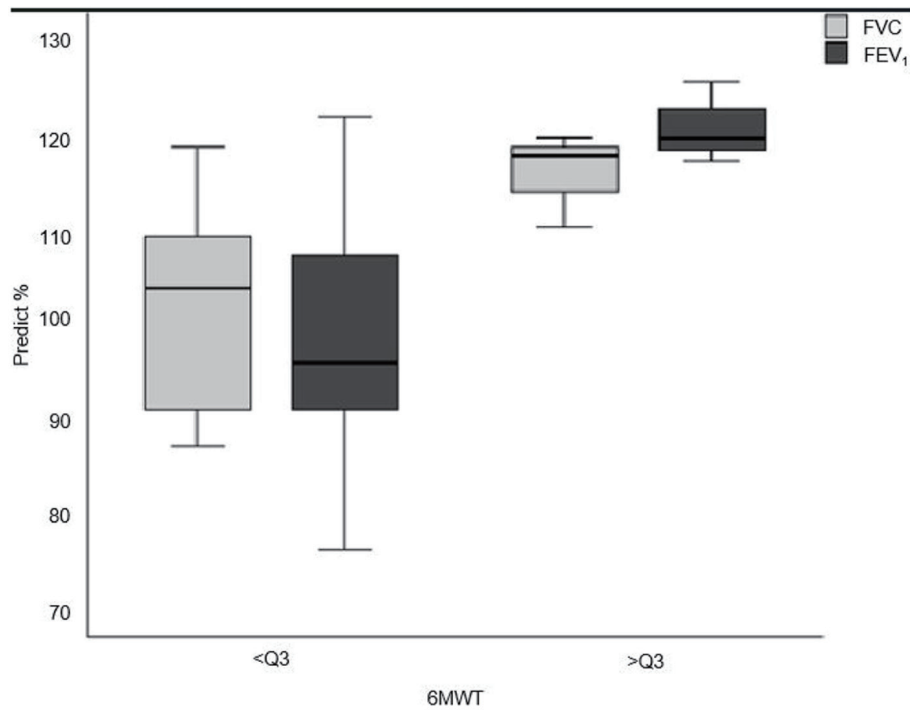


Figure 2. Group with < Q3 percentile compared to > Q3 on the 6MWT in relation to FVC and FEV₁. 6MWT: 6-min walk test; Q3: 75th percentile. FEV₁: forced expiratory volume at first second of FVC; FVC: forced vital capacity.

were classified as active in IPAQ, and the remaining as insufficiently active. This result is lower than the study by Basso et al, 2013 [36], with adolescents, where 63.1% were active or very active. However, in the cited study, all patients evaluated had a diagnosis of mild asthma, in contrast to the patients in this study with severe asthma.

Regarding respiratory muscle strength, most previous studies [11-13] showed no differences between healthy and asthmatic children and, when absolute values were observed, better results were achieved than our patients. However, none of the studies have been carried out in patients with severe asthma, showing that asthma severity may influence respiratory muscle strength. A possible explanation for the lower respiratory strength of our

patients with severe asthma is the changes that these muscles undergo due to the need of having to do a greater work to overcome the increased expiratory resistance caused by airway obstruction. At the same time, it is disadvantaged by pulmonary hyperinflation caused by air trapping, which leads to shortening of the inspiratory muscles and puts them at a mechanical disadvantage [37, 38]. These changes damage the kinetics of these muscles and may reduce their contraction strength.

Measurement of muscle strength through handgrip has been used as a general indicator for overall muscle strength [39] and as a complementary instrument in asthma monitoring in clinical practice [10]. In the study by Latorre-Roman et al, 2014 [10], it was observed that children with asthma had a re-

Table 3. Correlations Between PedsQL Asthma and Age, BMI, Maximal and Submaximal Exercise Capacity, Peripheral and Respiratory Muscle Strength

Variables	Asthma symptoms		Treatment problems		Worry		Communication	
	r	P	r	P	r	P	r	P
Age	-0.403	0.027	-0.262	0.162	-0.599	< 0.001	-0.284	0.136
BMI	-0.390	0.033	-0.170	0.370	-0.138	0.467	-0.243	0.204
MST	0.059	0.762	-0.060	0.758	-0.165	0.392	0.134	0.496
6MWT	-0.018	0.926	-0.047	0.805	0.076	0.691	0.177	0.359
MIP	0.141	0.474	0.047	0.813	-0.127	0.519	-0.340	0.083
MEP	-0.338	0.078	-0.398	0.036	-0.249	0.202	-0.053	0.794
HS	-0.522	0.004	-0.287	0.139	-0.504	0.006	-0.308	0.118

6MWT: 6-min walk test; BMI: body mass index; HS: handgrip strength; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MST: modified shuttle test; PedsQL: Pediatric Quality of Life Inventory Asthma Module.

duction of approximately 22% in handgrip strength compared to healthy ones and that the strength was about 13.6% lower in patients with moderate asthma compared to mild asthma. In the present study, we found higher values than the previously mentioned study, even though they are patients with severe asthma. Similarly to the study by Latorre-Roman et al, 2014 [10], a positive correlation between handgrip strength and both BMI and FEV₁ was observed.

Approximately half of the patients in this study are overweight or obese, very similar to those found by Glazebrook et al, 2006 [33]. Obesity is one of the factors directly related to the increased risk and severity of asthma, and asthma is more common in obese than in thin people [3]. We also observed a negative correlation between BMI and distance achieved in the MST, meaning that the higher the BMI, the worse the performance on the maximal exercise test. However, we did not find the same correlation between BMI and 6MWT in this study, as found by Rastogi et al, 2012 [40], where obesity contributed to worse performance of asthmatic adolescents in submaximal exercise capacity.

Quality of life is related to the level of control and severity of asthma in children and adolescents [34, 41]. In the present study, patients scored around 70 in the domains related to symptoms and worry with the disease, while in the domains related to problems with treatment or communication, the score was higher than 80. These findings are similar to studies [26, 42] with children and adolescents with different severities of asthma, that is, the patients with severe asthma in this study have a similar quality of life to patients with less severe asthma. We hypothesized that the reason for this finding is due to the fact that our patients maintained good clinical follow-up and disease control, which meets a better quality of life outcomes. All significant correlations found were negative, which means that the older and higher peripheral muscle strength, the worse the quality of life reported, which probably occurred due to the greater difficulty of understanding and reflection of younger children regarding the questions.

Our study has some limitations, such as the loss of some patients in the lung function test and the impossibility to assess the level of physical activity in the patients below 12 years old. Another limitation is that for comparison with normality, reference values published in the literature were used and not a group of healthy children and adolescents; however, these equations have been widely accepted in the literature.

In conclusion, the results of our study demonstrate that children and adolescents with severe asthma had lower maximal and submaximal exercise capacity and lower respiratory and peripheral muscle strength. Quality of life was lower in older patients, higher BMI and greater muscle strength. These results are slightly below normal and very similar to patients with less severe asthma, allowing us to infer that patients with severe asthma have a good functional condition when the disease is controlled.

Acknowledgments

Thanks to pediatric pulmonologist Andre Longhi for the opportunity provided and for helping with patients.

Financial Disclosure

This research did not receive any funding source.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Participants (7 years of age or older) and their legal guardians read, agreed and signed the consent forms.

Author Contributions

NM: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and final approval the version to be submitted. BB: acquisition of data, revising the article and final approval the version to be submitted. HTM and GBF: conception and design of the study, analysis and interpretation of data, revising the article and final approval the version to be submitted. JLL: conception and design of the study, analysis and interpretation of data, drafting the article and final approval the version to be submitted.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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