

PHYSIOLOGY

Analysis of Autonomic Modulation During Maximal and Submaximal Work Rate and Functional Capacity in Asthmatic Children

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Background. Children with asthma experience changes in functional capacity and autonomic control. The literature suggests that this imbalance is responsible for bronchial hyperresponsiveness, primarily during physical effort. **Objective.** The aim of the present study was to evaluate variables of autonomic modulation and functional capacity in asthmatic children after maximum and submaximum work rate. **Methods.** A cross-sectional study was carried out with 24 children [18 in the asthma group (AG) and 6 in the control group (CG)]. Evaluations involved heart rate variability (HRV) and functional capacity [shuttle walk test (SWT) and three-minute step test]. Pulmonary function was also evaluated through spirometry and the fractional concentration of expired nitric oxide (FeNO). **Results.** The asthma diagnostic variables FEV1 and FeNO differed significantly between groups ($p = .01$). Distance traveled on the SWT was lower in the AG (333.13 ± 97.25 m vs. 442.66 ± 127.21 m; $p = .04$). Perceived exertion was greater in the AG. The HRV variables rMSSD and HF did not decrease significantly during the SWT (maximum work rate) in the AG ($p = .01$ and $.04$). FeNO was negatively correlated with FEV1/FVC ($r = -0.70$; $p = .004$) and positively correlated with pNN50 ($r = 0.50$; $p = .03$) in the AG. **Conclusion.** From the autonomic standpoint, asthmatic and non-asthmatic children respond differently to stress. No withdrawal of parasympathetic cardiac modulation occurs in asthmatic children after maximum work rate. Children with asthma experience changes in functional capacity and lung function may vary depending on the degree of inflammation of the airways.

Keywords asthma children, FENO, heart rate variability, shuttle walk test

INTRODUCTION

Asthma is a chronic respiratory disease resulting from inflammation of the airways and manifested clinically by recurrent episodes of coughing, shortness of breath, and wheezing. These episodes are associated with partially reversible airflow obstruction (1, 2).

The autonomic nervous system (ANS) can both promote and inhibit inflammation. The ANS also regulates the tonus of the smooth muscles of the bronchi. These mechanisms are altered in children with asthma (3). As the ANS and heart are closely connected, the data suggest an association between heart rate variability (HRV) and inflammation, which are based on the same neural mechanisms (4). Marsland et al. (5) demonstrated that decreased vagal activity is associated with increased inflammation. Sloam et al. (6) confirmed the hypothesis that decreased vagal activation is related to an increased production of inflammatory cytokines.

HRV is a parameter for assessing the neural function of the heart, as autonomic modulation through the sympathetic and parasympathetic branches acts on the heart and directly influences oscillations in this variable. HRV can be measured by a variety of techniques

and enables the diagnosis of individuals at risk for cardiovascular disease. A number of studies have used HRV analysis (through the quantification of fluctuations in R-R intervals) as a non-invasive means of estimating the influence of sympathetic and parasympathetic tone on the sinoatrial node under different physiological conditions, especially in acute exercise and different forms of physical training (7, 8).

Asthma is associated with an autonomic abnormality involving increased bronchial sensitivity to cholinergic constrictors and possibly decreased sensitivity to β_2 -adrenergic dilators. During physical exertion, the autonomic nervous system responds to stimuli sent by the muscles, lungs, and diaphragm for the withdrawal of the parasympathetic system, resulting in an increase in the diameter of the airways to improve gas exchange in response to the increase in metabolic demand (9). One may, therefore, hypothesize that different degrees of physical stress trigger different changes in autonomic modulation in asthmatic children.

Studies on HRV are useful for identifying and quantifying components associated with lung function and inflammation. Investigations typically assess HRV following an exertion test. To date, however, few studies have evaluated the behavior of this variable after maximum and submaximum physical effort or have correlated autonomic variables with lung function and inflammatory variables (7, 8).

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The aim of the present study was to evaluate the variables of autonomic modulation and functional capacity in asthmatic children during maximum and submaximum work rate and correlate these variables with lung function and inflammation.

METHODS

A cross-sectional study was conducted at the Respiratory Functional Assessment Laboratory (LARESP) of the University Nove de Julho (UNINOVE, São Paulo, Brazil) from July 2011 to January 2012, involving 24 children aged 5–11 years (18 asthmatic subjects and 6 healthy controls). The study received approval from the Human Research Ethics Committee of the university under protocol number 463982/2011. The legal guardians of the subjects signed a statement of informed consent.

The inclusion criteria for the asthma group (AG) were a diagnosis of asthma based on the Guidelines for the Diagnosis and Management of Asthma (10), age 5 to 11 years, absence of regular physical activity, and expired nitric oxide (FeNO) > 20 ppb NIOX Mino™ equipment (Aerocrine- Solna-Sweden). The exclusion criteria were decompensation in the previous 60 days (indicated by bronchodilator and corticosteroid injection) and use of bronchodilator or corticosteroid aerosol within 12 hours prior to evaluation. The control group (CG) was made up of healthy children aged 5–11 years with no history of chronic illness and who did not engage in regular physical activity. Subjects were excluded from either group if they were feverish or showed signs of acute infection at the time of the evaluation. Their guardians were instructed to not give any kind of food or drink with caffeine to the subjects on the day of the assessment.

EXPERIMENTAL PROCEDURE

All children were assessed individually during morning hours. Anthropometric data (weight, height, and abdominal circumference with a tape measured at the height of the umbilical scar) (11) were collected and the body mass index (BMI) was calculated (weight/height^2). The first evaluation was HRV at rest for 10 minutes in the supine position at zero degrees of inclination using the Polar RS800CX™ (Polar Electro Oy, Kempele, Finland) heart monitor. HRV measurements were also obtained during 10 minutes of standing and after both the SWT and the ST3 tests.

The HRV indices in the time domain used were mean R-R intervals (iRR), standard deviation of all iRRs (SDNN/STDRR), root mean square of successive differences between adjacent normal iRRs (rMSSD), and the percentage of difference between adjacent normal R-R intervals greater than 50 ms computed over the entire height of the histogram created by charting all the R-R intervals (pNN50). The HRV indices in the frequency domain used were low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.4 Hz), and LF/HF ratio. Nonlinear

analyses for 1 and 2 standard deviations (SD1, SD2) were conducted with detrended fluctuation analysis (DFA α 1) and approximate entropy (ApEN) methods.

The fractional concentration of expired nitric oxide (FeNO) was measured in the sitting position with the NIOX Mino™ equipment (Aerocrine, Sweden), following the guidelines of the American Thoracic Society (ATS) (12, 13). The test was performed with the subject emptying the lungs until expiratory reserve volume, followed by inspiration through the oral cavity (with steps taken to eliminate the possibility of contamination) until achieving total lung capacity. The subject then exhaled slowly through the mouth piece maintaining a steady flow. After 1 minute 40 seconds, a reading was made of FeNO in parts per billion. The procedure was performed with a nasal clip to avoid contamination from air in the sinus cavities.

A lung function test was then performed following the criteria of the ATS (14) using the Easy One™ instrument (NDD), which was calibrated before use using reference values for children (15). Three tests were performed for each of the three classic maneuvers: slow vital capacity (SVC), forced vital capacity (FVC), and maximum voluntary ventilation (MVV).

The shuttle walk test (SWT) has progressive loading and 15 levels. The subject was instructed to walk quickly at increasing speeds over a course of 10 meters delimited at each end by a cone, which the subject walked around. An audible beep signaled the change in level and increase in speed during the test. The test was stopped when the subject was unable to reach the end of the 10-meter course by the time of the beep (16). Dyspnea upon exertion and at rest was measured using the Borg Scale (17). Respiratory rate, heart rate, and saturation of peripheral oxygen were also measured. Two tests were conducted, with a 30-minute interval between the tests. The trial on which the greater distance was traveled was used for analysis. The oxygen consumption was estimated by the formula: $\text{VO}_2 = 4.19 + (0.025 \times \text{distance}) \text{ ml} \cdot \text{min}^{-1} \cdot \text{Kg}^{-1}$ (18).

The last procedure was the three-minute step test (ST3). The subject was instructed to climb up and down a single rung (15 cm in height) within a period of 3 minutes. Dyspnea, heart rate, and oxygen saturation (SpO2) were recorded. As with the SWT, testing was performed twice with a 30-minute interval, and the trial with the greater number of steps was used for the analysis.

The Asthma Control Questionnaire (ACQ6) was applied, only in asthmatic patients (AG), in order to evaluate the control of the disease in these children. The disease is considered controlled when the ACQ6 had values less than or equal to 0.75 (19, 20).

STATISTICAL ANALYSIS

The unpaired Mann–Whitney test was used for the comparison of variables between groups. Spearman's rank correlation coefficients were calculated for the correlation analysis. The significance level was set to 5% ($p < .05$).

TABLE 1.—Characterization of the sample.

	Asthma Group (AG)	Control Group (CG)
Age(years)	7.33 ± 2.08	8.33 ± 1.75
Height (m)	1.27 ± 0.11	1.36 ± 0.09
Weight (kg)	25 ± 9.94	29 ± 8.96
BMI	15.52 ± 2.11	15.76 ± 2.02
Abdominal circumference (cm)	60.31 ± 8.43	58.66 ± 5.47
Percentile	70 (eutrophic)	60 (eutrophic)
Gender (M/F)	8/10	3/3
FEV 1 %	70.88 ± 15.88	92.33 ± 9.07*
MVV %	58.86 ± 12.04	77 ± 16.36
FeNO (ppb)	37.33 ± 18.21	13.00 ± 10.40*
ACQ6	11 ± 8.31	

* $p < .05$ on the comparison between groups

The Minitab 14 program was employed for the statistical analysis and the Kubios HRV software was used for processing HRV signal interference.

The sample calculation was performed from a pilot who had a standard deviation of 15.8 for FeNO, with a power of 90% and significance of 5%. The sample calculated was of 12 patients with asthma.

RESULTS

Table 1 displays the characterization of the sample. No significant differences were found in the anthropometric data or age. The variables [forced expiratory volume in first second (FEV1) and FeNO] differed significantly between groups ($p = .01$). Asthma severity was classified as moderate persistent, according to the criteria of the Global Initiative for Asthma (21) and International Consensus Report on the Diagnosis and Management of Asthma. In this group, only two children were regular

TABLE 2.—SWT data.

Physical performance SWT	Asthma ($n = 12$)	Control ($n = 6$)	p
Distance (m)	333.13 ± 97.28	442.66 ± 127.21	.04*
VO ₂ estimate	12.78 ± 3.14	015.05 ± 3.25	.254
Cardiovascular variables			
HR (bpm) initial	94.8 ± 6.03	80.83 ± 9.96	.01*
HR (bpm) final	146.6 ± 11.62	135 ± 19.41	.356
SAP (mmHg) initial	100 ± 6.66	100.8 ± 6.64	.704
SAP (mmHg) final	108 ± 9.44	108.33 ± 7.52	.744
DAP (mmHg) initial	65 ± 7.07	62.5 ± 4.18	.650
DAP (mmHg) final	72.5 ± 10.34	70.83 ± 8.01	.565
% of Max HR	68.99%	63.68%	.05**
Gas exchange variable			
SpO ₂ % initial	96.5 ± 2.50	96.6 ± 1.21	.706
SpO ₂ % final	95.5 ± 2.41	97 ± 0.89	.604
Variable of fatigue and dyspnea			
Borg dyspnea initial	0 (0–0.5)	0	.705
Borg dyspnea final	0.5 (0–4)	0.25(0–1)	.664
Borg fatigue initial	0 (0–1)	0 (0–1)	.870
Borg fatigue final	2 (0–4)	0.5 (0–2)	.04*

HR, Heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure. **SWT × ST3 = .05.

TABLE 3.—ST3 data.

Physical performance ST3	Asthma ($n = 12$)	Control ($n = 6$)	p
Number of steps	73.7 ± 11.01	64.33 ± 19.24	.115
Cardiovascular variables			
HR (bpm) initial	99.2 ± 8.08	86.83 ± 13.92	.04*
HR (bpm) final	138.3 ± 11.94	125.66 ± 15.13	.103
SAP (mmHg) initial	102 ± 7.88	101.66 ± 7.52	.956
SAP (mmHg) final	108.5 ± 6.68	107.5 ± 6.12	.870
DAP (mmHg) initial	68 ± 10.32	65.83 ± 4.91	1.00
DAP (mmHg) final	72.5 ± 11.36	75.83 ± 8.01	.364
% of Max HR	65.09%	58.96%	
Gas exchange variable			
SpO ₂ % initial	95.1 ± 3.24	96.83 ± 1.16	.447
SpO ₂ % final	96.3 ± 2.00	97 ± 1.41	.587
Variable of fatigue and dyspnea			
Borg dyspnea initial	0 (0–0.5)	0	.870
Borg dyspnea final	0 (0–3)	0 (0–4)	.956
Borg fatigue initial	0	0 (0–1)	.670
Borg fatigue final	2.5 (0–10)	0.75 (0–5)	.143

HR, Heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure.

users of inhaled corticosteroids (1 year); the rest did not receive specialized monitoring and had never undergone any lung function tests.

No significant difference between groups was found regarding the number of steps in 3 minutes (Table 3). However, the distance traveled on the SWT was significantly lower in the AG (Table 2). No significant differences between the groups were found regarding SpO₂ or VO₂ max. HR and perceived exertion were greater in the AG.

After the SWT, higher parasympathetic values (rMSSD and HF) were found in the AG in comparison to the CG (Table 4). Moreover, lung function (FeNO) was negatively correlated with FEV1/FVC ($r = -0.70$; $p = .004$) and positively correlated with pNN50 ($r = 0.50$; $p = .03$) (Figures 1 and 2).

DISCUSSION

In the present study, the children in the AG had a higher RMSSD after SWT than the children in the CG. Souza et al. (22) report the same pattern in asthmatic adults during postural changes.

In the frequency domain, the AG had higher LF, lower HF, and higher LF/HF ratio after the ST3, which was similar to the CG, as well as higher HF after the SWT. Tsai et al. (23) found similar LF and HF values in adults with and without asthma during moderate exercise. In nonasthmatic children, the HF value can decline as much as 96% during maximum work rate, suggesting the near complete withdrawal of parasympathetic cardiac modulation (24). The striking difference is the lack of a decrease in HF during maximum work rate in asthmatic children (25).

During physical exertion, heart rate and cardiac output increase mainly by vagal withdrawal stemming from a central command. In the transition to more intense activity associated with an increase in heart rate above 100 bpm, increased sympathetic activity becomes necessary, which

TABLE 4.—Values of heart rate variability in the time domain, frequency, and non-linear.

	HRV			
	Asthma SWT	Control SWT	Asthma ST3	ControlST3
TD				
Medial RR (ms)	493.93 ± 43.16	486.51 ± 69.24	453.51 ± 44.42	503.31 ± 43.91
STDRR (ms)	31.9 ± 11.79	27.2 ± 19.61	18.15 ± 21.74	24.20 ± 12.28
Medial HR (1/min)	123.41 ± 11.34	126.94 ± 16.78	134.03 ± 13.7	120.61 ± 11.33
rMSSD (ms)	12.83 ± 5.71	7.90 ± 7.34*	11.80 ± 4.29	13.16 ± 3.39
pNN50 (%)	0.67 ± 1.16	0.71 ± 1.75	0.16 ± 0.34	0
FD				
LFun	79.75 ± 9.76	81.35 ± 9.92	85.70 ± 6.18	73.45 ± 9.89*
HFun	22.25 ± 9.76	18.64 ± 9.92*	14.50 ± 6.18	26.55 ± 9.87*
LF/HF ratio	3.95 ± 3.82	4.38 ± 1.38	5.88 ± 2.84	2.90 ± 2.91*
HRV Non Linear				
SD1(ms)	8.35 ± 3.81	5.55 ± 7.03	5.30 ± 3.03	9.34 ± 2.64
SD2 (ms)	44.45 ± 26.35	38 ± 27.32	24.15 ± 30.86	32.90 ± 19.72
DFA _{α1}	1.38 ± 0.24	1.26 ± 0.09	1.21 ± 0.14	1.13 ± 0.15
DFA _{α2}	1.15 ± 0.14	1.17 ± 0.12	1.13 ± 0.23	0.79 ± 0.32*
ApEn	0.930 ± 0.25	1.00 ± 0.27	0.928 ± 0.32	0.932 ± 0.29

Data presented on average ± SD, RR: R-R interval, STDRR standard-deviation: average of all iR-R, HR: heart rate, rMSSD: square root of the sum of squared differences between RR, pNN50 (the percentage of difference between adjacent normal R-R intervals that are greater than 50 ms computed over the entire height of histogram created by the charting all the RR intervals). LF: low frequency, HF: high frequency, SD: standard deviation, DFA: analysis of purified fluctuations of trend, ApEn: approximate entropy * = $p < .05$ asthma × control.

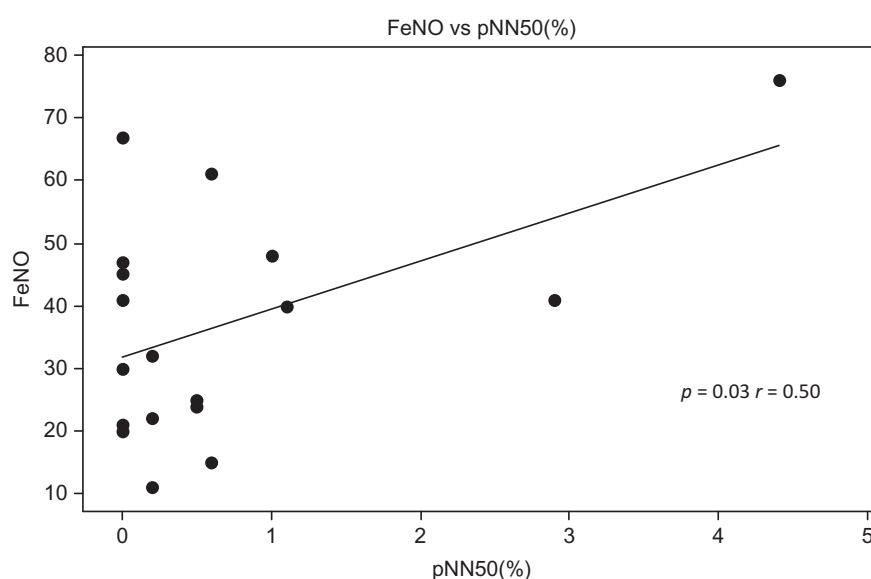


FIGURE 1.—Correlation between pNN50 and FeNO.

induces tachycardia, increased cardiac contractility, and peripheral vascular resistance. During maximum effort, this mechanism of vagal withdrawal and sympathetic activation appears to be altered and ineffective in asthmatic children (26). The vagal tone is being driven by the heart rate and it could be driven by other physiologic factors that have not been examined such as bowel activity, gastroesophageal reflux, or vasomotor tone.

The AG walked 108.87 m less than the CG on the SWT. This difference was significant. Villa et al. (27) demonstrated reductions in functional capacity in asthmatic patients and reduced muscle endurance of the lower limbs in moderately and severely asthmatic children.

Lanz et al. (28) found a reduction in FeNO (29) with a concomitant increase in FEV₁ in the treatment of acute asthma with corticosteroids in children with a mean age of 10 years. Cano-Garcinuño et al. (30) found that patients with a reduced FEV₁/FVC ratio had higher FeNO levels. The present results are in agreement with this finding, as a moderate negative correlation was found between these variables, showing that a smaller FEV₁/FVC ratio denotes greater lung inflammation.

Fuji et al. (5) found a positive correlation between the percentage of reduction in FEV₁ and HF after exercise in asthmatic children. In the present study, a positive correlation was found between PNN50 and FeNO, demonstrating that greater activation of the parasympathetic ANS is

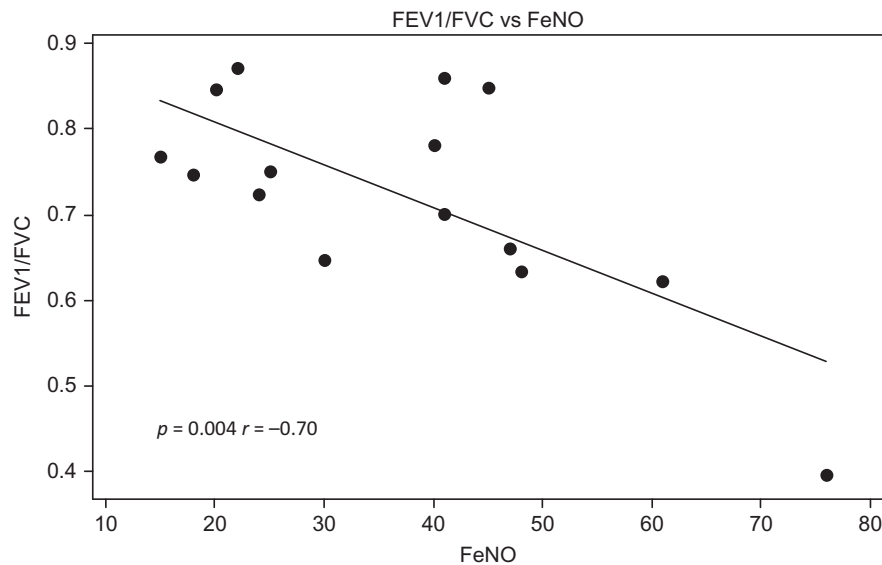


FIGURE 2.—Correlation between Fev1/CVF and FeNO.

related to an increased inflammatory reaction and, consequently, a smaller FEV₁. (9) Parasympathetic nerve stimulation has also been shown to evoke the contraction and relaxation of airway smooth muscles. Noncholinergic neurotransmitters mediate relaxation, and this nerve function may be altered in children with asthma.

Studies (9, 31, 32) suggest that ongoing afferent nerve activity arising from the airways and lungs drives baseline airway smooth muscle cholinergic tone. A number of afferent nerve subtypes induce the withdrawal of cholinergic tone, including baroreceptors, skeletal muscle and diaphragmatic afferents, and pulmonary stretch receptors. These disparate afferent inputs may be simultaneously recruited during exercise in healthy children. The dilation of the airways produced by exertion may match demands for gas exchange, but this mechanism can be altered during maximum effort in asthmatic children, as previously mentioned.

The basal heart rate in the AG was significantly higher than that in the CG, demonstrating a tendency toward tachycardia at rest, which can be caused by even mild asthma or a change in autonomic modulation.

The limitation of the study was the reduced control group sample.

CONCLUSION

From the autonomic standpoint, healthy and asthmatic children respond differently to different levels of stress, with no withdrawal of parasympathetic cardiac modulation in asthmatic children after maximum work rate. Children with asthma exhibit changes in functional capacity. Moreover, lung function may vary with inflammation of the airways.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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