

ORIGINAL ARTICLE

Increased sympathetic modulation and decreased response of the heart rate variability in controlled asthma

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Abstract

Objective: To compare the autonomic modulation of heart rate (HR) in asthmatic and healthy volunteers to correlate it with the forced expiratory volume in the first second (FEV₁). **Methods:** Ten healthy and 14 asthmatic volunteers were included in this cross-sectional study. The volunteers underwent a cardiopulmonary exercise test, spirometry and a register of both resting heart rate variability (HRV) in the supine and seated positions along with HRV during the respiratory sinus arrhythmia maneuver (M-RSA). **Results:** At rest in supine, asthmatic volunteers presented a higher HR (77.1 ± 9.9 vs. 68.7 ± 8.7 bpm), shorter interval between two R waves (R-Ri) (807.5 ± 107.2 vs. 887.5 ± 112.7 ms) when compared with the healthy volunteers, respectively. Moreover, in the frequency domain of HRV, there was increased low frequency (LF) index (50.4 ± 17.1 vs. 29.2 ± 11.1 n.u.) and decreased high frequency (HF) index (49.4 ± 17.1 vs. 70.7 ± 11.1 n.u.). During the M-RSA, the asthmatic presented higher HR (82.6 ± 10.0 vs. 72.4 ± 7.6 bpm) and lower values of R-Ri (746.4 ± 92.1 vs. 846.4 ± 81.4 ms) and approximate entropy (ApEn) (0.7 ± 0.0 vs. 0.8 ± 0.1). FEV₁ was strongly correlated with the change of the continuous beat-to-beat variability of HR (SD2) index from the seated to the supine position ($r=0.78$). **Conclusion:** Controlled asthma in adults appears to induce an increased sympathetic modulation and attenuated response to the postural changes and the M-RSA. Furthermore, there is a correlation between the airways' obstruction and HRV, especially during postural changes.

Keywords

Autonomic nervous system, heart rate control, lung obstructive diseases, physical therapy

History

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Introduction

Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, often reversible either spontaneously or with treatment. In adulthood this disease is more prevalent in women than in men [1]. Chronic cardiopulmonary diseases are known to cause imbalance in the sympathetic and parasympathetic control of heart rate (HR) [2,3], which is evidenced by a reduced heart rate variability (HRV). In the lungs, the autonomic nervous system has the primary role of regulating the caliber of the airways and studies have shown that the pathophysiology of asthma is associated with autonomic dysfunction [4–6]. The increase in the vagal activity during rest is usually an occurrence in acute asthma crisis [4,7,8]. In addition, according to Hashimoto et al. [5] it is the cause of bronchial hyper-reactivity.

The autonomic control of HR is also modulated by the respiratory cycles as a physiological phenomenon, which is

characterized by the changes in HR due to breathing, primarily mediated by a parasympathetic modulation in the sinus node. During the spontaneous breath, a synchronic interaction occurs between the respiratory phase and HR control. An increase in HR occurs in the inspiratory phase whereas in the expiratory phase there is a reduction of HR. This phenomenon is explained by the decrease and increase of the vagal activity, respectively [9]; which is known as respiratory sinus arrhythmia (RSA) [10,11]. Furthermore, in experimental conditions, the RSA can be exacerbated by controlled respiratory maneuvers (M-RSA) [12].

The data processing of the change in HR and the interval between two R waves in the electrocardiogram (R-Ri) allows the calculation of indices which are known as HRV and bring information regarding the control of the autonomic nervous system over the heart chronotropy. HRV analysis has been used as diagnostic markers and in the prognosis of several chronic respiratory and cardiac diseases. Also, the analysis of the change in HRV indices due to the M-RSA may provide some important assessment of the autonomic control of asthmatic patients.

Considering that asthma results in changes in the respiratory cycles, it is expected that this chronic respiratory illness might affect the autonomic control of HR even in controlled

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phases of the disease. Nevertheless, there is a lack of evidence in literature about the autonomic control of HR in patients with controlled asthma. Therefore, the aims of this study were: [1] to compare the indices of the autonomic modulation of resting HR, in the supine and seated positions and also during the M-RSA between asthmatic and healthy volunteers; and [2] to correlate HRV indices with the obstruction of the airways.

Methods

This cross-sectional study included 24 volunteers between the ages of 18 and 45. All volunteers gave written informed consent before participating in the study. Ethical approval was provided by the university research ethics committee (n°018/2012). The criteria of inclusion to the asthma group (AG) were clinical and spirometric diagnosis of asthma, classified according to its severity as intermittent and as its level of control as controlled. The volunteers had less than two daytime symptoms per week, no use of medicines prophylactically, only for the relief of symptoms. The volunteers had no limitations during mild exertion, no nocturnal symptoms and normal spirometry, according to the criteria established by the Global Initiative for Asthma [1]. Furthermore, the volunteers should present an absence of an exacerbation (unscheduled medical appointment) during the past three weeks [13], with a regular follow-up by the pneumologist. Additionally the absence of any other respiratory, metabolic or cardiovascular diseases was a requirement, as well as being non-smokers, not currently pregnant and not regular drinkers.

The control group (CG) consisted of volunteers with no previous history of respiratory cardiac or metabolic disease with spirometric values within the normal range [13]. Volunteers were excluded when they presented any signal of asthma exacerbation, when they did not accept to participate in the study or when they did not meet the criteria of inclusion.

Experimental procedures

The volunteers were assessed individually, in the afternoon, and underwent a clinical and physical therapeutic assessment, spirometry, cardiopulmonary exercise test (to assess functional capacity and characterize groups) and received instructions which had to be followed both the day before and on the day of the tests. The volunteers were instructed to avoid caffeinated drinks and exercise for 24 h before the assessment, to have light meals and a good night of sleep. Bronchodilators (BD) of short action were suspended for at least 6 h, BD [13] with long action and steroid inhalers were suspended for at least 12 h before the evaluations [14,15].

The maximum or symptom-limited cardiopulmonary exercise test was performed on a treadmill using the Modified Balke protocol [14,16], following guidelines to cardiopulmonary exercise test [14]. Ergospirometry equipment was used (Oxycon Mobile®, Mijnhardt/Jäger, Würzburg, German), and the volunteers were monitored using a digital electrocardiograph (USB/Wincardio–Brasília/Brasil).

The spirometry was conducted using the same ergospirometric equipment, using an oral-nasal mask. The performed

maneuvers were slow vital capacity and forced vital capacity (FVC), following the acceptability and reliability criteria of national guidelines [13]. Forced expiratory volume in the first second (FEV₁) and FEV₁/FVC ratio were determined.

The register of HR and R-Ri were done in a room with controlled temperature (22–24 °C), humidity (50–60%) and between 1 p.m. and 5 p.m. The cardiofrequencimeter used was the Polar®RS800CX™ (Polar Electro Co. Ltd., Kempele, Oulu, Finland), which was tied around the chest.

Firstly, the volunteers were asked to rest in the supine position for 10 min, so HR could return to resting values. Secondly, HR was measured for 10 min in that position followed by a 10 min measure in the seated position. These measurements were then taken while the patient performed a M-RSA for 4 min, in the seated position. In this maneuver, the researchers instructed the volunteers to perform a sequence of deep and slow inspirations and expirations, with the breathing volumes varying from the total pulmonary capacity to the residual volume; aiming that each breathing cycle lasted 10 s, 5 s of inspiration and 5 s of exhalation. During the maneuver, the volunteers guided themselves using an analogue clock and a verbal command of the researcher, in order to maintain the respiratory rate of six breaths per minute, which is expected to induce the maximum RSA [12]. All the registers were transferred to a computer using the software Polar Pro-Trainer 5™® (Kempele, Oulu, Finland).

Data processing

HRV was analyzed using the software Kubius HRV® (MATLAB, version 2.1, Kuopio, Finland). Initially, the selection of the interval of signals was done through a visual inspection of the total period of the R-Ri collection. Segments with more than 90% pure signal beats were included in the final analysis, the interval was at least 256 points long and were chosen when they presented the most stable section of the frequency sample [2]. The analysis performed included the time and frequency domains and non-linear analysis, which were calculated for the supine position, seated position and during the M-RSA. Furthermore, the indices from the seated position were deducted from the supine position to verify the response to postural changes (Δ seated-supine).

For the linear analysis of the time domain, the obtained indices were: mean HR, mean R-Ri and the root mean square of successive differences between adjacent normal R-Ri (rMSSD). In addition, the changes in HRV during the M-RSA were verified through the expiratory/inspiratory ratio of the mean R-Ri (E/I) and the difference between inspiration and expiration of the mean HR (Δ IE) [12]. The indices in the frequency domain of HRV were the low frequency (LF) and high frequency (HF), which reflects the sympathetic and the parasympathetic systems, respectively, both were described in normalized units (n.u.). Furthermore, the ratio between the two frequency spectrums (LF/HF) was calculated to verify the sympathovagal balance [2].

The non-linear analysis of HRV was obtained through the indices Alpha1 and Alpha2, SD1 and SD2, approximate entropy (ApEn) and sample entropy (SampEn), recurrence rate (REC), determinism (DET), and shannon entropy.

Alpha1 and Alpha2 were used to quantify the fractal property of the temporal series of the R-Ri, the first indicates short term fluctuations and the second indicates long term fluctuations of HRV; an Alpha1 value should be close to 1 and higher than Alpha2 in healthy conditions [17]. The instantaneous beat-to-beat variability of HR (SD1) is related to the parasympathetic activity, whereas the continuous beat-to-beat variability of HR (SD2) reflects total variability. The ApEn detects the changes in a time series and provides a non-negative number to the series, with higher values indicating more complexity of the data. Moreover, the SampEn, REC, DET and shannon entropy were obtained, which also point out the complexity or irregularity of HRV [18].

Statistical analysis

Initially, the Shapiro-Wilk test was used to verify the normality of the data distribution. Means and standard deviations (SD) were used to describe the data. The comparisons between the groups were performed using the *t*-tests for parametric variables and Wilcoxon or Mann-Whitney test for non-parametric variables. In the correlation analysis, Pearson or Spearman correlation coefficients were applied. The post-hoc power analysis was performed using the HF as a primary outcome and the power value found was 90%. In all analysis, the significance was defined as 5% ($p < 0.05$).

Results

Fourteen volunteers participated in the AG (Figure 1) and 10 in the CG. The demographic, anthropometric, spirometric, exercise capacity characteristics and the medications which the volunteers had been taking are presented in Table 1. The volunteers reported that they had used bronchodilators only in the presence of symptoms, none of them had used bronchodilators daily and ten volunteers had been without the medications for at least two weeks. The mean pre and post-bronchodilator FEV₁% values of the AG were 86.0 ± 15.0 (Table 2) and 103.0 ± 13 , respectively.

Significant difference between the two groups was only found for weight. There were no significant differences in other demographic and anthropometric measures. As expected, the pulmonary function was higher in the CG when compared with the AG (FEV₁) $97.2 \pm 13.4\%$ (86.0 – 124.0) vs. $86.0 \pm 15.0\%$ (65.7 – 118). In AG, the minimum and maximum values of FVC were 75% and 194.9%, respectively, and in CG the minimum and maximum values of FVC were 78% and 119%, respectively. For the FEV₁/FVC (%) ratio, the minimum and maximum values in AG were 42.1% and 93.2%, and in CG were 97% and 114%.

The group comparison of HRV (Table 3), in the supine position, found higher values ($p < 0.05$) of HR (77.1 ± 9.9 vs. 68.7 ± 8.7 bpm) and LF (50.4 ± 17.1 vs. 29.2 ± 11.1 n.u.) in the AG when compared with the CG. In addition, AG presented lower values ($p < 0.05$) of R-Ri (807.5 ± 107.2 vs. 887.5 ± 112.7 ms) and AF (49.4 ± 17.1 vs. 70.7 ± 11.1 ms) when compared with the CG. In the non-linear analysis of HRV, AG presented lower values than the CG ($p < 0.01$) of the Alpha2 in the supine and seated positions.

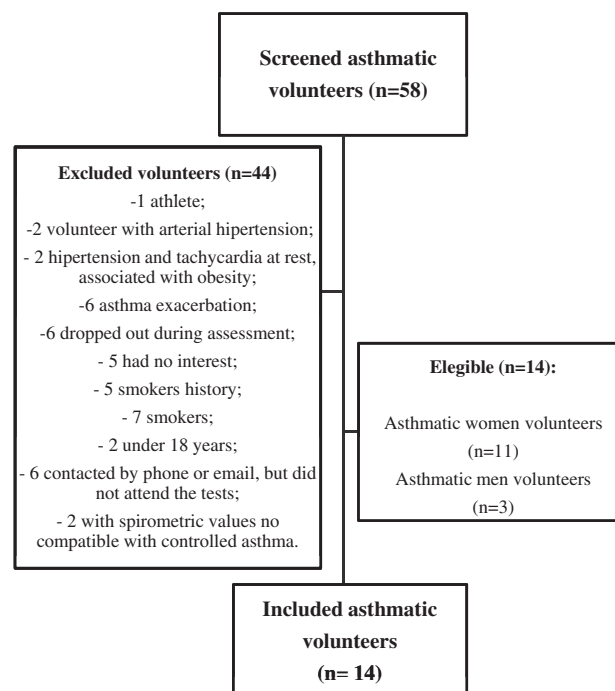


Figure 1. Flowchart of the study population.

During postural changes from supine to seated position (Table 3), the CG presented higher values ($p < 0.05$) of HR (68.7 ± 8.7 vs. 72.8 ± 8.7 bpm), LF (29.2 ± 11.1 vs. 47.4 ± 17.2 n.u.), and LF/HF (0.4 ± 0.2 vs. 1.1 ± 0.7), which demonstrate adequate response to postural changes. Furthermore, in the non-linear analysis, there was a reduction ($p < 0.05$) of SD1 and an increase in the indices Alpha1, REC and DET in the seated position in contrast with the supine position.

Nevertheless, in the AG, the postural changes from supine to seated position lead to an increase in HR (77.1 ± 9.9 vs. 82.9 ± 11.8 bpm), and reduction of the R-Ri (807.5 ± 107.2 vs. 740.6 ± 109.2 ms) and rMSSD (36.8 ± 19.1 vs. 28.0 ± 16.2 ms), however in the frequency domain, responses were not observed due to postural changes. The postural change (supine to seated) in the AG also induced alterations ($p < 0.05$) in the non-linear indices SD1 and SampEn, which was higher in the supine position. During this change the indices DET and REC were lower in the supine position.

During the M-RSA, when AG and CG are compared (Table 4), we found higher values of HR (82.6 ± 10.0 vs. 72.4 ± 7.6 bpm) and lower values of R-Ri (746.4 ± 92.1 vs. 846.4 ± 81.4 ms), respectively. In addition, we observed lower values of ApEn in the AG ($p < 0.05$). There were no differences between groups in other HRV indices during the maneuver.

Furthermore, the FEV₁% presented strong positive correlation with HF ($r = 0.83$, $p = 0.0001$) and negative correlation with LF ($r = -0.84$, $p = 0.0001$) as presented in Figure 2. The correlation using the FEV₁% and the difference of HRV indices in the two positions (Δ) (seated–supine) demonstrated a strong positive correlation with LF ($r = 0.78$, $p = 0.0009$) and positive correlation with SD2

($r=0.52$, $p=0.05$). Moreover, a negative strong correlation of FEV₁ and negative correlation of Δ of the HF ($r=-0.78$, $p=0.0009$) and Alpha2 ($r=-0.60$, $p=0.02$) indices were found (Figure 3).

Discussion

Main findings

The findings of the present study suggest that volunteers with asthma presented changes in the autonomic modulation of HR at rest and during the M-RSA, even in the presence

of clinical stability of the disease. Although the asthmatic volunteers had responses to postural changes for some indices in the time domain, we did not observe adequate responses in the frequency domain.

In addition, the FEV₁ presented a positive correlation with the Δ of the LF and SD2, which point out an alteration in the sympathetic modulation and the total variability, respectively. We also observed a negative correlation of the FEV₁ with the HF, which reflects the parasympathetic modulation. Those findings may indicate a more severe impairment of the autonomic control when the airway obstruction due to asthma is more severe.

Table 1. General characteristics of the study volunteers.

	CG (n = 10) Mean ± SD	AG (n = 14) Mean ± SD
Age (years)	31 ± 8.7	28 ± 8.5
Gender female/male	10/0	11/3
Weight (kg)	60 ± 7.7	70.3 ± 14.4*
Height (cm)	165 ± 7.3	168.9 ± 7.7
Body mass index (kg/m2)	21.8 ± 2.0	24.5 ± 4.3
FEV ₁ (% predicted)	97.2 ± 13.4	86 ± 15*
FVC (% predicted)	93.6 ± 11.7	105.6 ± 32.8
FEV ₁ /FVC (%)	102.1 ± 8.0	70.0 ± 13.0 [#]
VO ₂ predicted (ml/min)	1702.6 ± 271.3	1706.8 ± 121.8
VO ₂ peak (ml/min)	1663.9 ± 282.8	1808.5 ± 614.0
Mean heart rate (l/min)	69.6 ± 8.1	77.2 ± 9.4*
Mean R-Ri (ms)	887.8 ± 112.7	807.5 ± 107.2
Medications (number of patients)		
Budesonide (100 mcg)		3
Beclomethasone/salbutamol (50/100 mcg)		2
Momethasone furoate (200 mcg)		1
Salbutamol (100 mcg)		5
Beclomethasone/formoterol (100/6 mcg)		1
Formoterol fumarate/budesonide (12/400 mcg)		1
Fenoterol bromidrate (0.5 mg/ml)		1
Ipratropium bromide (0.25 mg/ml)		1
Beclomethasone dipropionate 200 mcg/dose		1

FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; VO₂: maximal oxygen consumption; R-Ri: R-R interval.
* = $p<0.05$, # = $p<0.01$

Autonomic control of HR at rest and due to postural changes

In the supine position, HR and LF were higher in the AG when compared with the CG, which suggests an increase of the chronotropy and the sympathetic modulation. Our findings agreed with previous studies, which had observed an increase of the chronotropy at rest [4,5,7,8,19]. Moreover, they were similar to the results found by Eryonucu et al. [20], who had observed marked changes in HRV of asthmatic patients after the inhalation of salbutamol and terbutaline, with an increase of the sympathetic modulation in the autonomic activity of the heart. However, differently from these previous studies [20–22], we excluded patients who have recently used BD, in order to verify the changes in HRV without the direct action of medication, and we were still able to find an impairment of the autonomic control of HR. This finding suggests the presence of physiological adaptations rather than changes due exclusively to the direct action of the medication on the autonomic nervous system.

Likewise, Jartti et al. [23] found an increased sympathetic modulation in asthmatic children after the use of salbutamol during two weeks, three times a day. Moreover, the increase lasted for 18h after the interruption of the medication. A higher sympathetic activity is known to increase the risk of cardiovascular conditions, such as insulin resistance, hypertension and the evolution of the cardiac

Table 2. Individual lung function values in AG.

AG	FEV ₁ predicted (l)	FEV ₁ pre (l)	FEV ₁ pre (%)	FEV ₁ post (l)	FEV ₁ post (%)	FVC predicted (l)	FVC pre (l)	FVC pre (%)	FVC post (l)	FEV ₁ /FVC pre (%)	FEV ₁ /FVC post (%)
1	3.2	2.4	75.0	3.6	112.5	3.7	3.3	89.2	3.9	72.7	92.0
2	3.2	3.2	99.0	3.7	115.6	3.9	7.6	194.9	8.0	42.1	46.0
3	3.0	2.1	70.0	2.9	96.7	3.6	2.8	78.0	2.9	75.0	100.0
4	3.2	3.0	93.8	3.3	103.2	3.8	3.8	99.0	3.8	79.0	87.0
5	3.1	2.7	87.0	3.2	103.0	3.6	3.8	105.1	3.8	71.1	83.8
6	3.4	2.9	85.0	3.6	105.9	4.1	3.1	75.0	3.8	93.2	94.8
7	3.1	2.2	71.0	2.9	93.5	3.7	3.4	91.9	3.6	64.7	80.6
8	3.5	2.3	65.7	3.0	84.9	4.2	3.4	80.0	3.8	68.2	78.2
9	3.5	2.4	68.5	2.9	82.8	4.1	3.6	87.8	4.0	66.0	72.5
10	3.5	2.8	80.0	3.2	91.4	4.2	5.0	119.0	5.0	56.0	64.0
11	3.2	3.8	118.0	4.3	134.3	3.8	6.0	157.9	6.1	63.3	70.5
12	4.1	3.8	92.0	4.1	100.0	5.2	5.0	96.0	5.3	75.0	76.0
13	4.6	4.1	89.1	4.4	95.0	5.1	5.2	102.0	5.3	79.0	83.0
14	4.8	5.2	108.0	5.7	118.8	5.8	6.5	112.0	6.8	80.0	83.8
Mean	3.5	3.0	86.0	3.6	103.0	4.2	4.5	106.0	4.8	70.0	80.0
SD	0.5	0.8	15.0	0.8	13.0	0.6	1.4	32.0	1.4	12.0	16.1

FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; SD: standard deviation; pre: pre bronchodilators; post: post bronchodilators.

Table 3. Indices of heart rate variability linear and non-linear at rest, in supine and seated positions among asthmatics and control.

	CG (n = 10)		AG (n = 14)	
	Mean $\pm$ SD		Mean $\pm$ SD	
	Supine	Seated	Supine	Seated
Respiratory rate	16.5 $\pm$ 0.3	15.4 $\pm$ 0.4	15 $\pm$ 0.5	13.7 $\pm$ 0.6
Linear				
Time domain				
Heart rate (bpm)	68.7 $\pm$ 8.7	72.8 $\pm$ 8.7 ^a	77.1 $\pm$ 9.9 ^c	82.9 $\pm$ 11.8 ^a
R-Ri (ms)	887.5 $\pm$ 112.7	835.4 $\pm$ 96.5 ^a	807.5 $\pm$ 107.2 ^c	740.6 $\pm$ 109.2 ^b
rMSSD (ms)	34.3 $\pm$ 23.4	23.4 $\pm$ 6.9	36.8 $\pm$ 19.1	28.0 $\pm$ 16.2 ^a
Frequency domain				
HF (n.u.)	70.7 $\pm$ 11.1	52.5 $\pm$ 17.2	49.4 $\pm$ 17.1 ^c	40.1 $\pm$ 12.1
LF (n.u.)	29.2 $\pm$ 11.1	47.4 $\pm$ 17.2 ^a	50.4 $\pm$ 17.1 ^c	59.8 $\pm$ 15.1
LF/HF	0.4 $\pm$ 0.2	1.1 $\pm$ 0.7 ^a	1.3 $\pm$ 0.7 ^c	2.0 $\pm$ 0.7
Non-linear				
Alpha1	0.7 $\pm$ 0.1	0.9 $\pm$ 0.2 ^b	1.0 $\pm$ 0.2	1.1 $\pm$ 0.1 ^c
Alpha2	0.8 $\pm$ 0.1	1.0 $\pm$ 0.2 ^a	0.4 $\pm$ 0.2 ^d	0.3 $\pm$ 0.1 ^d
SD1 (ms)	24.1 $\pm$ 16.6	16.7 $\pm$ 4.9 ^a	26.1 $\pm$ 13.5	19.8 $\pm$ 11.5 ^a
SD2 (ms)	41.5 $\pm$ 24.6	42.0 $\pm$ 16.2	47.8 $\pm$ 25.6	43.2 $\pm$ 20.9
ApEn	0.8 $\pm$ 0.1	0.8 $\pm$ 0.0	0.8 $\pm$ 0.0	0.9 $\pm$ 0.1
SampEn	1.8 $\pm$ 0.1	1.7 $\pm$ 0.2	1.7 $\pm$ 0.3	1.5 $\pm$ 0.2 ^{a,c}
REC (%)	19.9 $\pm$ 4.9	27.7 $\pm$ 6.4 ^b	23.2 $\pm$ 3.7	29.1 $\pm$ 6.5 ^b
DET (%)	95.5 $\pm$ 1.9	97.1 $\pm$ 1.6 ^a	96.5 $\pm$ 1.1 ^c	97.3 $\pm$ 1.2 ^a
Shannon entropy	2.7 $\pm$ 0.2	2.8 $\pm$ 0.2 ^a	2.9 $\pm$ 0.1 ^c	2.9 $\pm$ 0.2

R-Ri: R-R interval; rMSSD: root mean square of successive differences between adjacent normal R-Ri; HF: high frequency; LF: low frequency; LF/HF: ratio between LF and HF band; SD1: instantaneous beat-to-beat variability of HR; SD2: continuous beat-to-beat variability of HR; ApEn: approximate entropy; SampEn: sample entropy; REC: recurrence rate; DET: determinism.

^a $p \leq 0.05$ intergroup, ^b $p \leq 0.01$ intergroup, ^c $p \leq 0.05$ intergroup, ^d $p \leq 0.01$ intergroup.

Table 4. Linear and non-linear HRV indices between asthmatics and controls during a respiratory sinus arrhythmia maneuver (M-RSA).

	CG (n = 10)	AG (n = 14)	p Value
	Mean $\pm$ SD	Mean $\pm$ SD	
Linear			
Time domain			
HR (bpm)	72.4 $\pm$ 7.6	82.6 $\pm$ 10.0	0.01
R-Ri (ms)	846.4 $\pm$ 81.4	746.4 $\pm$ 92.1	0.01
rMSSD (ms)	55.2 $\pm$ 22.3	42.8 $\pm$ 20.	0.17
Δ IE (bpm)	20.8 $\pm$ 8.4	23.1 $\pm$ 6.9	0.06
Ratio E/I	1.32 $\pm$ 0.07	1.33 $\pm$ 0.07	0.90
Frequency Domain			
HF (n.u.)	8.2 $\pm$ 5.6	10.4 $\pm$ 15.6	0.67
LF (n.u.)	91.6 $\pm$ 5.6	89.4 $\pm$ 15.6	0.68
LF/HF	18.2 $\pm$ 15.4	20.2 $\pm$ 12.8	0.73
Non-linear			
Alpha1	1.5 $\pm$ 0.1	1.6 $\pm$ 0.2	0.15
Alpha2	0.0 $\pm$ 0.0	0.2 $\pm$ 0.1	0.06
SD1 (ms)	39.1 $\pm$ 15.8	30.3 $\pm$ 14.3	0.17
SD2 (ms)	106.9 $\pm$ 36.9	100.5 $\pm$ 38.2	0.68
ApEn	0.8 $\pm$ 0.1	0.7 $\pm$ 0.0	0.03
SampEn	1.0 $\pm$ 0.3	0.8 $\pm$ 0.2	0.07
REC (%)	28.7 $\pm$ 3.1	31.1 $\pm$ 3.9	0.14
DET (%)	98.5 $\pm$ 0.6	98.9 $\pm$ 0.6	0.27
Shannon entropy	3.3 $\pm$ 0.2	3.1 $\pm$ 0.2	0.06

HR: heart rate; R-Ri: R-R interval; rMSSD: root mean square of successive differences between adjacent normal R-Ri; Δ IE: mean difference heart rate in inspiration and expiration during a respiratory sinus arrhythmia maneuver (M-RSA); Ratio E/I: ratio of means R-Ri in expiration and inspiration during a respiratory sinus arrhythmia maneuver (M-RSA); HF: high frequency; LF: low frequency; LF/HF: ratio between LF and HF band; Alpha1 and Alpha2: short-term and long-term fluctuations of detrended fluctuation analysis; SD1: instantaneous beat-to-beat variability of HR; SD2: continuous beat-to-beat variability of HR; ApEn: approximate entropy; SampEn: sample entropy; REC: recurrence rate; DET: determinism.

hypertrophy [24]; therefore the linear and non-linear indices of HRV has been used to assess cardiovascular risk [25].

Furthermore, Skorodin [26] alerts that cardiovascular effects of the β -agonists should be assessed, since myocardial function impairments are found in asthmatic people; the prolonged use of this medication should be recommended only when it is absolutely necessary. In our study, even with the suspension of the regular use of the medication, we observed a higher HR at rest, and additionally, higher values of LF and lower values of HF. These findings convey that an increased cardiovascular risk exists in asthmatic patients, even when they are in a stable clinic condition.

During the postural change from the supine to the seated position, the AG presented a higher resting value of HR when compared with the CG and a small response of HR due to postural change, which demonstrates some adaptation even without the use of the medication to control asthma. The SampEn also had small values of change in the AG, which shows a smaller signal regularity in a temporal series. According to Ferreira et al. [17] the SampEn is a valuable prognostic measure, since an impaired autonomic control of HR may occur in individuals who this index is lower than normal, occasionally observed in cardiac patients.

Autonomic control of HR due to the M-RSA

During the M-RSA, the mean HR was higher and the mean R-Ri was lower in AG when compared with the CG. Additionally, the ApEn values were lower in AG, indicating that oscillations of HR, which are expected to be complex,

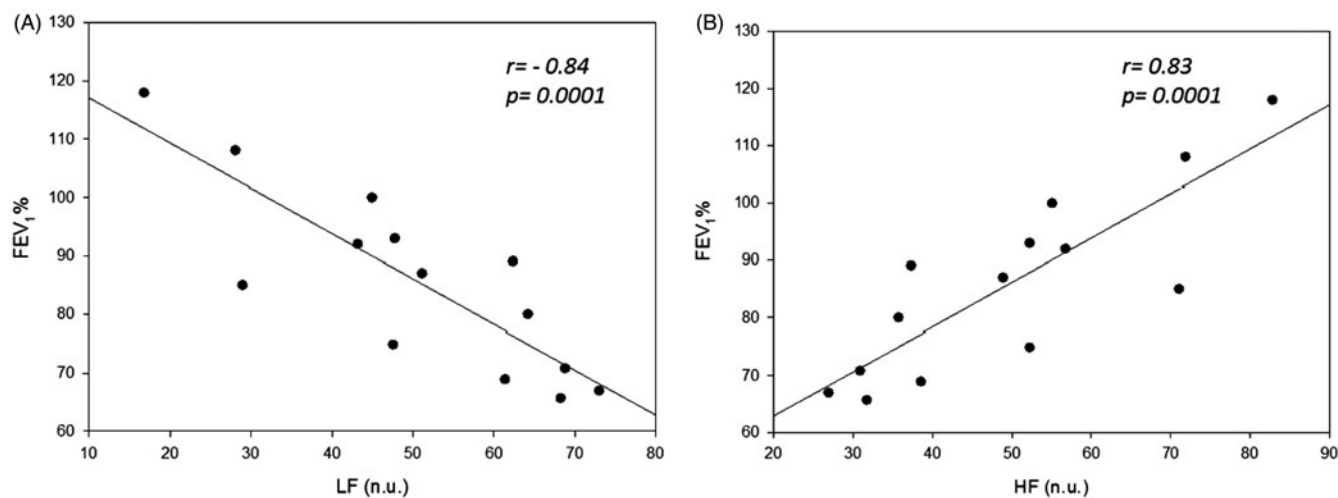


Figure 2. Correlation between FEV₁ (forced expiratory volume in 1 s) and LF (low frequency index) (A), FEV₁ and HF (high frequency index) (B) in AG supine position.

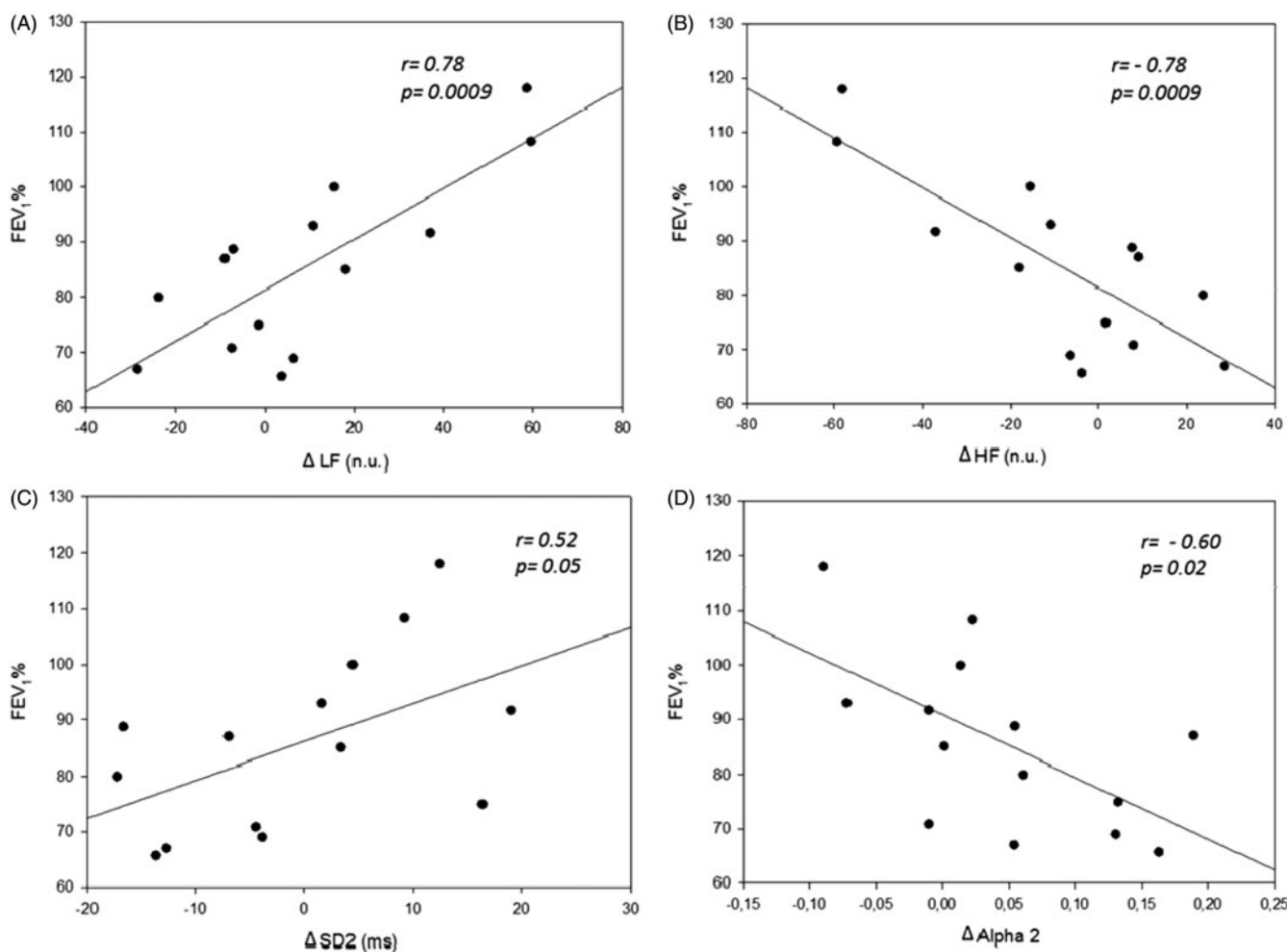


Figure 3. Correlation between FEV₁ (forced expiratory volume in 1 s) and changes (seated-supine = Δ) of LF (low frequency index) (A), HF (high frequency index) (B), SD2 (C) and Alpha2 (D).

irregular and unpredictable during the M-RSA were affected in stable asthmatic patients [17,18,27,28].

The RSA, a product of the interaction between the respiratory and cardiovascular systems, is influenced by the

respiratory rate and tidal volume [29]. In our study, since the respiratory rate was controlled during the M-RSA, the changes of the indices of HRV in the asthmatic group are expected to be related to the alterations in the tidal

volume; the reduction of HRV indices in the AG may occur due to changes in the pulmonary compliance and to the response of the pulmonary stretch receptors [12].

The results regarding the changes in HRV during the M-RSA reinforces the finding that the autonomic modulation of HR is unbalanced in asthmatic patients, with higher sympathetic and lower parasympathetic activity, in spite of the suspension of the medications before the tests.

Correlations between the FEV₁ and HRV indices

Moderate to strong correlations were found between the FEV₁ and the LF and HF indices, as well as correlations between FEV₁ and the Δ in the Alpha2 and SD2 due to postural changes in the AG. Our findings point out that the more severe the obstruction of the airways is, the more the autonomic control of HR is impaired, especially during postural changes. These results are consistent with those found by Stein et al. [30] who found similar associations between the FEV₁ and HRV indices ($r=0.65$ with HF, and $r=0.57$ with LF) in patients with chronic obstructive pulmonary disease. Care is warranted when making comparisons between these studies, because even though the diseases approached by them are known to cause airway obstruction, differences between the studied populations should be highlighted, such as a lower age, smoking habits, distinct pathophysiology and medications, which could also influence HRV indices.

Clinical implications of this study

HRV indices are important markers of autonomic dysfunction, and thereby are related to an increased risk of arrhythmias, worse prognosis, and an increased risk of sudden death [2,31–36]. Considering the young population in our study, these indices may be markers of cardiovascular compromise due to asthma. Nevertheless, future studies should be carried out to verify the consequences of impaired HRV indices in controlled asthma.

Limitations and conclusions

Some limitations from this study should be considered when analyzing the findings. We assessed only 14 stable asthmatic volunteers; however, the presence of clinical stability was rigorously controlled. Therefore, the considerations from this study should not be extrapolated to patients in exacerbation, with or without the use of medications. Another limitation was the absence of the assessment of inflammatory markers, which could support the presence of disease chronicity, even in the presence of disease stability.

We conclude that chronic and stable asthma seems to induce a predominance of the sympathetic modulation in young adult and the reduction of the adjustments due to sympathetic and parasympathetic stimulation of HR. Furthermore, the severity of the obstruction is associated with impairments of HRV adjustments due to postural changes.

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Declaration of interest

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