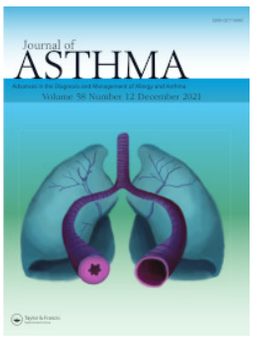

Journal of Asthma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijas20

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To cite this article: Cláudia Silva Schindel, Daniele Schiwe, João Paulo Heinzmann-Filho, Mailise Fátima Gheller, Natália Evangelista Campos, Paulo Márcio Pitrez & Márcio Vinícius Fagundes Donadio (2020): Determinants of exercise capacity in children and adolescents with severe therapy-resistant asthma, Journal of Asthma, DOI: 10.1080/02770903.2020.1833915

To link to this article: https://doi.org/10.1080/02770903.2020.1833915

Published online: 24 Oct 2020.

JOURNAL OF ASTHMA
https://doi.org/10.1080/02770903.2020.1833915

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Determinants of exercise capacity in children and adolescents with severe therapy-resistant asthma

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ABSTRACT

Objective: To evaluate the exercise capacity of children and adolescents with severe therapy resistant asthma (STRA) aiming to identify its main determinants.

Methods: Cross-sectional study including individuals aged 6–18 years with a diagnosis of STRA. Clinical (age and gender), anthropometric (weight, height and body mass index) and disease control data were collected. Lung function (spirometry), cardiopulmonary exercise testing (CPET) and exercise-induced bronchoconstriction (EIB) test were performed.

Results: Twenty-four patients aged 11.5 ± 2.6 years were included. The mean forced expiratory volume in one second (FEV_1) was 91.3 ± 9.2%. EIB occurred in 54.2% of patients. In CPET, the peak oxygen uptake (VO_{2peak}) was 34.1 ± 7.8 mL kg^{-1} min^{-1}. A significant correlation between ventilatory reserve and FEV_1 ($r = 0.57$; $p = 0.003$) was found. Similarly, there was a significant correlation between CPET and percent of FEV_1 fall in the EIB test for both V_E/VO_2 ($r = 0.47$; $p = 0.02$) and V_E/VCO_2 ($r = 0.46$; $p = 0.02$). Patients with FEV_1<80% had lower ventilatory reserve ($p = 0.009$). In addition, resting heart rate correlated with VO_{2peak} (r=-0.40; $p = 0.04$), V_E/VO_2 ($r = 0.46$; $p = 0.02$) and V_E/VCO_2 ($r = 0.48$; $p = 0.01$).

Conclusions: Exercise capacity is impaired in approximately 30% of children and adolescents with STRA. The results indicate that different aspects of aerobic fitness are influenced by distinct determinants, including lung function and EIB.

ARTICLE HISTORY
Received 22 July 2020
Revised 10 September 2020
Accepted 4 October 2020

KEYWORDS
Aerobic fitness; exercise-induced bronchoconstriction; oxygen consumption; lung function; cardiopulmonary exercise testing

Introduction

Asthma is a chronic obstructive respiratory disease that has a high prevalence among children and is considered a leading cause of hospitalization worldwide (1). Regarding disease severity, 5 to 10% of asthmatic patients have severe asthma (2,3), requiring high-dose prophylactic medication, such as inhaled corticosteroids, with variable response to drug therapy. A subset of children with severe asthma not responding adequately to treatment and not controlled despite best available clinical management has been classified as having severe therapy-resistant asthma (STRA) (4). Children with STRA have recurrent wheeze, cough, shortness of breath, disturbed sleep due to symptoms, continued use of medication, frequent emergency department visits and hospitalizations, missed school days and difficulty performing physical activities (5–7).

Reduced exercise tolerance is an important component of the disease that appears to be related to factors such as the degree of resting airflow obstruction, decreased ventilatory capacity, greater perceived dyspnea, and the occurrence of exercise-induced bronchoconstriction (EIB). These factors may contribute to premature cessation of physical activity, leading to a more sedentary lifestyle (5–8). However, it remains unclear which mechanisms are associated with the level of physical fitness in patients with STRA. Therefore, the assessment of exercise capacity is an important tool to objectively measure exercise intolerance, allowing for a safe and individualized exercise prescription (6,9). Cardiopulmonary exercise testing (CPET) is considered the gold standard for assessing exercise capacity, providing objective information on the level of physical fitness and the main determinants of exercise intolerance (10). Previous studies have also

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demonstrated that aerobic conditioning, psychological factors, and obesity are associated with poor physical fitness, especially in children with asthma (6,11,12).

A recent review on the clinical value of CPET in patients with asthma has shown that the majority of available studies are in patients with mild-to-moderate disease and adults (13). Studies in children with mild asthma have shown no aerobic fitness compromise (12,14). On the other hand, two previous reports have demonstrated that children with moderate to severe asthma had lower maximal aerobic capacity when compared to controls (15,16). Although evidence in adults with severe asthma is more robust (17–20), literature for children is still scarce and determinants of exercise capacity in STRA are unknown. Therefore, studies for STRA in childhood populations are needed to provide population-specific evidence rather than reliance on extrapolation from studies in adults.

Given the complex clinical presentation and treatment of patients with STRA, a better understanding of the factors that influence exercise capacity may contribute to a better clinical management of the disease. Therefore, the present study aimed to evaluate the exercise capacity of children and adolescents with STRA in order to identify the main determinants of aerobic fitness. To this end, CPET was performed and pulmonary function, disease control, and presence of EIB were evaluated to identify possible associations between these variables. We hypothesized here that lung function, disease control and EIB would be determinants of exercise capacity in children and adolescents with STRA.

Methods

This was a cross-sectional study including children and adolescents with STRA, of both sexes and between 6 and 18 years of age. The criteria used to select STRA patients followed the ERS/ATS international guideline: asthma which requires treatment on GINA steps 4 and 5 (high dose of inhaled corticosteroids and long-acting beta-agonists plus another controller therapy) in the previous year or systemic corticosteroids for 50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy (21). All patients were under regular follow-up and treatment in a referral asthma outpatient clinic, meaning that all efforts to optimize treatment are routinely performed. Patients were excluded if they had any cognitive/motor limitation or other chronic diseases (neurologic diseases, cardiac abnormalities, congenital anomalies, or immunodeficiencies) that could compromise the proposed assessments. In addition, on the day of the tests, patients who presented with signs indicative of pulmonary exacerbation, such as increased cough, sputum production, and wheezing, and those who were unable to perform a maximal CPET were also excluded. Sample size was calculated based on the oxygen consumption at peak exercise (VO_{2peak}) and its relationship with pulmonary function. To detect a minimum correlation of 0.40, with a significance of 0.05 and a power of 80%, a sample size of approximately 23 children and adolescents was necessary. Data were collected from March 2016 to July 2018. The study was approved by the institutional research ethics committee, approval number 47845415.4.0000.5336. Written informed consent was obtained from the parents or legal guardians for enrollment in the study, while informed assent was obtained from children/adolescents aged 8 years or over.

Study design

Eligible patients were invited to participate in the study during scheduled follow-up visits to the outpatient clinic. Parents and/or legal guardians who agreed to participate completed the GINA asthma control questionnaire and the patients were referred to the pediatric physical activity laboratory of the university for anthropometric assessment, pulmonary function testing (spirometry), and EIB assessment, on the same day. CPET was performed at a second visit, approximately 15 days later, as scheduled by the outpatient clinic staff. Patients were instructed not to use bronchodilators for at least 12 h before the tests. Clinical data were collected from the patients' medical records, including skin prick test results. Asthma control was classified in the day of evaluations using the GINA questionnaire: controlled asthma (4 negative answers); partially controlled asthma (1–2 negative answers); or uncontrolled asthma (3–4 positive answers). The primary outcome of the study was exercise capacity as measured by CPET. Secondary outcomes included the level of disease control, pulmonary function, and EIB.

Procedures

Anthropometric evaluation

Anthropometry was performed by measuring weight and height in triplicate. The final value was calculated by averaging the three measurements, with a maximum variation of 5% between measurements. The weight was obtained with individuals in the standing

position, with a minimum of clothes, without shoes and using a digital scale (G-Tech, Glass 1 FW, Rio de Janeiro, Brazil) previously calibrated with a precision of 100 g. Height was obtained with the participants barefoot, with their feet in parallel position, ankles joined, arms extended along the body and with the head in neutral position. Height measurements were obtained using a portable stadiometer (AlturaExata, TBW, São Paulo, Brazil) with a precision of 1 mm. From these measurements, the body mass index (BMI) was calculated (weight (kg)/height^2 (m)) and expressed as absolute values and z score (22).

Lung function

Lung function was performed using the flow-based KOKO (Louisville, CO, USA) spirometer. The spirometric parameters evaluated included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, and forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25-75\%}$). Patients were instructed to perform a maximal inspiration followed by a rapid, sustained maximal expiration for at least three seconds (23). Three acceptable curves and two reproducible curves were obtained. All technical procedures, as well as the acceptability and reproducibility criteria followed the recommendations of the American Thoracic Society - European Respiratory Society ATS/ERS (24). For the normalization of data, the international equation GLI 2012 (25) was used. In order to avoid possible influence on the other measurements, spirometry was performed without bronchodilator response evaluation.

Exercise-induced bronchoconstriction (EIB)

Testing for EIB followed the recommendations of the American Thoracic Society (ATS) (26). Patients underwent spirometry before and immediately after testing, and at 5, 10, 15, and 30 min after completion of the exercise protocol. The EIB test was performed on a treadmill (model KT-10400; Ibramed, Amparo, SP, Brazil) with adjustable slope and speed. All patients had been previously familiarized with the treadmill. The test was performed with a 15% incline, and the speed was increased until the patient reached a heart rate (HR) of 80–90% of predicted maximum (220 – age). Then, the patient continued exercise at that level for an additional 4–6 min, according to each subject's tolerance. The criteria for interruption were inability to continue exercise, as reported by the patient, and presence of wheezing or oxygen saturation (SpO_2) $< 88\%$ (26). Patients were monitored for the main physiologic variables (SpO_2, HR, respiratory rate, and blood pressure) before and immediately after the test. A test was considered positive for EIB if there was $a > 15\%$ fall in forced expiratory volume in the first second (FEV_1) after exercise (for up to 30 min) in relation to previously measured baseline values (26). Patients presenting EIB were evaluated by a pediatric pulmonologist and, whenever needed, Salbutamol was administered in order to certify FEV_1 return to baseline values.

Cardiopulmonary exercise testing (CPET)

Gas uptake was measured by an ergospirometry system using a gas analyzer ($VO2000$; Medical Graphics Corp., St. Paul, MN, USA). A face mask was adjusted to the patient's face and connected to a previously calibrated electronic device that allowed the exhaled breath to pass through. The test was conducted by a trained researcher and followed the recommendations of the American College of Sports Medicine (ACMS) (27). The test was performed with a ramp protocol adapted from a previous study (28). Using a handheld pulse oximeter (Nonin, Minneapolis, MN, USA), HR and SpO_2 were measured at baseline after a 15-min rest period, every 60 s during the test, and at the end of the test. Briefly, patients were instructed to walk for 2 min for familiarization with the treadmill, at 3 km/h without incline. Then, the incline was fixed at 3% and the speed was gradually increased by 0.5 km/h every minute, until completion of the test (28). All patients were encouraged to keep pace until exhaustion or onset of limiting signs/symptoms (dyspnea, leg pain, and/or dizziness). Patients were considered to have performed a maximal CPET if at least 3 of the following criteria were obtained: visible exhaustion; respiratory exchange ratio (RER) > 1.0; maximal HR $> 85\%$ of predicted maximum (208 – age $\times$ 0.7); and presence of a plateau in VO_{2peak} (29,30). The data were recorded and entered into the Aerograph software (Medical Graphics Corp.) for further analysis. The parameters evaluated included VO_{2peak} expressed in mL kg^{-1} min^{-1}, minute ventilation (V_E) expressed in L min^{-1}, ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2), VO_2 at the anaerobic threshold (AT), total treadmill time expressed in minutes, and maximal HR expressed in beats per minute (bpm). At the beginning and at the end of the protocol, patients were asked to rate the degree of perceived dyspnea using a modified Borg scale (31).

Table 1. Characteristics of the study subjects.

Variables	Total ($n = 24$)	Controlled and partially controlled ($n = 14$)	Uncontrolled ($n = 10$)	p
Demographics				
Age (years)	11.5 ± 2.6	11.2 ± 2.6	11.9 ± 2.6	0.5
Female, *n* (%)	11 (45.8)	5 (45.5)	6 (54.5)	0.2
Anthropometry				
Weight (kg)	44.5 ± 14.1	42.9 ± 16.2	46.6 ± 10.7	0.5
Height (cm)	143.4 ± 12.3	141.1 ± 14.4	146.6 ± 8.0	0.2
BMI (kg/m^2)	21.5 ± 6.5	21.3 ± 7.5	21.7 ± 5.1	0.8
BMI (*z* score)	0.68 ± 1.03	0.55 ± 1.2	0.86 ± 0.7	0.4
Lung function				
FEV_1 (%)	91.3 ± 9.2	95.0 ± 19.9	86.0 ± 17.8	0.2
FVC (%)	100.1 ± 14.9	103.5 ± 14.4	95.3 ± 15.0	0.1
FEV_1/FVC (absolute)	0.8 ± 0.1	0.8 ± 0.08	0.8 ± 0.1	0.5
$FEF_{25-75\%}$ (%)	78.4 ± 33.8	85.2 ± 36.9	66.9 ± 27.2	0.1
EIB ($n = 23$)				
Positive (>15%), *n* (%)	13 (54.2)	8 (61.5)	5 (38.5)	0.5
Fall severity ($n = 13$)				
Mild (15–24%), *n* (%)	8 (61.5)	5 (38.5)	3 (23)	0.4
Moderate (25–39%), *n* (%)	4 (30.8)	3 (23)	1 (7.7)	0.4
Severe (≥40%), *n* (%)	1 (7.7)	–	1 (7.7)	0.4
Medications				
ICS + LABA	24 (100.0)	14 (100.0)	10 (100.0)	–
Intranasal corticosteroids	18 (75.0)	10 (71.4)	8 (80.0)	0.2
Leukotriene receptor antagonist	4 (16.6)	3 (21.4)	1 (10.0)	0.1
Antihistamines	7 (29.2)	5 (35.7)	2 (20.0)	0.2
SABA	16 (66.6)	9 (64.3)	7 (70.0)	0.6
Omalizumab	15 (62.5)	8 (57.1)	7 (70.0)	0.4
CPET				
At rest				
HR (bpm)	89.1 ± 13.3	90.9 ± 13.1	86.6 ± 13.8	0.4
SpO_2 (%)	98.2 ± 1.4	98.4 ± 1.3	97.9 ± 1.4	0.4
RER	0.81 ± 0.07	0.82 ± 0.06	0.80 ± 0.09	0.4
VO_2 (L min^{-1})	0.30 ± 0.08	0.30 ± 0.07	0.31 ± 0.1	0.9
VO_2 (mL kg^{-1} min^{-1})	7.6 ± 3.1	7.9 ± 2.9	7.2 ± 3.5	0.6
At anaerobic threshold				
HR (bpm)	154 ± 25.4	158.2 ± 22.8	148.5 ± 28.6	0.4
VO_2 (L min^{-1})	1.1 ± 0.3	1.04 ± 0.3	1.08 ± 0.2	0.8
VO_2 (mL kg^{-1} min^{-1})	24.8 ± 6.5	25.1 ± 6.3	24.2 ± 6.8	0.7
VO_2 %max	73.4 ± 13.6	75.2 ± 14.3	70.8 ± 12.8	0.4
V_E (L min^{-1})	25.1 ± 7.1	24.8 ± 6.7	25.5 ± 7.9	0.8
At peak exercise				
HR (bpm)	184.6 ± 16.9	185.1 ± 8.8	183.9 ± 24.8	0.9
SpO_2 (%)	95.7 ± 2.4	95.7 ± 1.9	95.7 ± 2.9	0.9
RER	1.10 ± 0.06	1.1 ± 0.05	1.1 ± 0.07	0.8
VO_2 (L min^{-1})	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.3	0.4
VO_2 (mL kg^{-1} min^{-1})	34.1 ± 7.8	33.9 ± 7.8	34.3 ± 8.2	0.9
V_E (L min^{-1})	39.0 ± 11.7	37.1 ± 13.5	41.7 ± 8.5	0.3
V_E/VO_2	23.8 ± 2.0	23.3 ± 1.7	24.3 ± 2.3	0.2
V_E/VCO_2	23.4 ± 2.1	23.0 ± 1.8	23.8 ± 2.3	0.3
Ventilatory reserve (%)	47.6 ± 13.5	46.7 ± 16.0	37.9 ± 16.5	0.2
Total test time (min)	10.9 ± 1.9	11.0 ± 1.9	10.9 ± 2.0	0.9

Values expressed as percentage, except age, anthropometric measures and lung function (mean ± standard deviation). BMI: Body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEV_1/FVC: ratio between forced expiratory volume in one second and forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25 and 75% of vital capacity; EIB: exercise-induced bronchoconstriction; ICS: inhaled corticosteroids; LABA: long-acting β2 agonists; SABA: short-acting β2 agonists; CPET: cardiopulmonary exercise testing; HR: heart rate; SpO_2: oxygen saturation; VO_2: oxygen uptake; V_E: minute ventilation; V_E/VO_2: ventilatory equivalent for oxygen uptake; V_E/VCO_2: ventilatory equivalent for carbon dioxide production; RER: respiratory exchange ratio.

Statistical analysis

Data normality was assessed by the Shapiro–Wilk test. Variables with symmetric distribution were presented as mean and standard deviation, while asymmetric variables were presented as median and interquartile range. Categorical data were presented in absolute and relative frequency. Comparisons between two groups were assessed by the Student's t test for independent samples or Pearson's chi-square test for categorical variables. Correlations were tested using Pearson's correlation test and classified according to the correlation coefficient (r) as weak ($r \leq 0.39$), moderate ($r = 0.4$–0.69) and strong ($r = 0.7$–1.0). All analyzes were performed using the SPSS software (version 17.0) and differences were considered significant when $p < 0.05$.

Results

A total of 24 children and adolescents (45.8% female, all Caucasian) diagnosed with STRA and with a mean

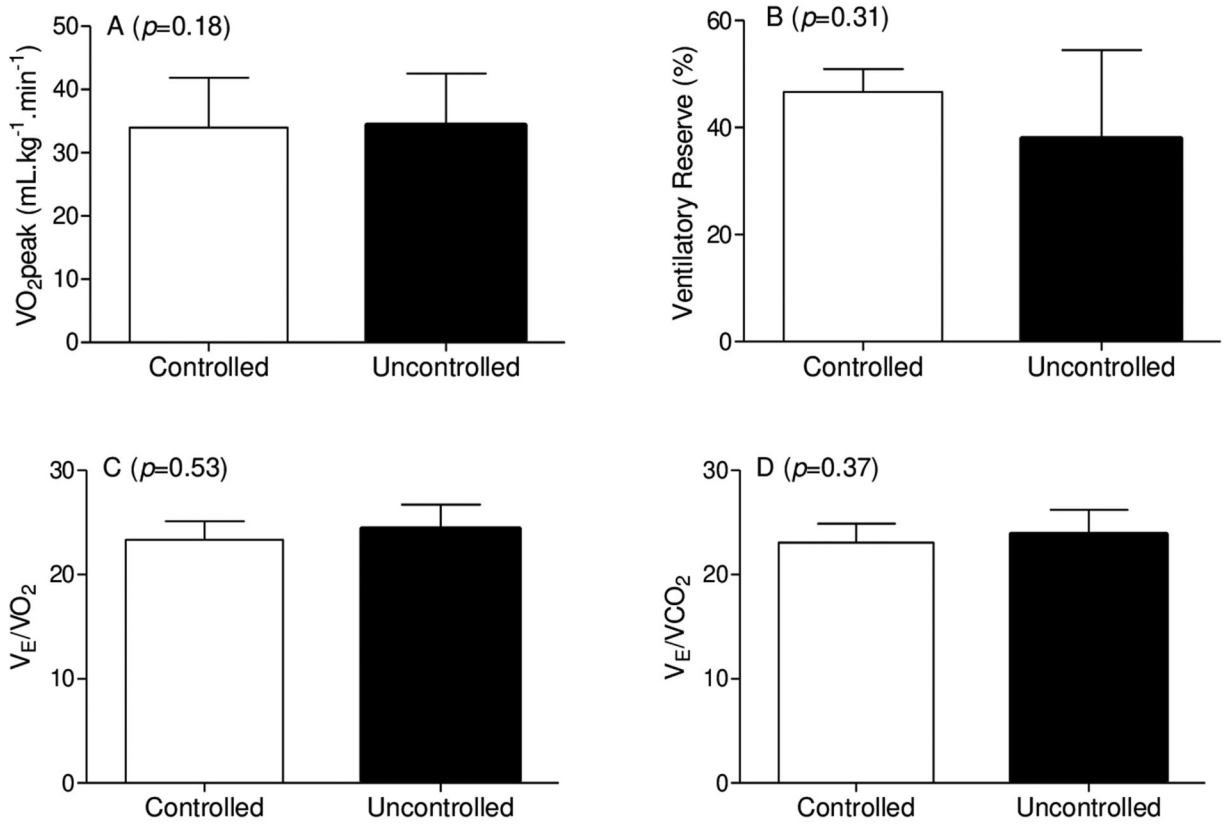

Figure 1. Comparison of exercise capacity variables evaluated through the cardiopulmonary exercise testing (CPET) between individuals with different asthma control levels. Asthma (controlled/controlled partially and uncontrolled) and oxygen uptake peak (VO_{2peak}) (A), ventilatory reserve (B), ventilatory equivalent for oxygen uptake (V_E/VO_2) (C) and equivalent for carbon dioxide production (V_E/VCO_2) (D). Data presented as mean and standard deviation. The Student's *t* test for independent samples was used for comparisons. Significance level set at 5%.

(SD) age of 11.5 (2.6) years were included. Fifteen (62.5%) patients were under monoclonal antibody therapy (Omalizumab) and all individuals were using inhaled corticosteroids with a median (IQR) dosage (μg/day) of 800 (500–800). Most patients (90.5%) had atopic asthma. Regarding disease control, 10 (41.7%) patients had uncontrolled asthma, 7 (29.2%) had partially controlled asthma, and 7 (29.2%) had controlled asthma. Mean (SD) FEV_1 (%) was 91.3 (9.2), and 8 (33.3%) patients showed reduced ($< 80\%$) FEV_1. EIB with $a > 15\%$ fall in FEV_1 occurred in 54.2% of patients with STRA. Regarding CPET results, at peak exercise, mean (SD) VO_2 was 34.1 (7.8) mL kg^{-1} min^{-1} and V_E was 39.0 (11.7) L min^{-1}, both values were within the reference range.[23] Seven (29.2%) patients had reduced VO_{2peak} (below the 5th percentile), indicating poor physical fitness. The mean (SD) maximal HR was 184.6 (16.9) bpm and RER was 1.10 (0.06), indicating a test performed at maximal effort. There was no fall in SpO_2. Table 1 shows the demographic, anthropometric, pulmonary function, the response and intensity of EIB and the main physiological variables obtained from CPET, according to the classification of asthma obtained with the GINA asthma control questionnaire.

No significant differences were observed in exercise capacity when the main CPET variables were compared between patients with controlled/partially controlled asthma and patients with uncontrolled asthma (Figure 1). When correlating CPET and pulmonary function testing variables in patients with STRA, there was a significant moderate correlation between ventilatory reserve and FEV_1 values ($r = 0.57$; $p = 0.003$). Likewise, percentage fall in FEV_1 in the EIB test was significantly and moderately correlated with V_E/VO_2 ($r = 0.47$; $p = 0.02$) and V_E/VCO_2 ($r = 0.46$; $p = 0.02$). All other variables showed no significant correlations (Figure 2).

Patients with STRA were stratified by FEV_1 ($> 80\%$ or $< 80\%$) to assess the influence of pulmonary function on exercise capacity. When comparing the main CPET variables, patients with $FEV_1 < 80\%$ had a significantly lower ventilatory reserve than patients with $FEV_1 > 80\%$ ($p = 0.009$). However, there was no

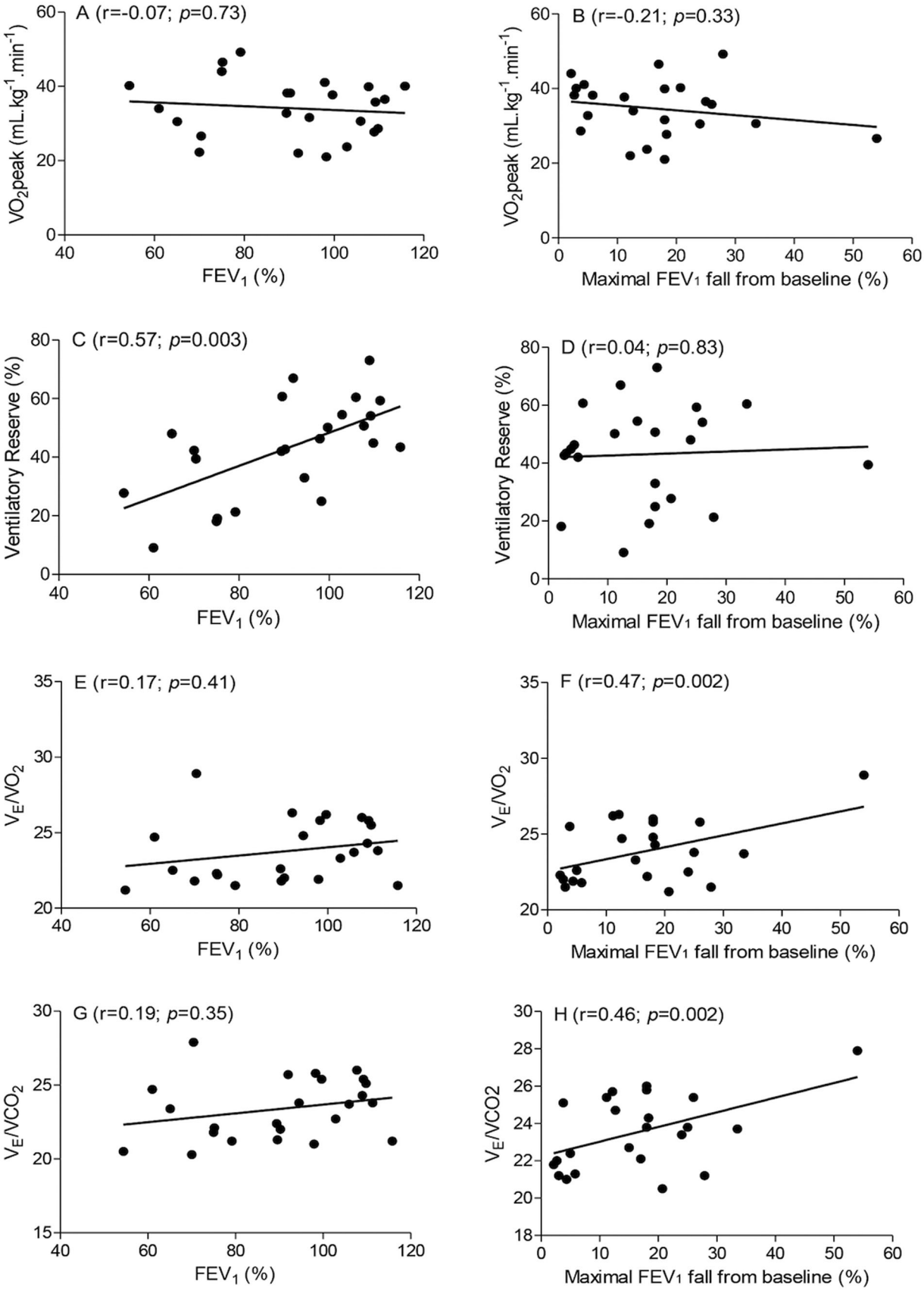

Figure 2. Correlation of exercise capacity variables (cardiopulmonary exercise testing) with lung function and percent of fall in the exercise-induced bronchoconstriction test. *Left panel*: Forced expiratory volume in one second (FEV_1) and peak oxygen consumption (VO_{2peak}) (A), ventilatory reserve (C), ventilatory equivalent for oxygen uptake (V_E/VO_2) (E) and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) (G). Right panel: Percent of FEV_1 fall in the exercise-induced bronchoconstriction test and peak oxygen consumption (VO_{2peak}) (B), ventilatory reserve (D), ventilatory equivalent for oxygen uptake (V_E/VO_2) (F), and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) (H). The Pearson's correlation test was used. The regression line is presented and each dot represents a single patient.

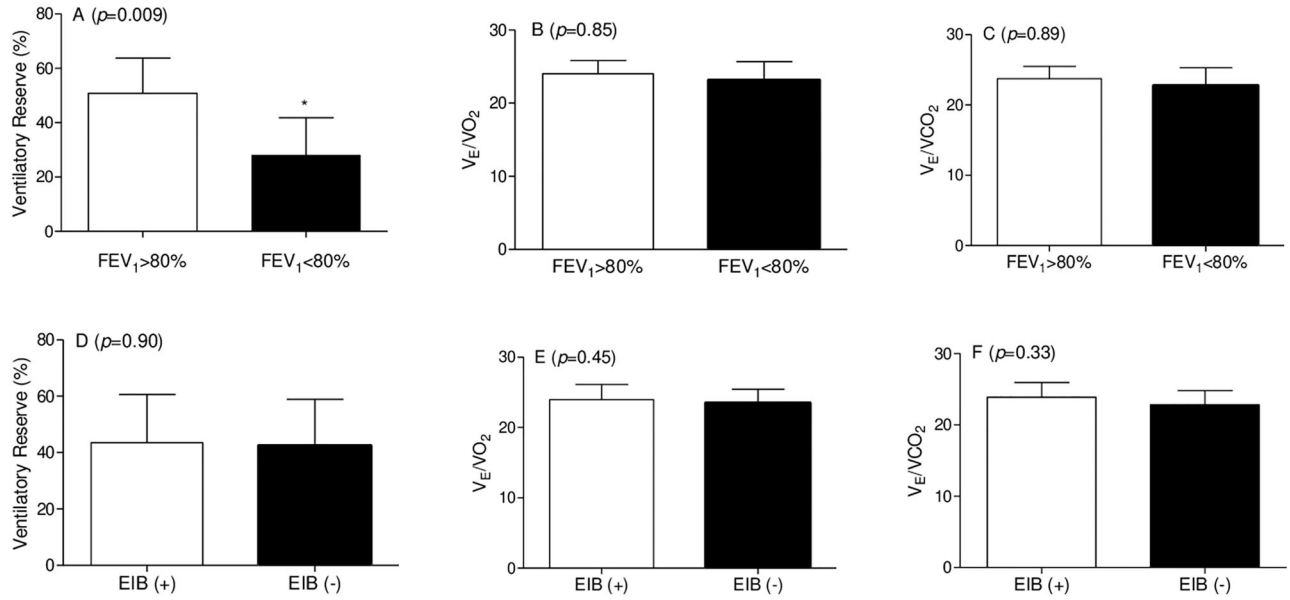

Figure 3. Comparison of exercise capacity variables (cardiopulmonary exercise testing variables) according to lung function and the presence of exercise-induced bronchoconstriction (EIB). Above: Forced expiratory volume in one second (FEV_1 higher or lower than 80% of predicted) and ventilatory reserve (A), ventilatory equivalent for oxygen uptake (V_E/VO_2) (B) and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) (C). Bottom: Positive or negative EIB and ventilatory reserve (D), ventilatory equivalent for oxygen uptake (V_E/VO_2) (E) and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) (F). Data presented as mean and standard deviation. The Student's *t* test for independent samples was used for comparisons. * indicates significant differences ($p < 0.05$).

significant difference in the main CPET variables at peak exercise between patients with STRA stratified by the presence or absence of EIB (Figure 3).

In addition, resting HR showed significant moderate correlations with the main CPET variables at peak exercise: VO_2 ($r = -0.40$; $p = 0.04$); V_E/VO_2 ($r = 0.46$; $p = 0.02$); and V_E/VCO_2 ($r = 0.48$; $p = 0.01$) (Figure 4). Individuals with resting HR $\geq$ 100bpm also presented and increased ($p = 0.01$) HR at the AT when compared to subjects with a resting HR $<$ 100bpm (172.0 ± 17.7 vs. 146.1 ± 24.5, respectively).

Discussion

The results of the present study demonstrated that exercise capacity appears to be only slightly compromised in children and adolescents with a diagnosis of STRA, although more than half of the sample had bronchial hyperreactivity to exercise and poorly controlled disease. In addition, most of children and adolescents with STRA showed normal lung function, with a few patients presenting an obstructive ventilatory pattern. It was also demonstrated that different variables representing exercise capacity are associated with pulmonary function, presence of EIB, and physiologic markers, such as resting HR.

Most patients with STRA evaluated in the present study had VO_{2peak} values within the reference range (32). However, 7 (29.2%) patients had reduced VO_{2peak} (below the 5th percentile), which indicates poor physical fitness. This seems to be in agreement with a previous study showing that asthma severity was not associated with oxygen consumption (6). In addition, the results for other variables of exercise tolerance, such as V_E and ventilatory reserve, appeared to be reduced when compared with data from a previous study (12) that evaluated children and adolescents with mild-to-moderate asthma and showed V_E of 42.9 L min^{-1} and ventilatory reserve of 56.7%, suggesting that exercise capacity may be somewhat reduced because of ventilatory limitations present only in STRA. Two previous reports concluded that children with moderate to severe asthma had lower maximal aerobic capacity when compared to controls (15,16). Although the results may appear to be in disagreement, a few issues deserve considerations. The study of Villa et al. (16) shows a VO_{2peak} for severe patients of only 28.2 ml kg^{-1} min^{-1}. The apparently high ventilatory reserve (66.0%) would suggest submaximal effort (33). Unfortunately, no maximum HR or criteria used to consider the test as maximum were provided (16). The use of a cycle ergometer as compared to treadmill may also play a role in the differences found. In the work of Alioglu et al. (15) although a significant reduction was found when data was compared to controls, the mean

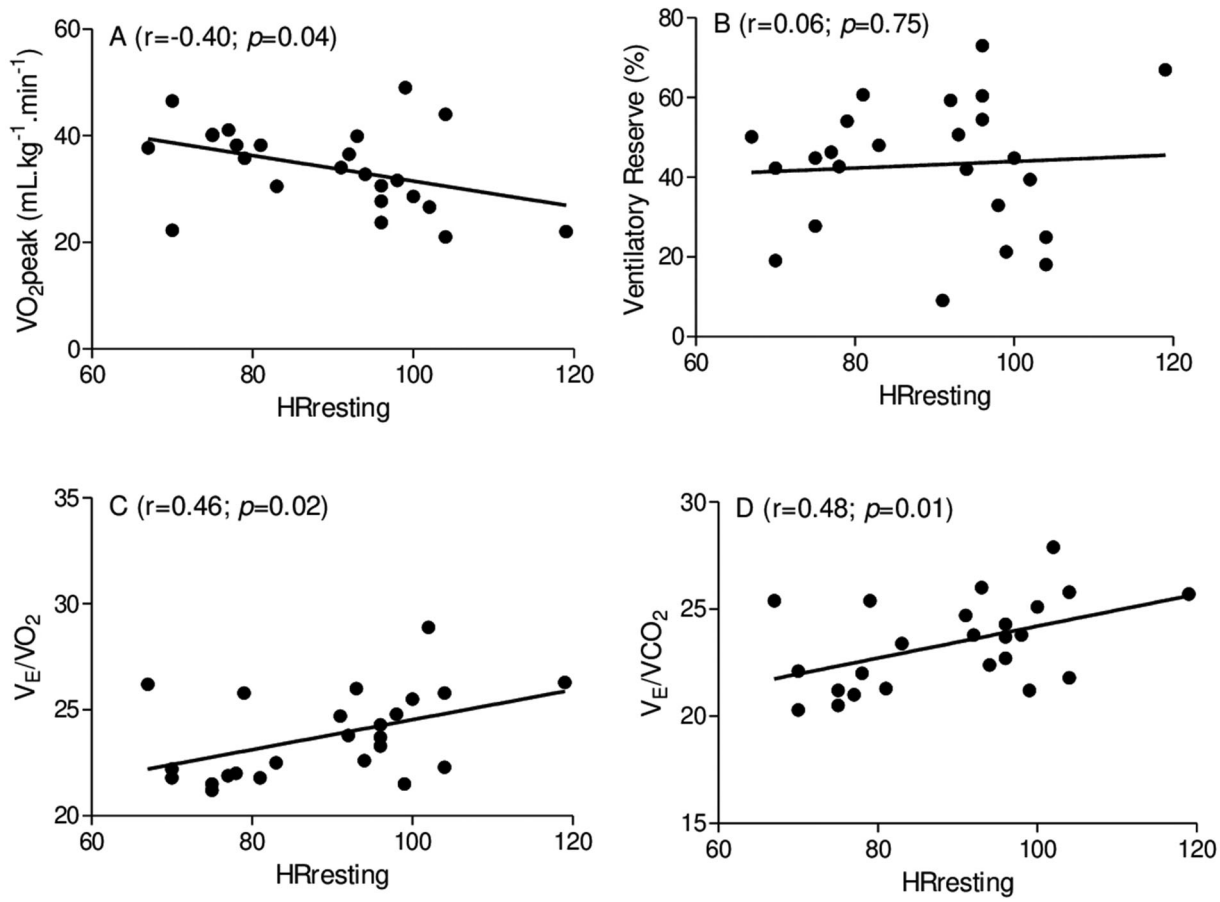

Figure 4. Correlation between the main exercise capacity variables (cardiopulmonary exercise testing) and resting heart rate. Resting heart rate (HRresting) and peak oxygen consumption (VO_{2peak}) (A), ventilatory reserve (B), ventilatory equivalent for oxygen uptake (V_E/VO_2) (C), and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) (D). The Pearson's correlation test was used. The regression line is presented and each dot represents a single patient.

VO_{2peak} reported was 42.5 ml kg^{-1} min^{-1}, which is much higher than both values presented here and in the study of Villa et al. (16). We believe the criteria for severity level classification, new drug treatments available and distinct exercise test protocols used may play a role in explaining such differences.

Although benefits of exercise training for asthma control have already been described for children (34), we were not able to find studies comparing exercise capacity between children with controlled or uncontrolled STRA. An association of exercise and control of asthma has already been demonstrated in a large population-based study in adults (35). In addition, in children, a recent study has shown that asthmatic patients with uncontrolled asthma achieved a decreased distance in the 6-min walk test when compared to controlled subjects, although no information on disease severity of patients was provided (36). In the present study, when stratifying patients with STRA by level of disease control, there were no significant differences in CPET results at peak exercise between patients with controlled/partially controlled *vs.* uncontrolled asthma. Therefore, it is reasonable to assume that, even in a group of patients with STRA, there are quite heterogeneous clinical features that may influence the parameters evaluated. Moreover, these results may be related to the fact that the children and adolescents with STRA studied here were under regular outpatient clinical follow-up, with regular appointments that allowed medications and doses to be adjusted and omalizumab to be prescribed for some patients.

The FEV_1 values found in the analysis of pulmonary function showed that children and adolescents with STRA had normal pulmonary function or mild airway obstruction. Patients with FEV_1<80% of predicted had a significantly lower ventilatory reserve in CPET than those with FEV_1>80%, suggesting that airway obstruction may contribute to increased exercise intolerance. However, when other CPET variables

(VO_{2peak} and ventilatory equivalents) were correlated with pulmonary function, no significant correlations were observed. It seems possible that shorter temporal exposure to the disease, impaired airway remodeling, and use of modern pharmacotherapy may help explain these findings in pediatric samples (37–41). In asthmatic patients, pulmonary function impairment appears to become more relevant in early adulthood, which may be associated with an excessively labile bronchomotor tone in children with STRA, thereby explaining the few spirometric changes even in the presence of frequent symptoms (35).

EIB assessment showed that, of 23 children and adolescents with STRA evaluated, 54.2% were positive for EIB with $a > 15\%$ fall in FEV_1. A study of asthmatic children (not receiving inhaled corticosteroids) that evaluated EIB and the effects of asthma severity reported a prevalence of 45.7% of EIB in children with severe asthma (42), which is consistent with our findings, although the use of corticosteroids were not withheld in the present study and may have influenced results. In addition, evidence from mild-to-moderate children with asthma has shown that aerobic fitness, as measured by VO_2max, did not correlate with EIB, although no other CPET variables were reported (43). The present results showed a correlation between exercise-induced bronchospasm and ventilatory efficiency at peak exercise, suggesting that patients with greater airway responsiveness have lower ventilatory efficiency in eliminating CO_2, thus contributing to a reduction in exercise tolerance. Despite the multifactorial determinants of exercise intolerance, these factors may contribute to premature cessation of physical activity, leading to a more sedentary lifestyle (5,6,39).

Although aerobic fitness, as an isolated factor, does not differ between mild-to-moderate asthmatics and healthy children, the interaction between habitual physical activity levels and exercise tolerance may impact asthmatic patients (12). In the present study, VO_{2peak} and ventilatory efficiency were significantly correlated with resting HR. This finding may be of clinical and prognostic relevance because individuals with good aerobic fitness tend to have lower resting HR (42), and HR measurement is a simple and inexpensive procedure. In addition, healthy adolescents with higher levels of habitual physical activity also present lower resting HR (44). Other determinant factors that may contribute to exercise intolerance include the concern that physical exertion might trigger bronchial obstruction and obesity. In a study examining the relationships among asthma severity, level of physical activity, aerobic fitness, and body weight in asthmatic children, asthma severity was not associated with oxygen consumption, but there was a strong association of aerobic fitness with perceived competence in physical activity, weight gain, and greater medication needs (6). The elevated heart rate found in the present study, both at rest and at the AT, may indicate deconditioning, although other possible influencing factors, as anxiety levels in patients with asthma, cannot be ruled out.

Limitations of this study include the lack of assessment of the level of daily physical activity of the children and adolescents, which could influence the results of exercise capacity. Furthermore, the fact that some patients used omalizumab (nonspecific anti-IgE immunotherapy) may have contributed to an improved performance because of the well-known benefits of the medication for patients with STRA, which may have influenced the results of exercise capacity, pulmonary function, disease control, and EIB (45,46). However, it is deemed unethical to discontinue medication for study purposes. Vocal cord dysfunction and exercise-induced laryngeal obstruction were not directly evaluated and could play a role in the present results. In addition, the influence of obesity was not addressed, as only few patients with overweight were included.

Conclusions

The results of the present study indicate that exercise capacity is impaired in approximately 30% of children and adolescents with STRA. Pulmonary function and EIB seems to be associated with different aspects of physical fitness. Resting HR may be an easy-to-use clinical marker, as it correlated with several performance parameters in CPET. Recommendations for the practice of physical activity should be reinforced also in patients with STRA.

Disclosure statement

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

Funding

The researchers would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – finance code 001 – and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support.

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