Original Article

Assessment of Subclinical Derangement of Cardiovascular Autonomic Regulation in Stable Asthmatic Patients

Rajesh Gupta, Anupama Gupta[1], Navneet Kumar Kaushik[1], Rajat Chabbra, Sushma Sood[1]

Departments of Respiratory Medicine and [1]Physiology, Pt. B.D. Sharma, PGIMS, Rohtak, Haryana, India

Abstract

Background and Aim: Autonomic nervous system (ANS) is linked to asthma. The ANS controls several aspects of airway function. It was planned to assess the autonomic cardiovascular regulation in stable asthmatic patients by short-term heart rate variability (HRV) analysis. **Methods:** The present study was conducted in the Department of Respiratory Medicine in collaboration with the Department of Physiology, Pt. B.D.S PGIMS, Rohtak in a total of eighty subjects/patients with comparable age, sex, weight, and height. Two groups with forty subjects/patients in each were formed as follows: Group 1: stable asthmatics and Group 2: nonasthmatics (controls). Electrocardiography and HRV of the participants were measured using digitalized polyrite-D as per the standard protocol. **Results:** Frequency domain parameters showed statistically significant difference between two groups. Low frequency (LF) (nu) was (48.9 ± 17.8 vs. 53.3 ± 16.9) significantly less ($P < 0.05$), while high frequency (HF) (nu) significantly more (41.4 ± 15.19 vs. 38.3 ± 1.2) in Group 1 as compared to Group 2. LF/HF (1.2 ± 0.6 vs. 1.39 ± 0.78) ratio was decreased significantly ($P < 0.05$) in Group 1. **Conclusion:** An overall reduced HRV (sympathetic activity) and deranged sympathovagal balance with vagal dominance (decreased LF, increased HF) in stable asthmatics. Hence, HRV could serve as a potential noninvasive tool to assess autonomic cardiovascular regulation in asthmatics.

Keywords: Asthma, heart rate variability, sympathovagal

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Introduction

Asthma is a chronic inflammatory condition of airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at night or in the early morning. These episodes are associated with widespread but variable airway obstruction within lung that is often reversible either spontaneously or with treatment.[1]

Asthma is a major cause of disability, health resource utilization, and poor quality of life for those who are affected. It accounts for considerable health-care costs and loss of work productivity. Recently, it was estimated that 300 million people worldwide have asthma and projected that this number would increase to 400 million by 2025 as countries become more urbanized.[2]

There is no definite cause of asthma. There are host factors (genetics, obesity, and sex) and environmental factors (indoor allergens, air pollution, infections, tobacco smoke, etc.) that influence the risk of development of asthma.[3] Autonomic nervous system (ANS) is also linked to asthma. The ANS controls several aspects of airway function. Any abnormality in autonomic regulation of the airways may lead to bronchospasm, airway edema, and excessive mucous secretion, which are the events that place in pathogenesis of airway obstruction in bronchial asthma.[4]

The measurement of heart rate variability (HRV) is a relatively new powerful noninvasive methodology which can evaluate sympathovagal balance within the body. Impaired autonomic regulation of heart rate has been associated with various lung diseases such as asthma and chronic obstructive lung disease. Therefore, it was planned to assess the autonomic

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Address for correspondence: Dr. Rajesh Gupta, H. No. 32/9J, Medical Campus, PGIMS, Rohtak - 124 001, Haryana, India. E-mail: drrgupta63@gmail.com

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cardiovascular regulation in stable asthmatic patients by short-term HRV analysis.

Materials and Methods

The present study was conducted in the Department of Tuberculosis (TB) and Respiratory Medicine in collaboration with the Department of Physiology, Pt. B.D.S PGIMS, Rohtak. The study design involved eighty individuals which were divided into two groups as follows:

- Group 1: Stable asthmatics ($n = 40$)
- Group 2: Age- and sex-matched healthy controls ($n = 40$).

Study participants were selected using the following inclusion and exclusion criteria.

Inclusion criteria

Stable asthmatic patients having

- Symptom frequency <2 per week
- Night time symptoms <2 per month
- % forced expiratory volume in 1 s (FEV1) <80% of the predicted
- %FEV1 variability of <20%
- %FEV1 improvement of >12% following bronchodilator therapy.[5]

Exclusion criteria

- Patients not willing to be assessed as per study protocol
- Patients having acute exacerbation of asthma
- Patients having any other cardiac or respiratory disease, hypertension, diabetes mellitus, and other diseases affecting ANS
- Patients on drugs which are known to modify ANS, for example, beta blockers.

Spirometry was also done to measure the indices namely

- FEV1
- Forced vital capacity (FVC)
- FEV_1/FVC ratio.

This study included patients attending the Outpatient Department of TB and Respiratory Medicine.

Electrocardiography (ECG) and HRV of the subjects were measured with digitalized "POLYRITE D" as per the standards laid down by a task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[6] Following settings were used:

- Sensitivity – 20 mv
- Low-pass filter – 2 KHz and high-pass filter – 0.5 Hz
- Smoothening type – triangular (Bartlett) window
- FFT (Fast Fourier transformation) size – 1024 (1K)
- Frequency band used is 0.04 <low frequency (LF) <0.15 <high frequency (HF) <0.4.

Procedure

After the preliminary history taking and examination, subjects were asked to lie down on the couch in front of the POLYRITE D system. The three disposable adhesive electrodes were attached to the left arm, right arm, and left leg, respectively, and for ECG measurement, lead 2 was selected. The basal recording of ECG (lead 2) was done for 5 min.

The artifacts produced due to movement may cause a discrepancy in the result which is a major limitation in the interpretation of the same. We took utmost care to minimize the movements as the subjects were instructed not to move and not to speak while the recording is in progress to eliminate the artifacts.[7,8] We carried out the recordings in supine position to avoid the influence of posture.[9]

ECG report was autogenerated by the machine. The heart rate is based on the duration of time interval between two R waves, graphically represented in the form of RR interval tachogram. The following variables were generated and used in the study.

Time domain parameters (in milliseconds) include:

- SDNN – Standard deviation of the all NN interval
- SDANN – Standard deviation of the average NN intervals calculated over short periods, usually 5 min
- rMSSD – Square root of the mean of the sum of the squares of differences between adjacent NN interval
- NN50 – Adjacent NN intervals that are the > 50 ms
- pNN50 (%) – Percentage of difference between adjacent NN intervals that are greater than 50 ms.

Frequency domain indices include

- TP (ms^2) – Total power
- VLF (ms^2) – Very LF band variation
- LF (AV) absolute values in ms^2 and in normal units (nu) – LF band variation
- HF (AV) in ms^2 and in nu – HF band variation
- LF/HF ratio

Subjects were explained the purpose of the study, the study protocol, and the informed consent was taken.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). Mean and standard deviation of time and frequency domain HRV indices were measured, and significance of the difference between the two groups was tested by applying Student's *t*-test. Statistical significance was tested at 5% and expressed in terms of "*P*" value with $P < 0.05$ = statistically significant.

Results

The study was carried out in the Department of Tuberculosis and Respiratory Medicine in collaboration with the Department of Physiology, Pt. B.D.S PGIMS, Rohtak. Two groups of study subjects were examined in the study. Group 1 comprised of forty stable asthmatics and Group 2 of forty age- and sex-matched healthy controls.

Anthropometric characteristics of the subjects are shown in Figure 1.

Body mass index (BMI) of the Group 1 differed significantly ($P < 0.01$) from Group 2, BMI being higher in Group 1.

Figure 2 shows a comparative analysis of the spirometric indices, i.e. FEV_1, FVC, peak expiratory flow rate (PEFR), and $FEV_{1\%}$ between the two groups. The figure clearly illustrates the statistically significant ($P < 0.05$) difference between the two groups in relation to the spirometric parameters which have been found to be low in Group 1 (stable asthmatics).

Figure 3 compares the time domain parameters between the control group and Group 1. All the time domain parameters were decreased in Group 1, and the difference was statistically significant ($P < 0.05$).

Figures 4 and 5 compare the frequency domain parameter between the two groups. All the frequency domain parameters showed statistically significant ($P < 0.05$) difference between the two groups. TP, VLF, LF, and LF/HF ratio were decreased and HF increased in Group 1 as compared to Group 2.

Discussion

Asthma is defined as the disease of the airways characterized by airway hyperresponsiveness, chest tightness, and wheeze.[1] Asthma is linked to ANS abnormalities. ANS controls several aspects of airway function such as airway tone and mucous secretion. Altered cardiovascular and respiratory responses reflecting autonomic abnormality are due to the common central origin of cardiovascular and respiratory autonomic efferent fibers. ANS abnormalities can be measured by measurement of HRV. HRV is a simple method to evaluate sympathovagal balance at the sinoatrial level. HRV represents continuous fluctuations in heart rate.

Time domain analysis of HRV uses statistical methods to quantify the variation of the standard deviation or the differences between successive R-R intervals. Frequency domain analysis of HRV enables us to calculate the respiratory-dependent HF and LF powers. HF power is mediated by vagal activity, while LF power has been suggested to represent both sympathetic and parasympathetic activity but predominantly sympathetic modulation. Whereas LF/HF ratio reflects global sympathovagal balance.[10]

Our study showed that time domain parameters were decreased significantly in Group 1 (stable asthmatics) as compared to Group 2 (controls), and this difference was statistically significant ($P < 0.05$). Comparison of frequency domain parameters revealed that TP, VLF, LF, and LF/HF ratio were decreased and HF increased in Group 1 as compared to Group 2 and these changes were significant statistically ($P < 0.05$). These results were comparable with the earlier HRV researches in

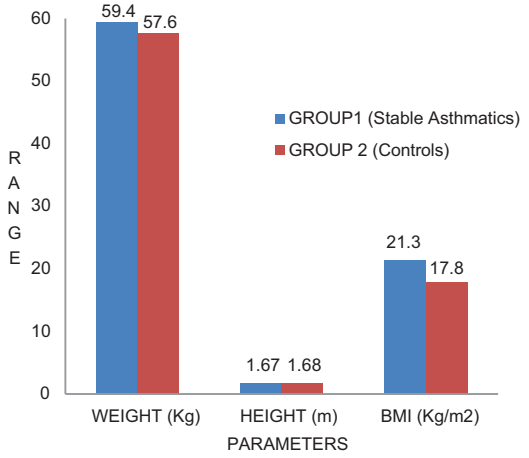

Figure 1: Anthropometric characteristics of the study subjects

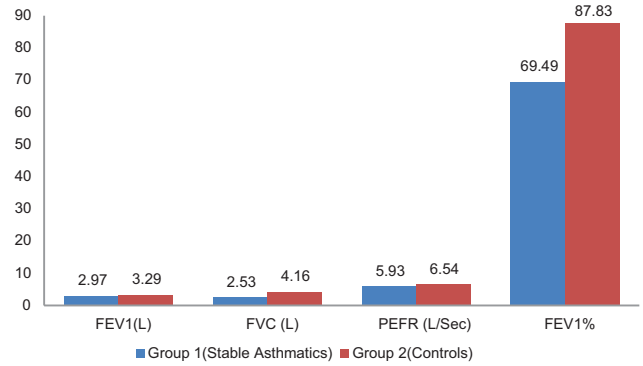

Figure 2: Comparison of spirometric indices between Group 1 and Group 2

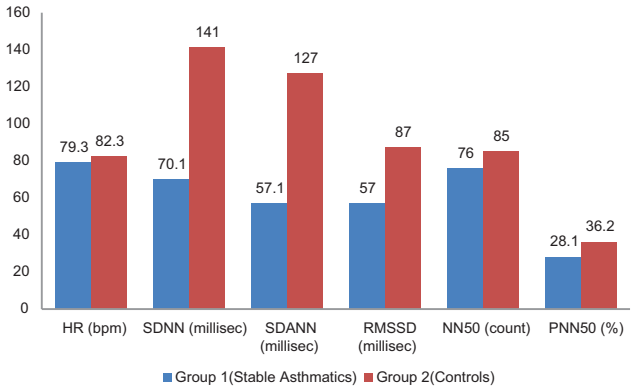

Figure 3: Comparison of time domain parameters between Group 1 and Group 2

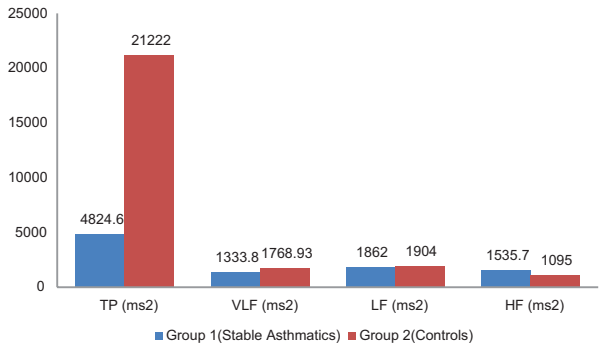

Figure 4: Comparison of frequency domain parameters between Group 1 and Group 2

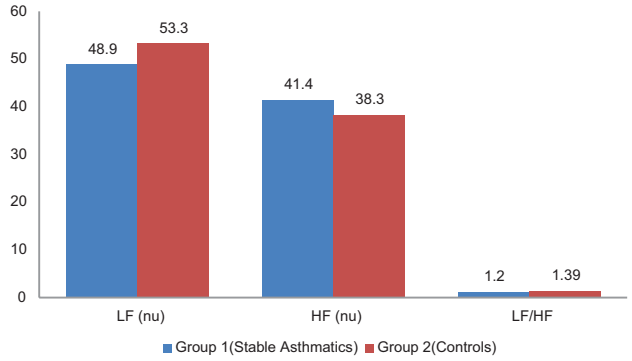

Figure 5: Comparison of frequency domain parameters between Group 1 and Group 2

asthmatic patients. Garrard *et al*. evaluated ten healthy controls, nine asymptomatic, untreated asthmatic subjects, and ten asthmatic patients during treatment of asthma, by measurement of variation in resting heart rate using frequency spectrum analysis. The study showed a significantly lower LF component in both asymptomatic and acute asthma subjects as compared to the controls. However, this study failed to prove the dominance of parasympathetic modulation (HF component) in asthmatic subjects.[11] In contrast, Du *et al*. were able to demonstrate enhanced vagal tone when comparing 23 healthy volunteers and 69 asthmatic young adults. In addition, the study showed diminished LF and SDANN in the test group.[12]

Kazuma *et al*. analyzed the 24h HRV in asthmatic children (ages 5–15 years). These subjects were divided into groups according to the severity of their asthma. The autonomic nerve function (ANF) of asthma subjects was lower in comparison to the normal group. SDNN and LF were lowest in severe asthma group. Kazuma *et al*. also examined the circadian rhythm of nervous function in asthmatic children. Circadian rhythm disappeared in 11.25% of asthmatic children and was observed in all the healthy children. Moreover, the parasympathetic activity was low during periods of remission.[13] Ostrowska-Nawarycz *et al*. reported that, at resting conditions, a tendency for HF component of HRV to be higher with greater intensity of asthma. They observed that, in youth group with moderate asthma, the HF component at rest was significantly high.[14] A study by Gupta *et al*. showed significantly low VLF component of HRV in asthmatic group as compared to the control group.[15] Another study by Behera *et al*. correlated spirometric indices, namely, FEV_1, PEFR, and FEV_1/FVC with HRV parameters HF and LF in chronic smokers.[16] It is evidenced from these studies that higher level of asthma control is associated with improved sympathetic (LF Norm and LF/HF) and depressed parasympathetic (HF Norm) modulations.

Conclusion

It can be deduced from the observations of our study that a probable compromised central sympathetic outflow and enhanced vagal tone in asthmatics lead to an imbalance in the sympathovagal interplay at the periphery and an increased propensity to airway obstruction, an essential feature of bronchial asthma. Hence, HRV could serve as a potential noninvasive tool in monitoring the patients of bronchial asthma. However, further elaboration and validation will be needed for HRV to become an effective diagnostic and prognostic clinical indicator in patients of bronchial asthma.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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