Comparative analysis of autonomic modulation in children with acute and controlled asthma

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Summary

Background: We aimed to compare autonomic modulation in children with acute and controlled asthma at rest.

Material/Methods: Twenty-five children aged 5 to 13 years participated in the study: 19 with asthma analyzed both during an attack (acute asthma group) and after controlling the condition (controlled asthma group), and 6 without asthma (control group). Peak flow, spirometric variables and C-reactive protein were analyzed. Heart rate variability (HRV) was evaluated at rest for 10 min in the supine position using frequency and time domains as well as non-linear variables. Asthma was characterized as persistent/moderate based on the classification of severity.

Results: A predominance of the sympathetic nervous system was found in the acute asthma group, as demonstrated by the RMSSD, LF/HF ratio, SD1, and SD2. No difference was found between controlled asthma and control groups. Peak flow was lower among the children with asthma in comparison to the control group. Moreover, no statistically significant difference in peak flow was found between the acute and controlled asthma groups. A positive correlation was detected between C-reactive protein and LF/HF ratio.

Conclusions: Differences in autonomic modulation were found in the groups studied, with predominant action of the parasympathetic system in the controlled asthma group. Unexpectedly, predominance of the sympathetic system was found in the acute asthma group, which was likely an attempt to assist in bronchodilation and may explain the systemic inflammatory response triggered in these patients.

key words: asthma • heart rate variability • autonomic nervous system

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**BACKGROUND**

Asthma is a chronic respiratory disease commonly found in children, stemming from inflammation of the airways and characterized by partially reversible bronchial hyperresponsiveness to limited airflow [1,2]. According to the 2011 Global Asthma Report, this condition affects approximately 235 million people throughout the world, with a significant increase every year [3].

Anti-inflammatory therapies can reduce some manifestations of asthma, such as bronchial hyperresponsiveness and bronchospasm, but do not definitively resolve the symptoms. The accentuated bronchoconstriction in response to different stimuli may derive from both inflammation and an autonomic imbalance [4].

The autonomic nervous system (ANS) influences different apparatuses and systems of the body, playing an essential role in the preservation of physiological equilibrium. This system operates through visceral reflexes, which control the activities of different organs by means of unconscious reflex responses [5]. The activation of the autonomic mechanism in the respiratory system is due to the reflex response of receptors located in the airways, and regulates bronchial contractility [6–9].

Besides its essential functions in the cardiovascular system, the ANS plays an important role in the regulation of bronchial smooth muscle contractions, which are altered in conditions such as asthma [10]. An imbalance of the ANS leads to increased bronchial sensitivity to cholinergic constriction and decreased sensitivity to B2-adrenergic bronchodilators [11].

Asthma severity is directly correlated to autonomic dysfunction, even when the patient is not in the throes of an attack. Moreover, the functions of the ANS in individuals with asthma differ from those without this condition [12,13]. The hypothesis tested herein is that greater autonomic dysfunction of the parasympathetic system is found in acute asthma in comparison to periods in which asthma is controlled.

The aim of the present study was to compare autonomic modulation in children with acute and controlled asthma at rest.

**MATERIAL AND METHODS**

**Ethical considerations**

This study was approved by the Human Research Ethics Committee of the *Universidade Nove de Julho* (Brazil) under protocol n° 77913/2012 and was carried out in compliance with the principals of the Declaration of Helsinki, Good Clinical Practice guidelines, and Resolution 196/96 of the Brazilian National Health Council. All parents/guardians signed a statement of informed consent agreeing to the participation of their children.

**Study design**

Observational, analytical, cross-sectional study.

**Study location and sample**

This study was conducted between August and October 2012. Heart rate variability (HRV) and laboratory data were determined in children with acute asthma (acute asthma group) at the emergency ward of Mandaqui Hospital (Sao Paulo, Brazil). The same children were asked to undergo an additional HRV determination 1 month later at the Functional Respiratory Evaluation Laboratory of the *Universidade Nove de Julho*, thereby constituting the controlled asthma group. A control group of children without asthma was also evaluated at the same laboratory. Twenty-five children aged 5 to 13 years participated in the study: 19 with asthma (acute and controlled asthma groups) and 6 without asthma (control group).

The children were diagnosed by pulmonologists based on the classification proposed in the guidelines of the Global Initiative for Asthma [14]. The acute asthma group was classified with persistent/moderate asthma by the frequency of symptoms and spirometric variables [forced expiratory volume in 1 second (FEV1) and the FEV1/forced vital capacity (FVC) ratio]. All participants refrained from the use of a bronchodilator for at least 8 hours prior to data collection. In the laboratory exams, C-reactive protein (CRP) was considered a marker of systemic inflammation, with reference values lower than 0.1 mg/dL (1 mg/L).

**Analysis of heart rate variability**

Following the determination of height and weight, data on the activity of the sympathetic and parasympathetic nervous systems were collected by means of HRV analysis in the supine position, the most stable sections containing 256 points within 10 min were selected using a Polar® S810i monitor [15]. The following time domain indices were evaluated: mean heart rate (HR), mean of all normal R-R intervals, standard deviation of R-R intervals (SDRR), and root mean square of successive differences between normal sinus R-R intervals (RMSSD). The following frequency domain indices were evaluated: low frequency (LF; 0.04 to 0.15 Hz), high frequency (HF; 0.15 to 0.4 Hz), and LF/HF ratio. The following nonlinear variables were analyzed: SD1, SD2, approximate entropy (ApEn), and detrended fluctuation analysis (DFA: DFA1q, and DFA1q).

**Lung function test and peak flow**

The lung function test was performed on the controlled asthma and control groups following the criteria of the American Thoracic Society [15] and using the Easy One™ spirometer (NDD Medical Technologies), which was previously calibrated in an acclimatized room using the reference values proposed by Polgar and Pronadhat [16] adjusted to children for the characterization of asthma severity. Three readings were taken of each of the 3 classic maneuvers: slow vital capacity, FVC, and maximum voluntary ventilation. In the acute asthma group, peak flow was determined using Access™ equipment. Three readings were taken with a nasal clip and the highest reading was considered for the analysis.

**Sample calculation and statistical analysis**

The sample size was calculated based on a previous study [12]. Considering a standard deviation of 0.53 to detect a difference of 0.50 in the LF/HF ratio, β error of 0.1, and
The Kolmogorov-Smirnov test was used to determine adherence to the Gaussian curve. As normal distribution was demonstrated, the data were expressed as mean ±SD; F – female; M – male; N/A – not assessed; FEV1 – forced expiratory volume in first second; FEV1/FVC – forced expiratory volume in first second/forced vital capacity ratio.

### Table 1. Characteristics of sample.

<table>
<thead>
<tr>
<th></th>
<th>Acute asthma (n=19)</th>
<th>Controlled asthma (n=19)</th>
<th>Control (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F: 10 M: 9</td>
<td>F: 10 M: 9</td>
<td>F: 3 M: 3</td>
</tr>
<tr>
<td>Age</td>
<td>7.94±2.73</td>
<td>7.94±2.73</td>
<td>8.8±1.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>31.55±9.9</td>
<td>31.55±9.9</td>
<td>28.2±9.77</td>
</tr>
<tr>
<td>Peak flow (l/min)</td>
<td>142.7±40.98</td>
<td>152.23±46.51</td>
<td>242.6±81***</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>N/A</td>
<td>71.22±15.47</td>
<td>92.33±9.07*</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>N/A</td>
<td>81.05±14.57</td>
<td>90.83±7.54*</td>
</tr>
</tbody>
</table>

* p<0.05 control group x controlled asthma group; ** p<0.05 control group x acute asthma group; data expressed as mean ±SD; F – female; M – male; N/A – not assessed; FEV1 – forced expiratory volume in first second; FEV1/FVC – forced expiratory volume in first second/forced vital capacity ratio.

### Table 2. Data on heart rate variability.

<table>
<thead>
<tr>
<th></th>
<th>Acute asthma (n=19)</th>
<th>Controlled asthma (n=19)</th>
<th>Control (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean R-R (ms)</td>
<td>550.2±159.60*</td>
<td>636.02±60.29</td>
<td>649.72±78.90</td>
</tr>
<tr>
<td>SDRR (ms)</td>
<td>35.90±17.07*</td>
<td>46.90±20.37</td>
<td>39.72±9.20</td>
</tr>
<tr>
<td>Mean HR (1/min)</td>
<td>110.80±12.09*</td>
<td>94.04±11.83</td>
<td>93.87±11.74</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>16.80±5.96*</td>
<td>29.20±12.45**</td>
<td>21.05±6.06</td>
</tr>
<tr>
<td><strong>Frequency domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>71.55±17.17</td>
<td>66.62±13.18</td>
<td>65.92±9.02</td>
</tr>
<tr>
<td>HF</td>
<td>28.45±17.17</td>
<td>33.38±13.18</td>
<td>34.07±9.01</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>4.16±3.31*</td>
<td>2.44±1.35**</td>
<td>2.10±0.78</td>
</tr>
<tr>
<td><strong>Nonlinear HRV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD1 (ms)</td>
<td>11.90±4.22*</td>
<td>14.50±8.78</td>
<td>14.91±4.39</td>
</tr>
<tr>
<td>SD2 (ms)</td>
<td>49.00±24.19*</td>
<td>64.05±27.85</td>
<td>53.89±13.20</td>
</tr>
<tr>
<td>DFAα</td>
<td>1.21±0.25</td>
<td>1.27±0.19</td>
<td>1.24±0.13</td>
</tr>
<tr>
<td>DFAα2</td>
<td>1.12±0.11*</td>
<td>1.09±0.12</td>
<td>0.98±0.10</td>
</tr>
<tr>
<td>ApEn</td>
<td>1.13±0.21</td>
<td>1.17±0.17</td>
<td>1.21±0.19</td>
</tr>
</tbody>
</table>

Data expressed as mean ±SD; Mean R-R – mean of all normal R-R intervals; SDRR – standard deviation of mean of all R-R intervals; HR – heart rate; RMSSD – square root of sum of squared differences between R-R intervals; LF – low frequency; HF – high frequency; HRV – heart rate variability; SD1 – standard deviation of line perpendicular to identity line on Poincaré plot (instantaneous variability in R-R interval); SD2 – standard deviation of identity line on Poincaré plot (continuous variability in R-R interval); DFA – detrended fluctuation analysis; ApEn – approximate entropy; * p<0.05 in comparison to control group; ** p<0.05 in comparison to acute asthma group.

α error of 0.05, the minimum sample size was determined to be 12 patients.

The Kolmogorov-Smirnov test was used to determine adherence to the Gaussian curve. As normal distribution was demonstrated, the data were expressed as mean and standard deviation values. The paired t-test was used for comparisons between the acute and controlled asthma groups. The unpaired t-test was used for comparisons between the acute asthma group and the control group. Pearson’s correlation coefficients were calculated to determine correlations between variables. The Minitab14 program was used for data analysis, with the level of significance set to 5% (p<0.05).

### RESULTS

Table 1 displays the characteristics of the different groups (age, sex, weight, peak flow, FEV1, and FEV1/FVC). No significant differences were found regarding sex, age, or weight. Statistically significant differences were found between the acute asthma group and control group in spirometric variables and peak flow.

Table 2 displays the results of the HRV analysis. Time domain indices (mean R-R and SDRR) were significantly lower in the acute asthma group in comparison to the controlled asthma group (p<0.05). In comparison to the control group, RMSSD was lower in the acute asthma group and higher.
in the controlled asthma group. In the frequency domain, the LF/HF ratio was the only variable that differed significantly between the acute asthma group and the controlled asthma group. In nonlinear analysis, SD1 and SD2 were significantly lower, and DFA5, was significantly higher in the acute asthma group in comparison to the other groups.

Figure 1 demonstrates a correlation between peak flow and RMSSD in the children during an asthma attack.

Table 3 displays the results of the laboratory exams performed upon admission to the emergency ward (acute asthma group). CRP was higher than the reference value (0.1 mg/dL), whereas no abnormalities were detected on the other exams. Moreover, CRP was correlated with the LF/HF ratio (Figure 2).

**DISCUSSION**

Our findings demonstrate that children during a persistent/moderate asthma attack experience greater activity of the sympathetic nervous system, whereas the parasympathetic system predominates in periods in which asthma is controlled. These findings are in disagreement with the hypothesis of vagal hyperactivity in the acute phase. Previous studies on children and adults with asthma confirm parasympathetic activation in periods of control and correlate RMSSD with disease severity [12,15].

The inflammatory process in asthma is more pronounced during periods of exacerbation. Indeed, the increase in vagal tone during periods of control may be an attempt to maintain control of inflammation. Neural mechanisms are responsible for regulating inflammation. The activation of the vagus nerve inhibits the activation of macrophages and the synthesis of tumor necrosis factor alpha (TNF-α), which are also inhibited by the activation of the reticuloendothelial system for the release of acetylcholine [18]. Acetylcholine interacts with specific receptors in the membrane of macrophages, inhibiting the release of pro-inflammatory cytokines. Approximately 80% of the vagus nerve fibers are sensory fibers, which “perceive” the presence of pro-inflammatory cytokines and send a signal to the central nervous system. The efferent signal from the vagus nerve stimulates the release of acetylcholine, which inhibits the production of TNF-α by macrophages [17,18]. The brain and heart are closely connected and data suggest an association between HRV and inflammation involving the same neural mechanisms [19].

As the sympathetic system exhibits both anti-inflammatory and pro-inflammatory action, it may affect the production of TNF-α by macrophages, giving rise to an inflammatory cascade that produces CRP [20]. In the present study, CRP was positively correlated with the higher LF/HF ratio upon the admission of children during an asthma attack, demonstrating that increased systemic inflammation is accompanied by poorer autonomic modulation. The altered CRP may indicate that systemic inflammation is associated with lung function and the ANS. In asthma, the importance of both airway inflammation and systemic inflammation has been well established. A number of studies report that a high level of serum CRP is associated with hyperresponsiveness of the airways and low FEV1 [20–22].

The correlation between RMSSD and peak flow demonstrates that greater activation of the parasympathetic system in acute asthma is accompanied by greater peak flow. It is likely that this correlation demonstrates that lesser inflammation (due to greater vagal activation) results in greater peak flow. Initially, this supposition seems incorrect, because greater cholinergic activation is thought to be related to bronchoconstriction. However, parasympathetic activation was much lower in the acute asthma group in comparison to the control group, thus demonstrating values below those considered normal.

**CONCLUSIONS**

Differences in autonomic modulation were found in the groups studied, with predominant action of the parasympathetic system in the controlled asthma group. Unexpectedly, predominance of the sympathetic system was found in the
acute asthma group, which was likely an attempt to assist in bronchodilation and may explain the systemic inflammatory response triggered in these patients.

REFERENCES: