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Cardiac autonomic modulation assessed by heart rate variability in children with asthma

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Abstract

Objective: To assess cardiac autonomic modulation, measured by short-term frequency domain analysis of heart rate variability (HRV), in children with asthma.

Methods: We conducted an observational study at a tertiary care teaching hospital. The sample consisted of 119 children aged 7 to 15 years with asthma and 56 age-matched healthy controls. Frequency domain HRV measures included low-frequency (LF; 0.04-0.15 Hz), high-frequency (HF; 0.15-0.4 Hz), and LF/HF ratio. The LF and HF components were expressed in both absolute values of power (ms^2) and in normalized units (nu).

Results: Compared with healthy controls, asthmatic children had significantly higher value of HF (nu) (mean ± standard deviation: 45.9 ± 14.6 vs 40.7 ± 13.6; $P = .02$), and lower values of LF (nu) (54.1 ± 14.6 vs 59.3 ± 13.6; $P = .02$) and LF/HF ratio (median, interquartile range: 1.12, 0.82-1.88 vs 1.59, 1.02-2.08; $P = .03$). We did not find significant differences between children with persistent and intermittent asthma, and between children with well-controlled and partially-controlled or uncontrolled asthma, in terms of HRV measures.

Conclusions: Children with stable chronic asthma may have a cardiac autonomic imbalance with a possible enhanced parasympathetic modulation, as assessed by short-term frequency domain analysis of HRV. Neither asthma severity nor asthma control was significantly associated with HRV measures, but the study did not have enough power to draw a firm conclusion on this point.

KEYWORDS
asthma & early wheeze

1 | INTRODUCTION

Asthma is characterized by chronic airway inflammation, bronchial hyperresponsiveness, and variable airflow limitation. The pathogenesis of asthma is complex and not fully understood. One of the proposed mechanisms is an imbalance of the autonomic nervous system (ANS), with enhanced excitatory pathways (cholinergic, α-adrenergic, and excitatory nonadrenergic, noncholinergic-NANC mechanisms) or reduced inhibitory pathways (β-adrenergic and inhibitory NANC mechanisms).[1-3]

Studies have shown that autonomic dysfunction in asthma is not confined to the airways, but is generalized as evidenced by several autonomic function tests.[2,4,5] One recently used test for an autonomic function is the analysis of heart rate variability (HRV), which describes the oscillation of the intervals between consecutive heartbeats (the time elapsed between two successive R waves of the QRS signal [RR intervals]) that reflects cardiac autonomic modulation. In 1996, the Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) established the standards for HRV measurement and interpretation.[6] HRV can be measured using time and frequency domain methods, but the latter is preferred when investigating short-term (5 minutes) recordings. The frequency domain (power spectral density) analysis

describes the oscillations of the heart rate signal, decomposed at different frequencies and amplitudes, and provides information on how power (ie, variance) distributes as a function of frequency. It gives an estimate of the degree of both cardiac sympathetic and parasympathetic modulation and the balance between two pathways.[6]

Over the last decades, there has been a substantial increase in publications that report autonomic dysfunction assessed by HRV in a broad range of clinical conditions, such as diabetes mellitus,[7] cardiovascular diseases,[8,9] neuropsychological disorders,[10,11] and chronic obstructive pulmonary disease.[12] However, the number of studies that investigate ANS function via HRV in asthma is limited, especially in childhood asthma.[13-15]

The aim of this study was to assess cardiac autonomic modulation measured by short-term frequency domain analysis of HRV in children with asthma, compared with healthy control children. We also investigated the relationship between cardiac autonomic modulation and asthma severity and control.

2 | METHODS

2.1 | Study design

We conducted an observational study in two groups of children: asthmatics and healthy controls. The Health Research Ethics Committee of the Federal University of Rio Grande approved the research project (N° 186/2015), and written informed consent was obtained from parents or guardians. The study was performed in concordance with the Declaration of Helsinki.

3 | PARTICIPANTS

3.1 | Children with asthma

we consecutively recruited children aged 7 to 18 years with the diagnosis of asthma who attended regularly the Pediatric Pulmonology outpatient clinic of a teaching hospital in southern Brazil between December 2015 and November 2016. Asthma was diagnosed if a child met all of the following criteria:[16] (a) recurrent episodes of wheeze, cough, breathing difficulties or chest tightness, particularly at night or in the early hours of the morning; (b) respiratory symptoms improve spontaneously or after treatment (bronchodilators associated or not with corticosteroids); (c) presence of triggers or aggravating factors such as exposure to allergens or irritants, physical exercise, weather changes or emotional stress; (d) personal history of atopy (allergic rhinitis or eczema) and/or family history of atopy (asthma, allergic rhinitis or eczema) in first-degree relatives.

We excluded children with bronchopulmonary dysplasia, cystic fibrosis, congenital cardiopulmonary diseases, immunodeficiency, and chronic encephalopathy. These clinical conditions may not only confound the diagnosis of asthma but also compromise the interpretation of the HRV analysis.

3.2 | Healthy control children

Age-matched healthy control children were recruited in a local public elementary school. The school had a total of 122 children aged 7 to 15 years, and 86 (70.5%) agreed to participate in the study. We recruited children with no history of asthma, allergic rhinitis, atopic dermatitis, and other chronic diseases. Children's health information was obtained through an interview with the parents or guardians using a predefined questionnaire and the International Study of Asthma and Allergies in Childhood questionnaire.

3.3 | Asthma severity and control classification

Asthma severity was classified into intermittent or persistent (mild, moderate, and severe), based on the clinical information reported by parents or guardians and spirometry tests.[17] Asthma control was assessed by a validated tool—Asthma Control Test (ACT).[18] The level of asthma control was classified as well-controlled (ACT ≥ 20), partially-controlled (ACT 16 to 19), and uncontrolled (ACT ≤ 15).

3.4 | Analysis of HRV

Short-term frequency domain analysis of HRV was performed by one trained investigator who was blind to asthma severity and control classification. The guidelines of the ESC/NASPE Task Force[6] were followed for HRV measurement and interpretation, and all exams were performed in the morning between 9 and 11 AM Children were instructed to lie quietly in the supine position with normal breathing in a room with a temperature of approximately 23°C. RR intervals at a sampling rate of 1000 Hz were recorded for 10 minutes using a heart rate monitor (Polar model RS800CX; Polar Electro Oy Inc, Kempele, Finland). This portable device has been previously validated for the acquisition of HR signals for HRV analysis.[19,20] The RR interval data were then downloaded to a computer using Polar ProTrainer 5 software. We selected the 5-minute RR intervals with a stable heart rate, generally between 3 and 8 minutes of the whole 10-minute recording. Each 5-minute RR series were corrected for aberrant beats and errors using the default Polar ProTrainer 5 software correction algorithm (ie, moderate filter power and minimum protection zone of 6 bpm). We also visually inspected the time series of RR intervals, and any remaining artifacts were manually removed. We used Kubios software version 2 (Biosignal Analysis and Medical Image Group, Department of Physics, University of Kuopio, Finland) for HRV analysis. The power spectral density was estimated using the fast Fourier transform algorithm. Three main spectral components were distinguished in the spectrum of 5-minute recordings: very low frequency (VLF; ≤0.04 Hz), low-frequency (LF; 0.04-0.15 Hz), and high-frequency (HF; 0.15-0.4 Hz). We did not use the VLF component when interpreting the results of power spectral density because VLF derived from short-term recordings is considered a dubious measure.[6] The HF component is generally defined as a marker of parasympathetic (vagal) modulation, while the LF/HF ratio reflects global sympathovagal balance.

Disagreement exists in the interpretation of the LF component which is considered by some as a marker of sympathetic modulation (especially when expressed in normalized units), but by others as a parameter that reflects both sympathetic and vagal influences.[6] The LF and HF components were expressed in absolute values of power (ms^2), as well as in normalized units (nu) which represent the relative value of each power component in proportion to the total power minus the VLF component.

3.5 | Spirometry test

Spirometry was performed with a Jaeger MasterScope spirometer (Jaeger, Hoechberg, Germany). Reproducibility and acceptability standards developed by the American Thoracic Society/European Respiratory Society Task Force were followed.[21] Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and FEV_1/FVC ratio were recorded. The measurements were expressed as a percentage of predicted values for age, height, and gender. We did not perform bronchodilator reversibility testing.

3.6 | Statistical analysis

Double data entry was performed using EPI-data 3.2 software. All statistical analyses were conducted using Stata 11 (Stata Corp College Station). The normality of data was verified by the Kolmogorov-Smirnov test. Data were presented as means and standard deviation (SD) or median and interquartile range, as appropriate. For comparison of continuous outcomes between two groups, unpaired the Student *t* tests were used for data with normal distribution and the Mann-Whitney *U* test otherwise. The χ^2 test was used for comparison of categorical data. A two-tailed $P < .05$ was defined as statistically significant.

4 | RESULTS

Of 134 patients assessed for eligibility, 12 were excluded for the study because of nonasthmatic diagnosis (n = 5), concomitant chronic neurological disease (n = 1), and refusal to participate in the study (n = 6). We excluded three eligible asthmatic patients aged over 15 years from the analysis because the age of children in the control group raged from 7 to 15 years. Among 86 school children agreed to be the controls, 30 were excluded because of allergic rhinitis (n = 15), asthma (n = 10), atopic dermatitis (n = 2), and other chronic diseases (n = 3). Thus, the study sample consisted of 119 children with asthma (85 persistent asthma) and 56 healthy controls. No significant differences were found between two groups regarding age, gender, height, weight, and body mass index (Table 1). Of 85 patients with persistent asthma, 64 (75.3%) were receiving inhaled corticosteroids, and 21 (24.7%) were being treated with inhaled corticosteroids associated with long-acting β_2-agonists. The mean values ± SD of FVC, FEV_1 and FEV_1/FVC ratio were 90.5% ± 14.1%, 94.0% ± 12.3%, and 81.9% ± 5.4% in patients with persistent asthma, and 85.3% ± 16.3%, 93.7% ± 17.4%, and 82.4% ± 3.8% in patients with intermittent asthma. Asthma control was classified as well-controlled in 85 (71.4%) patients, partially-controlled in 14 (11.8%) patients, and uncontrolled in 20 (16.8%) patients.

Compared with healthy controls, asthmatic children had significantly higher value of HF (nu) and lower values of LF (nu) and LF/HF ratio, suggesting cardiac autonomic imbalance with enhanced parasympathetic modulation (Table 2). We did not find significant differences between the two groups in terms of the absolute values of HF (ms^2) and LF (ms^2).

No significant differences were found between children with persistent and intermittent asthma (Table 3), and between children with well-controlled and partially-controlled or uncontrolled asthma (Table 4), in terms of HRV measures.

5 | DISCUSSION

The cardiovascular and respiratory autonomic efferent fibers have a common central origin,[22] and hence cardiovascular autonomic modulation may reflect autonomic control of the respiratory system. This study revealed a possible cardiac autonomic imbalance with enhanced parasympathetic modulation in children with stable chronic asthma, as assessed by short-term frequency domain analysis of HRV. Neither asthma severity nor asthma control was significantly associated with HRV measures. Autonomic nerves regulate many aspects of airway function, including smooth muscle tone, mucus secretion, bronchial microcirculation, and recruitment and activation of inflammatory cells.[23] An abnormality in the autonomic neural control of the airways, with an imbalance between excitatory and inhibitory pathways, is expected to cause bronchospasm, mucosal edema, excessive mucus secretions, and airway inflammation which are the key pathophysiological features of asthma.

Parasympathetic (cholinergic) nerves are the dominant neural bronchoconstrictor pathway in animal and human airways.[24] Previous studies have shown that the airways of asthmatic patients were hyperreactive to inhaled cholinergic agonists,[25,26] and the bronchoconstriction induced by nonspecific stimuli could be prevented by

TABLE 1 General characteristics of the study sample

Variables	Asthmatics (n = 119)	Healthy controls (n = 56)	*P* values
Age, mean ± SD, y	9.51 ± 2.1	9.69 ± 2.1	.59*
Gender (male), n/%	69/57.9	30/53.6	.58**
Weight, mean ± SD, kg	39.39 ± 12.7	37.77 ± 12.6	.43*
Height, mean ± SD, cm	139.69 ± 13.2	139.53 ± 12.2	.93*
BMI, mean ± SD, kg/m^2	19.72 ± 4,0	18.91 ± 3.7	.21*

Abbreviations: BMI, body mass index; SD, standard deviation.
*The Student *t* test.
**The χ^2 test.

TABLE 2 Heart rate variability in asthmatic children and healthy controls

Frequency domain measures	Asthmatics (n = 119)	Healthy controls (n = 56)	*P* value
LF, median (IQR), ms^2	1081.0 (549.0-1985.0)	1155 (590.5-1923.0)	.81*
HF, median (IQR), ms^2	995.0 (416.0-1842.0)	803.5 (440,5-1257.0)	.21*
LF, mean ± SD, nu	54.1 ± 14.6	59.3 ± 13.6	.02**
HF, mean ± SD, nu	45.9 ± 14.6	40.7 ± 13.6	.02**
LF/HF, median (IQR), ms^2	1.12 (0.82-1.88)	1.59 (1.02-2.08)	.03*

Abbreviations: HF, high-frequency; IOR, interquartile range; LF, low-frequency; nu, normalized units; SD, standard deviation.
*The Mann-Whitney *U* test.
**The Student *t* test.

TABLE 3 Heart rate variability and asthma severity

Frequency domain measures	Persistent asthma (n = 85)	Intermittent asthma (n = 34)	*P* values
LF, median (IQR), ms^2	1137 (549.0-1910.0)	922.5 (571.0-2258.0)	.79*
HF, median (IQR), ms^2	999.0 (528.0-1670.0)	872.5 (310.0-2002.0)	.75*
LF, mean ± SD, nu	53.2 ± 14.8	56.3 ± 14.2	.28**
HF, mean ± SD, nu	46.8 ± 14.8	43.7 ± 14.2	.28**
LF/HF, median (IQR), ms^2	1.09 (0.72-1.88)	1.24 (1.0-2.09)	.25*

Abbreviations: HF, high-frequency; IOR, interquartile range; LF, low-frequency; nu, normalized units; SD, standard deviation.
*The Mann-Whitney *U* test.
**The Student *t* test.

atropine.[27] Asthmatics were also found to have increased sweating and pupillary responses to cholinergic agonists.[28,29] There was an enhanced cardiac parasympathetic modulation in asthmatic patients assessed by HRV, as shown by this study and by others.[30] An increased parasympathetic neural drive to the sinoatrial node in asthmatic patients was also evidenced by a greater magnitude of respiratory sinus arrhythmia induced by deep breathing.[31] All these results suggest a widespread abnormality of the cholinergic pathway in asthmatic patients, and provide support for the hypothesis that enhanced parasympathetic modulation may play a role in the pathogenesis of asthma.[32]

This study did not find a statistically significant association between either asthma severity or asthma control and HRV measure. Low statistical power due to relatively small patient numbers might have contributed to the negative results. In contrast, in an observational study with 77 asthmatic children (7-12 years) and 40 gender- and age-matched control subjects, Emin et al[13] reported a significant correlation between asthma severity and parasympathetic nervous system dysfunction, as assessed by heart rate response to deep breathing and heart rate responses to Valsalva maneuver. The possible reasons for the discrepancy of the results between our study and the study by Emin et al[13] might be the difference in the study sample, asthma severity classification, and methods for ANS assessment. We did not find studies in children that investigated asthma control and ANS function.

TABLE 4 Heart rate variability and asthma control

Frequency domain measures	Well-controlled asthma (n = 85)	Partially-controlled or uncontrolled asthma (n = 34)	*P* values
LF, median (IQR), ms^2	1031.0 (623.0-1985.0)	1114.5 (427.0-1884.0)	.69*
HF, median (IQR), ms^2	999.0 (411.0-2002.0)	885.5 (436.0-1319.0)	.62*
LF, mean ± DP, nu	54.2 ± 14.5	53.7 ± 15.2	.89**
HF, mean ± DP, nu	45.8 ± 14.5	46.2 ± 15.2	.89**
LF/HF, median (IQR), ms^2	1.17 (0.89-1.85)	1.07 (0.71-1.98)	.83*

Abbreviations: HF, high-frequency; IOR, interquartile range; LF, low-frequency; nu, normalized units; SD, standard deviation.
*The Mann-Whitney *U* test.
**The Student *t* test.

Studies have also reported other types of autonomic nervous imbalance in asthmatic patients, such as increased a-adrenergic responsiveness and β-adrenergic hyporeactivity.[4,33] An enhanced NANC excitatory or reduced NANC inhibitory mechanism has also been proposed in asthma.[1,3,34] Different types of autonomic defects in asthmatic patients may contribute to the heterogeneity of asthma phenotype and treatment responses.

Airway inflammation is believed to be central to the pathogenesis of asthma, and inhaled corticosteroids are considered the cornerstone treatment for asthma.[16,17] However, current evidence suggests that these potent anti-inflammatory drugs are effective in controlling symptoms but not change the natural history of asthma.[35] The recognition of neural mechanisms in the pathogenesis of asthma raises the hypothesis that there may be a complex interplay between inflammation and neural control in the airways, with effects of inflammatory mediators on neurotransmission and neurotransmitters, and in turn, modulating the inflammatory response in the airways.[1,36] A better understanding of interactions between airway inflammation and autonomic nervous control may open up new perspectives for more effective interventions for patients with asthma. Unfortunately, the number of studies that investigate neural mechanisms in asthma is still limited, in contrast to a huge body of publications on airway inflammation.[37]

A short-term frequency domain analysis of HRV provides a feasible noninvasive method to assess autonomic nervous function in children. In this study, the difference in autonomic nervous modulation between asthmatic children and healthy controls was evidenced using LF and HF in normalized units (nu) rather than in absolute values of power (ms^2). The LF (nu) and HF (nu) components represent a controlled and balanced behavior of the sympathetic and parasympathetic nervous system, and may be more discriminative than the LF and HF in ms^2 in detecting autonomic abnormality. Despite standardized methodology established by ESC and NASPE and increasing use in several clinical situations, there are still uncertainties and debates on methodological issues in short-term frequency domain analysis of HRV.[38] Its main disadvantage is that the short-term HRV analysis may not be stable owing to the constant fluctuation of HRV parameters.[39] Moreover, there are no well-established reference values for HRV measures in both adults and children. There were large discrepancies in the reported "normal" values for short-term HRV measures in healthy children, probably due to difference in study sample (ethnic and demographic characteristics, sample size and definition of "healthy") and in methodological approaches for measurement (methods for acquisition and analysis of HRV signal, and control of confounding factors).[13,14,40] The discrepancies in normal values make a between-study comparison difficult.

Some methodological issues should be taken into account when interpreting the results of this study. We did not calculate a prior sample size, and we recruited eligible patients attending our clinic during a period of 1 year. A sample size of 119 patients with asthma had very low statistical power for comparing LF nu. and HF nu. between persistent and intermittent asthma (20%), and between well-controlled and partially-controlled or uncontrolled asthma (5%). Several studies have shown that respiration may have a significant effect on the HR oscillations and parasympathetic activity is very closely related to respiratory sinus rhythm.[41,42] Both asthmatic children and control subjects were instructed to breathe normally during the HRV assessment, but we did not record respiratory rates. This precluded us from taking respiratory rates into account in HRV analysis. However, there is still no consensus on the needs for controlling respiration in HRV analysis. Malik et al[43] argued that a distinction is needed between the use of HRV in physiological and clinical studies. Different confounders including respiration should be controlled in physiological investigations. However, the power of clinical risk assessment studies increases by considering the autonomic homeostatic maintenance comprehensively. Adjusting HRV measurements for confounders that are also under autonomic control may affect their predictive value. Moreover, breathing frequency is only one and probably a simpler descriptor of respiration. Twenty-one patients with persistent asthma were receiving regular treatment with inhaled corticosteroids associated with long-acting β_2-agonists. The use of β_2-agonists may have affected autonomic modulation. However, this type of drug generally increases sympathetic activity and reduces the cardiovagal response.[44,45] Thus, the use of long β_2-agonists might not confound the study results since patients with asthma had enhanced parasympathetic activity. We used clinical criteria for diagnosis of asthma because most of the patients were under 5 years of age at the moment of diagnosis. However, the diagnosis of asthma has been confirmed in all patients by regular follow-up and assessment. Both intermittent and persistent asthmatic children had normal mean spirometric measured at study entry.

In conclusion, children with stable chronic asthma may have a cardiac autonomic imbalance with a possible enhanced parasympathetic modulation, as assessed by short-term frequency domain analysis of HRV. Neither asthma severity nor asthma control was significantly associated with HRV measures, but the study did not have enough power to draw a firm conclusion on this point.

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