

## Relationship between aerobic fitness and clinical indicators of asthma severity in children\*

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In order to assess the relationship between the physical fitness of asthmatics and the clinical expression of the underlying disease, the authors studied 39 physically active children with moderate to severe but stable asthma. The patients (25 boys and 14 girls, aged between 9 and 16 years) were submitted to clinical evaluation; spirometry before and after bronchodilator (BD); maximal cardiopulmonary exercise test in cycle ergometer with breath-by-breath analysis of ventilatory and gas exchange variables; and, on a separate day, an exercise challenge test. As expected by the clinical stability, FEV<sub>1</sub> post-BD was in the normal range in most of the children (mean  $\pm$  SD = 93.8  $\pm$  13.7% predicted). Maximal oxygen uptake (VO<sub>2</sub>max) was higher than the lower 95% confidence interval in 31/39 children; and in 29/39, the oxygen uptake at the anaerobic threshold (VO<sub>2</sub>AT) showed values above the lower limit of normality. Seven patients with low tolerance to exercise (reduced VO<sub>2</sub>max) presented suggestions of circulatory limitation (cardiovascular and/or peripheral) and only 1 had ventilatory limitation. There was no association or correlation between the lower ventilatory reserve (VE<sub>max</sub>/MVV% ratio > 80%) and the decreased VO<sub>2</sub>max. Reduction in VO<sub>2</sub>AT, but not VO<sub>2</sub>max, was associated with some clinical indicators of asthma severity, e.g. (i) higher daily inhaled beclomethasone and frequent courses of oral steroids (p < 0.05) and (ii) higher exercise-induced bronchospasm occurrence (p < 0.01). The results show that (i) most patients with moderate to severe asthma, when clinically stable and physically active, present an adequate level of exercise tolerance; (ii) in estimation of the clinical severity of bronchial asthma in children, VO<sub>2</sub>AT is a better aerobic index than VO<sub>2</sub>max. (*J Pneumol* 1998;24(1):3-10)

### Relação entre capacidade aeróbia e indicadores clínicos da gravidade da asma em crianças

Para avaliar a relação entre o desempenho cardiorrespiratório aeróbio de asmáticos e a expressão clínica da doença, os autores estudaram 39 crianças fisicamente ativas, com asma brônquica estável, de grau moderado a grave. Os pacientes (25 meninos e 14 meninas, com idade entre 9 e 16 anos) foram submetidos a avaliação clínica, espirometria pré e pós-broncodilatador (BD), teste de exercício cardiopulmonar máximo em cicloergômetro, com análise respiração por respiração da ventilação e das trocas gasosas. Num dia separado, foi realizado um teste de esforço para avaliar broncoespasmo induzido por exercício (BIE). Como esperado pela estabilidade clínica, o VEF<sub>1</sub> pós-BD foi normal na maioria das crianças (média  $\pm$  DP = 93,8  $\pm$  13,7% previsto). O consumo máximo de oxigênio (VO<sub>2</sub>max) foi maior que o limite de normalidade (95% do intervalo de confiança) em 31 das 39 crianças; e em 29 de 39 o VO<sub>2</sub>max e o limiar anaeróbio (VO<sub>2</sub>AT) mostrou valores acima deste limite. Sete pacientes com baixa tolerância ao exercício (VO<sub>2</sub>max reduzido) tiveram sinais de limitação circulatória (cardiovascular e/ou periférica) e somente um teve limitação ventilatória. Não houve associação ou correlação entre a baixa reserva ventilatória (VE<sub>max</sub>/VVM% > 80%) e valores reduzidos do VO<sub>2</sub>max. Redução no VO<sub>2</sub>AT, mas não do VO<sub>2</sub>max foi associado com: (i) maior uso diário de beclometasona e frequentes períodos de uso de corticosteróide oral (p < 0,05); e (ii) maior ocorrência de BIE (p < 0,01). Nossos resultados mostram que a maioria dos pacientes com asma moderada a grave, quando clinicamente estáveis e ativos, apresentam níveis adequados de tolerância ao exercício. Na avaliação de gravidade clínica da asma brônquica em crianças, VO<sub>2</sub>AT é um indicador aeróbio melhor que o VO<sub>2</sub>max.

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## INTRODUCTION

Cardiorespiratory fitness in normal individuals presents marked differences according to genetic characteristics, sex, age and usual level of physical activity<sup>(1)</sup>. Patients with chronic respiratory diseases tend to show less tolerance to exercise because of actual pulmonary limitation, self-restriction to activities (fear of dyspnea) or lack of physical activity due to medical orientation or family influence<sup>(2)</sup>. Thus, subjects with bronchial asthma, primarily those with a clinically more severe disease, tend to present a marked sedentary lifestyle<sup>(2,3)</sup>. This trait is particularly common in patients with exercise-induced bronchospasm who more frequently avoid dyspnea-generating activities<sup>(3)</sup>.

Most studies that analyzed tolerance to dynamic exercise in asthmatic children evaluated patients with mild to moderate disease or those taking part in aerobic physical training programs<sup>(4-6)</sup>. Although asthmatics are usually considered to be less fit for dynamic exercise, the relationship between the clinical aspects of the underlying disease and the objective parameters of exercise performance has been described in a conflicting way<sup>(6,7)</sup>. Thus, Ludwick *et al.*<sup>(6)</sup> found that 49% of the sixty-five severe asthmatic children studied had a reduced maximal exercise performance, but no clinical features of disease severity were associated with an abnormal exercise response. On the other hand, Strunk *et al.*<sup>(7)</sup> found that an episodic or continuous steroid use in the year before testing was significantly related to a decreased nine-minute running performance ( $p = 0.0004$ ) in a sample of 76 moderate to severe asthmatic children.

Therefore, the purpose of this study was twofold: (i) to evaluate the overall tolerance to exercise of a group of moderate to severe asthmatic children and (ii) to analyze a possible association between aerobic performance and clinical and functional markers of severity of the underlying disease.

## METHODOLOGY

### SUBJECTS

Thirty-nine asthmatic children (25 boys and 24 girls), aged between 9 and 16 years (mean  $\pm$  SD = 12.4  $\pm$  1.8 years), were studied. Means  $\pm$  SD of body mass and height were 41.4  $\pm$  9.8 kg and 148.8  $\pm$  10.3 cm, respectively (table 1). According to the clinical parameters of the "International Consensus Report on Diagnosis and Management of Asth-

## Abbreviations

BD – Bronchodilator  
 EIB – Exercise-induced bronchospasm  
 f – Respiratory rate  
 FEV<sub>1</sub> – Forced expiratory volume in one second  
 FVC – Forced vital capacity  
 HR – Heart rate  
 max – At maximal exercise  
 MVV – Maximal voluntary ventilation  
 O<sub>2</sub> pulse – Oxygen pulse (VO<sub>2</sub>/HR)  
 PEFr – Peak expiratory flow rate  
 pred – Predicted  
 R – Respiratory exchange ratio  
 SaO<sub>2</sub> – Oxyhemoglobin saturation  
 Ti/Ttot – Inspiratory duty cycle  
 VCO<sub>2</sub> – Carbon dioxide production  
 V<sub>E</sub> – Minute ventilation  
 V<sub>E</sub>/VCO<sub>2</sub> – Ventilatory equivalent for carbon dioxide  
 V<sub>E</sub>/VO<sub>2</sub> – Ventilatory equivalent for oxygen  
 VO<sub>2</sub> – Oxygen uptake  
 VO<sub>2</sub>AT – VO<sub>2</sub> at the anaerobic threshold  
 V<sub>I</sub>/Ti – Mean inspiratory flow  
 WR – Work rate

ma", 1992<sup>(8)</sup>, 24 of 39 patients (61.6%) were classified as severe asthmatics presenting: a) frequent bronchospasm exacerbation and nocturnal asthma symptoms almost daily; b) peak expiratory flow rate (PEFR) values < 60% predicted at baseline despite optimal therapy; c) daily use of inhaled anti-inflammatory agent at high doses (beclomethasone > 800  $\mu$ g/day) and frequent use of systemic corticosteroids. The remainder 15 children were considered moderate asthmatics presenting: a) symptoms requiring inhaled B<sub>2</sub>-agonist almost daily and nocturnal asthma symptoms > 2 times a month but not daily; b) PEFr values between 60-80% predicted at baseline but normal after bronchodilator; c) daily

**TABLE 1**  
**Anthropometric and spirometric characteristics of the children with moderate to severe but stable asthma (n = 39; 25 boys and 14 girls)**

Variables	Values (Mean $\pm$ SD)	Range
Age (years)	12.4 $\pm$ 1.8	9-16
Weight (kg)	41.4 $\pm$ 9.8	27.5-80
Height (cm)	148.8 $\pm$ 10.3	131-179
FVC pre-BD (% pred)	99.9 $\pm$ 13.0	72-130
FEV <sub>1</sub> pre-BD (% pred)	82.9 $\pm$ 13.8	47-106
FEV <sub>1</sub> pre-BD (L)	2.01 $\pm$ 0.61	1.01-4.29
FEV <sub>1</sub> /FVC pre-BD	0.71 $\pm$ 0.11	0.59-0.81
FEV <sub>1</sub> post-BD (% pred)	93.8 $\pm$ 13.7	59.5-112
FEV <sub>1</sub> post-BD (L)	2.40 $\pm$ 0.44	1.32-4.56
FEV <sub>1</sub> /FVC post-BD	0.78 $\pm$ 0.07	0.65-0.84

Definition of abbreviations: FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in one second of FVC; BD: bronchodilator; pred: predicted.

use of anti-inflammatory agent at low or moderate doses (beclomethasone < 800 µg/day). All patients were on inhaled corticosteroid (beclomethasone between 400 and 1500 µg/day) and 24 had a past history of frequent courses of oral corticosteroids; nevertheless, no patient was on systemic steroids at the time of the study. According to the "Guidelines for the Evaluation of Impairment/Disability in Patients with Asthma", 1993<sup>(9)</sup>, 61.6% of the patients (24 out of 39) presented a medication score > 3, requiring for clinical asthma control: bronchodilator on demand, inhaled beclomethasone in a daily dose equal to or higher than 800 µg or frequent courses of oral steroids.

The patients were referred to the Center of Sport Practices of the University of São Paulo (CEPEUSP) where they were undertaking an 8-week multidisciplinary follow-up program for asthmatics, including recreational and sport activities. Although physically active, the patients did not follow an individualized or supervised aerobic training program. All studied children had a regular medical follow-up by a staff physician (A.L.B.C.) and were at a stable phase of the disease, with no symptoms or exacerbation 15 days prior to the tests. None of the tested individuals presented any orthopedic limitation to the exercise or contraindication for the exercise tests. Informed consent was obtained from the patients and their parents, after explanation of the procedures to be carried out.

#### STUDY DESIGN

The patients were evaluated initially at the Exercise Laboratory of the Respiratory Division of the Federal University of São Paulo – Paulista School of Medicine (Unifesp-EPM). They were submitted to a brief clinical history and physical examination, spirometry before and after bronchodilator and then to cardiopulmonary exercise test on a cycle ergometer. Afterwards, on a separate day, the patients were submitted to a protocol for detection of exercise-induced bronchospasm at the Center of Sport Practices of the University of São Paulo (CEPEUSP).

#### SPIROMETRY

Spirometric tests were performed in all subjects, before and ten minutes after the inhalation of 200 µg of salbutamol given by pressurized metered-dose inhaler (MDI) connected to a spacer. The equipment used was a CPF-S (Medical Graphics Corp. – MGC, St. Paul, MN, USA) with flow measurement carried out with a pneumotachygraph Fleisch No. 3. Technical procedures, acceptability and reproducibility criteria were those recommended by the American Thoracic Society, 1991<sup>(10)</sup>. Predicted normal values for all spirometric variables were those of Knudson *et al.*<sup>(11)</sup>. Maximal voluntary ventilation (MVV) was estimated from the product of the forced expiratory volume in one second ( $FEV_1$ ) x 40<sup>(12)</sup>. A positive response to bronchodilator was defined as a 15% and 200 mL increase in  $FEV_1$ <sup>(10)</sup>.

#### CARDIOPULMONARY EXERCISE TESTING (CPX)

Exercise tests were performed using a digital computer-based exercise system (MGC-CPX System, Medical Graphics Corp. – MGC, St. Paul, MN, USA). The maximal exercise test was carried out on a calibrated electromagnetically braked cycle ergometer (CPE 2000, Medical Graphics Corp. – MGC, St. Paul, MN, USA), modified with children pedal cranks. The selected work rate was continuously increased in a linear ramp pattern (15 watts per minute if height < 150 cm or 20 watts per minute if height > 150 cm)<sup>(13)</sup> so that the incremental exercise test duration was greater than 8- and lower than 12-minutes<sup>(14)</sup>. During the test, subjects used a nose-clip and breathed through a mouthpiece connected to a low-resistance, two-way non-rebreathing Hans-Rudolph 2600 valve (60 ml dead space). Expired airflow was measured by a pneumotachygraph Fleisch No. 3 in the flow/volume system's module. Expired gases were withdrawn at a flow of 1 ml/sec from a point just proximal to the mouthpiece; signals proportional to the fractional concentrations of carbon dioxide and oxygen were generated by rapidly responding infrared and fuel zirconium cell analyzers, respectively. A microprocessor ("waveform analyzer") received, through specific channels, the different analogue signals. Since the generation of these signals was not simultaneous, the microprocessor temporally aligned them, promoting a calibrated delay ("phase delay"), allowing breath-by-breath analysis of metabolic, ventilatory and cardiovascular variables<sup>(14)</sup>. The analogue signals of cardiac electric activity (Funbec 4A-1CN cardioscoper, Funbec ECG-3 electrocardiograph) and oxyhemoglobin saturation (OxyShuttle™ SensorMedics pulse oxymeter, SensorMedics Corp., Anaheim, CA, USA) were also sent to the microprocessor. Afterwards, the signals were digitized and sent to a host computer that, through a specific software (Desktop Series, MGC) displayed the variables, in graphical and numerical forms for a follow-up in real time, saving them for further analysis. The cardiopulmonary exercise test consisted of the metabolic, ventilatory and cardiovascular analysis for 2 minutes at rest; 2 minutes with real zero workload, obtained through electrical moving of the ergometer freewheel at 60 rpm; and afterwards during exercise. The children were actively encouraged throughout the test to maintain a pedaling rate as constant as possible between 50 and 70 rpm following a pedaling rate meter. A servomechanism in the electronic braking system of the ergometer maintained the input work to an accuracy error of 1% within a range of these pedaling rates. The selected workload (15 or 20 watts per minute) was linearly increased with the patient pedaling until maximal symptom-limited workload. The variables were also measured during the first two minutes of the recovery phase and subsequently the subjects were asked about the nature and intensity of the limiting symptoms (modified Borg scale)<sup>(15)</sup>.

The data were calculated automatically using standard formulae<sup>(14)</sup> and displayed in descriptive numerical (every 20 seconds) and graphical (8 breaths moving average) forms. The following data were obtained breath-by-breath: oxygen uptake ( $\dot{V}O_2$ , ml/min STPD); carbon dioxide production ( $\dot{V}CO_2$ , ml/min STPD); respiratory exchange ratio (R); minute ventilation ( $\dot{V}_E$ , l/min BTPS); respiratory rate (f, bpm); ventilatory equivalent for  $O_2$  and  $CO_2$  ( $\dot{V}_E/\dot{V}O_2$  and  $\dot{V}_E/\dot{V}CO_2$ ); end-tidal partial pressures of  $O_2$  and  $CO_2$  ( $P_{ET}O_2$  and  $P_{ET}CO_2$ , mmHg); inspiratory duty cycle ( $T_i/T_{tot}$ ); mean inspiratory flow ( $\dot{V}_T/T_i$ , l/s); heart rate (HR, bpm) and oxygen pulse ( $\dot{V}O_{2/HR}$ , ml/beat). The predicted  $\dot{V}O_{2max}$  was calculated from the equations of Cooper *et al.* for children<sup>(16)</sup> who consider the  $\dot{V}O_{2max}$  as the largest breath-by-breath  $\dot{V}O_2$  value achieved by the subject submitted to a ramp protocol. In order to smooth the high intra- and inter-breath variability of the breath-by-breath data, we took the  $\dot{V}O_{2max}$  as the highest  $\dot{V}O_2$  value of the last 8 test breaths ("peak  $\dot{V}O_2$ ") and expressed it in absolute values (ml/min), corrected for actual weight (ml/min  $\times$   $kg^{-1}$ ) and as percent of the predicted (% pred). Considering the close demographic and anthropometric similarity of our population and the one studied by Cooper *et al.*<sup>(16)</sup> and also the similarity of the method of  $\dot{V}O_{2max}$  analysis in both studies, the lower limit of normality for  $\dot{V}O_{2max}$  was defined according to the values proposed by these authors (lower 95% confidence limit; mean  $-1.64 \times$  SD). For girls < 11 years = 26 ml/min  $\times$   $kg^{-1}$ ; girls > 11 years = 27 ml/min  $\times$   $kg^{-1}$ ; boys < 13 years = 32 ml/min  $\times$   $kg^{-1}$ ; boys > 13 years = 37 ml/min  $\times$   $kg^{-1}$ . The  $\dot{V}O_2$  at the anaerobic threshold ( $\dot{V}O_{2AT}$ ) was estimated by the gas exchange method inspecting visually the inflection point of  $\dot{V}CO_2$  regarding  $\dot{V}O_2$  (modified V-slope)<sup>(17)</sup> and by the ventilatory method, when  $\dot{V}_E/\dot{V}O_2$  and  $P_{ET}O_2$  increased while  $\dot{V}_E/\dot{V}CO_2$  and  $P_{ET}CO_2$  remained stable. The reading was performed independently by two experienced observers without knowledge of other results or subject identities. In case of discordance, a third reviewer would be used to reach a consensus or to eliminate the subject. In this study a consensus was always reached and the  $\dot{V}O_{2AT}$  was identified in all studied patients. The lower limit of normality for  $\dot{V}O_{2AT}$  was defined at 40% of  $\dot{V}O_{2max}$  predicted, considering that from 109 children evaluated by Cooper *et al.*, only one presented a value below this cutoff<sup>(16)</sup>.

In order to analyze the ventilatory response to  $\dot{V}CO_2$  during the incremental test – an useful index of ventilatory stress<sup>(18)</sup> – a graphical presentation of  $\dot{V}_E$  as a function of  $\dot{V}CO_2$  was used to establish the point at which  $\dot{V}_E$  increases out of proportion to  $\dot{V}CO_2$  (respiratory compensation point – RCP). Linear regression techniques were used to fit the best-line from the data starting at 60 seconds after the onset to exercise to the RCP, and the slope ( $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ ) was calculated for each subject. The obtained values were then compared to weight-based predicted from Cooper *et al.*<sup>(18)</sup>:  $\Delta\dot{V}_E/\Delta\dot{V}CO_2 = -0.099 \times$  weight (kg) + 28.7. The oxygen costs at maxi-

mal exercise for each child were calculated ( $\dot{V}O_{2max}/WR_{max}$ , l/min/w) and compared to predicted proposed by Zanconato *et al.*<sup>(19)</sup>, as a function of height ( $-0.095 \times$  height (cm) + 29.11).

Analysis of the factors limiting exercise followed recommendations of Wasserman *et al.*<sup>(14)</sup>, and Nery *et al.*<sup>(20)</sup>. Briefly, circulatory limitation (cardiovascular and/or peripheral) was considered in subjects with reduced  $\dot{V}O_{2max}$ ,  $\dot{V}O_{2AT}$ , oxygen pulse and leg pain as the main limiting symptom. Pulmonary limitation was suggested in patients with decreased  $\dot{V}O_{2max}$ , ventilatory pattern of high frequency and low tidal volume in addition to dyspnea as the main symptom at maximal exercise. The presence of an elevated  $\dot{V}_{Emax}/MVV\%$  ratio (> 80%) was suggestive of the ventilatory limitation and a > 4% oxyhemoglobin desaturation showed abnormality in pulmonary gas exchange.

#### EXERCISE CHALLENGE TEST

The test for exercise-induced bronchospasm (EIB) detection was carried out with a mechanically-braked Monark® cycle ergometer. Methylxanthines and  $B_2$ -adrenoceptor agonist were withheld 12 hours prior to the test. Before the exercise, the patient performed a forced expiratory maneuver (Vitrace® spirometer) with assessment of forced vital capacity (FVC) and  $FEV_1$  basal values. The test was carried out only in patients with normal spirometry at rest:  $FEV_1$  above 80% of the predicted<sup>(11)</sup> (n = 32). The tests were accomplished on ambient temperature between 18 and 22 C, barometric pressure between 680 and 720 mmHg and on air relative humidity between 55 and 80%. After one minute of light exercise on the cycle ergometer, the workload was quickly increased until the heart rate corresponding to 80% of predicted (220-age)<sup>(14)</sup>, then being maintained for 6 minutes<sup>(21)</sup>. This target workload was selected in order to set an intense exercise, with high ventilatory rates and great heat and water loss *via* the bronchial mucosa. Spirometric evaluations were performed successively at 5, 10 and 20 minutes after the exercise. EIB was defined as present if  $FEV_1$  showed a reduction equal to or greater than 10% of its pre-exercise values<sup>(21)</sup>.

#### STATISTICAL ANALYSIS

The values are reported as mean  $\pm$  SD and their ranges. The following statistical tests were used: a) Linear regression technique to determine the slope of the  $\Delta\dot{V}_E/\Delta\dot{V}CO_2$  relationship during the maximal exercise test and the correlation between  $\dot{V}_{Emax}/MVV\%$  ratio and  $\dot{V}O_{2max}$ ; b) Paired *t* test to compare the  $\Delta\dot{V}_E/\Delta\dot{V}CO_2$  slopes and  $\dot{V}O_{2max}/WR_{max}$  relationship with their predicted values (Cooper *et al.*<sup>(16)</sup>); c) Non-paired *t* test for independent samples, in the comparison of data among patients with and without EIB; d) Chi-square (Fisher Exact) test for association between the variables. Level of statistical significance was always set at  $p < 0.05$ .

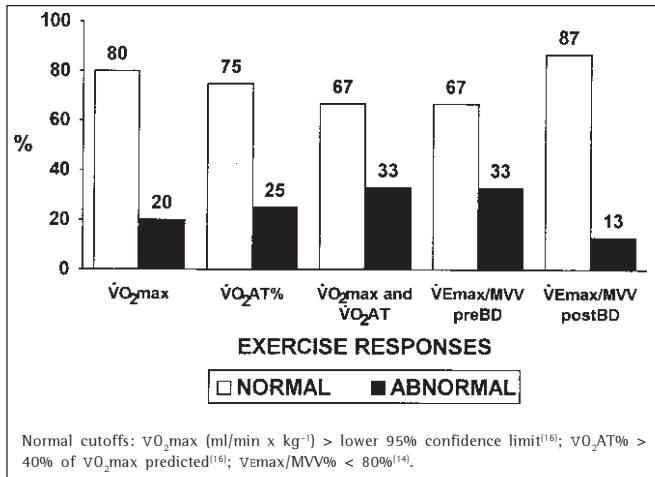


Figure 1 – Percentage of patients with normal or abnormal metabolic and ventilatory responses at maximal exercise (n = 39)

RESULTS

Mean ± SD values for spirometry of the clinically stable studied population were within the normal range; FEV<sub>1</sub> post-bronchodilator (BD) being 93.8 ± 13.7% of the predicted (table 1). Only 4 patients presented post-BD FEV<sub>1</sub> below 80% of the predicted. In 17 children (43%) a positive response to BD was obtained.

The results of the cardiopulmonary exercise test showed that the patients, as a group, had metabolic and cardiovascular variables close to the predicted values for normal children (table 2)<sup>(16)</sup>.  $\dot{V}O_{2max}$  was above the lower 95% confidence limit (see METHODS) in 31 of the 39 individuals (mean ± SD = 37.8 ± 7.8 ml/min x kg<sup>-1</sup>). In 29 children (75%), the  $\dot{V}O_{2AT}$  was considered normal (> 40%  $\dot{V}O_{2max}$  pred; mean ± SD = 47.4 ± 10.6%) and in 26 patients (67%) both were within the normal range (figure 1). Additionally, the oxygen

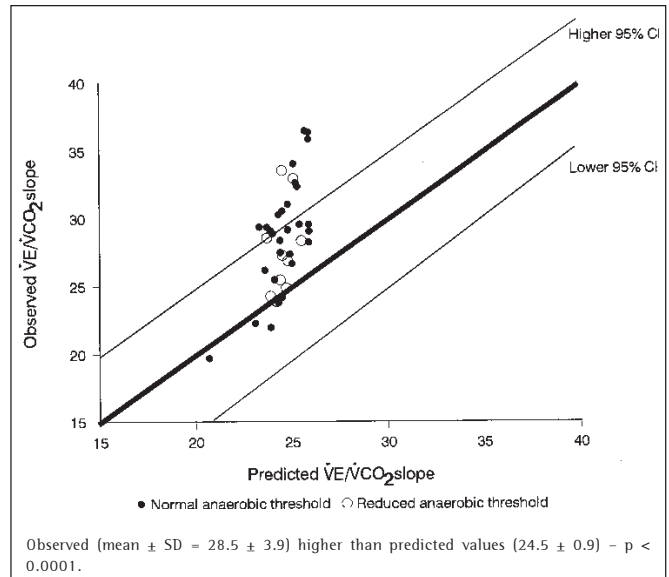


Figure 2 – Comparison between observed and predicted  $\Delta VE/\Delta VCO_2$  slopes during incremental exercise in asthmatic children with normal (•) or reduced (○)  $\dot{V}O_{2AT}$

costs of exercise for the whole group ( $\dot{V}O_{2max}/WR_{max}$ ; mean ± SD = 15.4 ± 3.4) were not significantly different than its predicted values<sup>(19)</sup> (mean ± SD = 14.9 ± 1.0); on the other hand, as expected, a significantly reduced oxygen costs were found in patients with reduced  $\dot{V}O_{2AT}$  (observed = 12.0 ± 0.7; predicted = 14.6 ± 0.6 – p < 0.0001). Analyzing the mechanisms of exercise limitation, we found that from 8 asthmatic children with effective reduction in maximal aerobic tolerance (reduced  $\dot{V}O_{2max}$ ), 7 presented evidences of circulatory (cardiovascular and/or peripheral) and one of ventilatory limitation. None of the patients presented suggestions of pulmonary gas exchange abnormalities.

The  $\dot{V}Emax/MVV\%$  ratio was greater than 80% in 13 patients when MVV was estimated from pre-BD FEV<sub>1</sub> and in only 5 when post-BD FEV<sub>1</sub> was used (figure 1). There was no association of higher  $\dot{V}Emax/MVV\%$  ratio with lower aerobic performance, since 4 of these 5 patients had  $\dot{V}O_{2AT}$  and  $\dot{V}O_{2max}$  above of predicted values. Although ventilatory factors were not related to maximal performance, we found in increased ventilatory response to metabolic load (steeper  $\Delta VE/\Delta VCO_2$  slopes) in 16/39 children, independently of a normal or reduced  $\dot{V}O_{2AT}$  (p < 0.0001 – figure 2).

In order to investigate the relationship between aerobic performance at maximal exercise and clinical parameters of the underlying disease, we compared the association of a sensitive indicator of asthma severity (medication score) with the main metabolic variables ( $\dot{V}O_{2max}$  and  $\dot{V}O_{2AT}$ ). There was a significant association between reduced  $\dot{V}O_{2AT}$  and high medication score (> 3)<sup>(9)</sup>. Thus, 90% of the patients with reduced  $\dot{V}O_{2AT}$  had a daily use of 800 µg or more of inhaled

Variables	Values (Mean ± SD)	Range
% $\dot{V}O_2$ (% pred)	87.3 ± 17.6	57-117
$\dot{V}O_{2max}$ (ml/min x kg <sup>-1</sup> )	37.8 ± 7.8	21.6-51.4
$\dot{V}O_{2max}$ (ml/min)	1,550 ± 500	895-3,819
WR <sub>max</sub> (watts)	110.5 ± 35.2	68-228
$\dot{V}O_{2AT}/\dot{V}O_{2max}$ pred (%)	47.4 ± 10.6	33.8-67.3
HR <sub>max</sub> (% pred)	90.4 ± 8.1	76.3-110.5
O <sub>2</sub> pulse max (% pred)	98.0 ± 19.4	66.8-145
$\dot{V}Emax/MVV$ (%)	63.4 ± 13.2	35.1-87.4
SaO <sub>2</sub> max (%)	95.2 ± 3.2	92-98

Definition of abbreviations:  $\dot{V}O_{2max}$ : maximum oxygen uptake; WR: work rate;  $\dot{V}O_{2AT}$ : oxygen uptake at the anaerobic threshold; HR: heart rate;  $\dot{V}e$ : minute ventilation; MVV: maximal voluntary ventilation; SaO<sub>2</sub>: oxygen saturation.

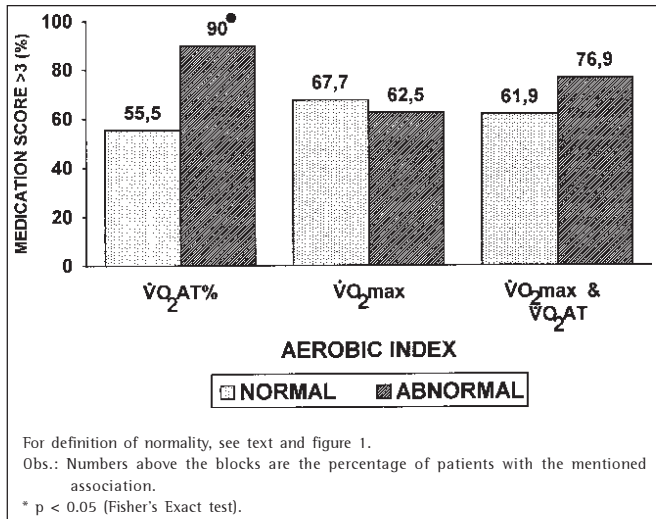


Figure 3 – Association between high medication score (> 3) and normality or not of the aerobic indexes at maximal exercise (n = 39)

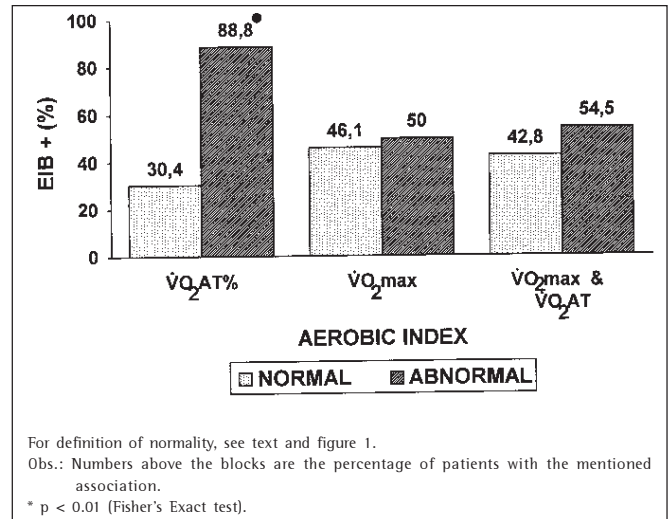


Figure 4 – Association between a positive exercise challenge test (EIB+) and normality or not of the aerobic indexes at maximal exercise (n = 32)

beclomethasone and frequent courses of oral steroids, contrasting with 55% of the patients with normal  $\dot{V}O_{2AT}$  and use of high doses of medication ( $p < 0.05$ ). The reduced  $\dot{V}O_{2max}$ , alone or in addition to reduced  $\dot{V}O_{2AT}$ , was not associated with high medication score (figure 3).

From 39 evaluated patients, 32 performed an exercise challenge test (basal  $FEV_1 > 80\%$  predicted). In 17 of them (53%), a positive response was obtained. Spirometric and clinical indicators of asthma severity did not differ between responders and non-responders, regarding EIB (table 3). However, 88.8% of the patients with reduced  $\dot{V}O_{2AT}$  had EIB and only 30.4% of the individuals with normal  $\dot{V}O_{2AT}$  presented EIB ( $p < 0.01$ ). Reduced  $\dot{V}O_{2max}$ , alone or in addition to reduced  $\dot{V}O_{2AT}$ , was not significantly associated with a higher EIB occurrence (figure 4).

TABLE 3  
Spirometric and clinical findings of asthmatic children with and without exercise-induced bronchospasm (EIB)

	EIB positive <sup>a</sup> (n = 15)	EIB negative (n = 17)
Spirometry (mean ± SD)		
FEV <sub>1</sub> pre BD (% pred)	79.4 ± 9.1	82.5 ± 17.8
FEV <sub>1</sub> post BD (% pred)	91.8 ± 10.2	93.7 ± 13.8
Clinical (% frequency)		
Positive BD response <sup>b</sup>	10 (66.6%)	6 (35.2%)
Severe asthma	13 (86.6%)	13 (76.4%)

a Decrease of FEV<sub>1</sub> > 10%, determined by 6-minute exercise at 80% of pred HRmax<sup>(21)</sup>;  
b Positive response to bronchodilator, with increase of FEV<sub>1</sub>, above 15% and 200 ml in relation to basal<sup>(19)</sup>.  
Obs.: Differences between mean values were not statistically significant (non-paired t test).

## DISCUSSION

In this study we evaluated the aerobic performance of children with moderate to severe bronchial asthma and we found an adequate level of cardiorespiratory fitness, reflected in the  $\dot{V}O_{2max}$ ,  $\dot{V}O_{2max}/WR_{max}$  relationship,  $\dot{V}O_{2AT}$ , and maximal O<sub>2</sub> pulse values. These findings are at variance with several former studies<sup>(3,6,7)</sup> and probably influenced by the homogeneity of the group regarding clinical stability and level of physical activity. On the other hand, our data are in accordance with the findings of Fink *et al.*<sup>(23)</sup> who showed that moderate to severe trained patients had an adequate overall aerobic performance compared to asthmatic controls.

However, a small number of patients presented reduction of exercise tolerance (decreased peak  $\dot{V}O_2$ ) primarily due to “circulatory” factors (7 out of 8). Although Varray *et al.*<sup>(24)</sup> have suggested a cardiogenic role for the lower tolerance to exercise in severe asthmatics, our results indicate a peripheral origin for this limitation, since the clinical evaluation was not able to detect any cardiac abnormality. In agreement with most of the previous studies<sup>(3,4,6)</sup>, neither spirometric nor clinical severity factors were associated with the lower maximal aerobic power. Although no psychological profile of our patients was obtained, and the effective extent of individual adherence to sport activities was unknown, differences in attitudes toward the disease and physical exercise could, at least partially, explain these findings<sup>(25,26)</sup>. Strunk *et al.*<sup>(25)</sup> evaluated 90 children with moderate and severe asthma, correlating through multivariate regression, the cardiorespiratory fitness during exercise with clinical and functional variables at rest and indicators of psychological maturity. The authors showed that the wide variability in aerobic performance was mainly due to the degree of social and

disease adjustment, the medical indicators being of little help. Engström *et al.*<sup>(26)</sup> evidenced in a group of 10 severe asthmatic children submitted to physical training that only psychological modifications correlated significantly with metabolic improvement ( $p < 0.001$ ). Thus, individual variations regarding acceptance and knowledge of the disease seem to definitely influence the usual level of physical activity of asthmatic children and, therefore, their degree of fitness.

Ventilatory limitation to exercise was evidenced in only 1 child. Although other 4 subjects presented a high  $v_{E\max}/MVV\%$  post-BD ratio ( $> 80\%$ ), in these patients the  $v_{O_2AT}$  was normal and the  $v_{O_2\max}$  was above the lower 95% confidence interval. Such findings, as a whole, suggest that this low ventilatory reserve did not limit these particularly fit children. However, considering the low sensitivity and specificity of the  $v_{E\max}/MVV\%$  ratio as isolated indicator of ventilatory limitation and the possible different exercise  $MVV$ <sup>(27)</sup>, this ratio should be used with caution in the diagnosis of ventilatory limitation in asthma. Even so, the decrease in the number of patients with low ventilatory reserve from 13 ( $MVV$  estimated from pre-BD  $FEV_1$ ) to 5 individuals ( $MVV$  estimated from post-BD  $FEV_1$ ) illustrates the importance for asthmatics to perform exercise with the best pre-exercise lung function. A particularly interesting finding was the excessive ventilatory response in relation to metabolic load (steeper  $\Delta V_E/\Delta VCO_2$  slope) in 16 of 39 children. This response could be linked to a reduced ventilatory efficiency ( $v/\dot{Q}$  inhomogeneities with larger deadspace ventilation) and/or an increased ventilatory drive (lower  $CO_2$  set-point)<sup>(18)</sup>.

Analyzing the indicators of aerobic performance to exercise we observed that only the reduced  $v_{O_2AT}$  values were associated with a greater use of daily anti-inflammatory medication, a particularly valuable indicator of the clinical severity of the disease<sup>(9)</sup>. Utilization of the  $v_{O_2AT}$  as effort-independent metabolic index is particularly advantageous in the pediatric group, in which the necessary cooperation and motivation for  $v_{O_2\max}$  assessment may not be obtained<sup>(26)</sup>. The above mentioned association could mean a cause-effect type relationship, assuming the possibility of corticosteroid-induced myopathy. Chronic steroid use can induce a reduction in proximal muscle strength (reducing endurance capacity), modify lactate metabolism and reduce selectively the type-II anaerobic fibers<sup>(29)</sup>. On the other hand, the association may only express the fact the asthmatics with a greater daily need for corticoids to control symptoms present recurrent periods of physical inactivity, resulting in lower  $v_{O_2AT}$  values to exercise because of more sedentary lifestyle.

The association of lower  $v_{O_2AT}$  with a higher occurrence of EIB could be interpreted as secondary to hyperventilation caused by early lactacidosis of the more severe patients<sup>(30)</sup>. Bevegard *et al.*<sup>(31)</sup> showed that patients with severe asthma present higher plasma lactate concentration during exercise than those with moderate disease. Henriksen and Nielsen<sup>(32)</sup>

evidenced a close relationship between plasma lactate during activity and presence of EIB. So, the sedentary lifestyle of the more severe patients, associated to a greater occurrence of EIB would induce lower  $v_{O_2AT}$  values and a greater ventilatory response, increasing EIB occurrence<sup>(33)</sup>.

In this study we found a lower occurrence of positive exercise challenge test in moderate to severe asthmatic children than previously reported<sup>(34)</sup>; it may be related to the use of a less asthmogetic exercise (cycle ergometer) compared to treadmill running with mouth breathing of dry and cold air. Another possibility is that the ventilatory stress was not sufficient for an efficient bronchospasm provocation; however, assuming a *quasi*-linear  $v_{O_2}$ -HR relationship in children<sup>(35)</sup>, all tests were performed on a supra-AT domain suggesting an intense ventilatory stimulus.

Generalization of the findings of this study to the usually outpatient population of asthmatic children presents some important limitations. Our patients were clinically stable, received a multidisciplinary follow-up and although they did not participate in a systematic aerobic training, were maintained physically active. Further, the cardiopulmonary exercise testing was performed with the best basal pulmonary function (post-BD). The study of another population with a profile more frequently found in clinical practice could show a higher incidence of ventilatory and peripheral limitation to exercise, with an increase in EIB prevalence. On the other hand, the results obtained with this sample in controlled conditions signal to the effective possibility of fitness maintenance of asthmatic children, even if they have a clinically more severe disease and are steroid-dependent.

In conclusion, our results show that most children with moderate to severe asthma present adequate tolerance to maximal exercise, when clinically stable and physically active. The anaerobic threshold ( $v_{O_2AT}$ ), but not  $v_{O_2\max}$ , was significantly associated with clinical (higher medication score) and functional (positive exercise challenge test) indices of disease severity. These findings suggest that  $v_{O_2AT}$  is a valuable effort-independent index to evaluate the clinical severity of bronchial asthma in children.

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