Original Article

Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability

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ABSTRACT

Background: Although enhanced cholinergic activity of asthmatics has been established early on, little heart rate variability (HRV) studies were done on asthma patients. Previous HRV studies were based on 24-hour recordings and therefore have not considered the extremely labile activity of bronchial asthma. **Objective:** To evaluate the pattern of autonomic modulations in asthmatic patients based on short-term HRV studies. **Materials and Methods:** The study involved 100 asthmatic patients with an age range of 20-40 years. Asthma activity was evaluated over the last month prior to patients' assessment using asthma control test (ACT). Allflow Spirometer was used for assessing pulmonary function, while Biocom 3000 electrocardiography recorder was used for studying 5-minute HRV. Data was analyzed using the Statistical Package for the Social Sciences Software. Heart rate and asthma medications were introduced as a covariate when studied variables were screened for significant correlation between measurements of asthma severity and heart rate variability indices using partial correlations. **Results:** The level of asthma control correlate positively with both normalized low frequency (LF Norm) and the ratio of low frequency/high frequency (LF/HF) (CC = 0.302, 0.212 and *P* = 0.002, 0.036, respectively) and negatively with HF Norm (CC = -0.317, *P* = 0.001). Duration of asthma correlates positively with normalized high frequency (HF Norm) (CC = 0.235, *P* = 0.020) and negatively with LF Norm (CC = -0.250, *P* = 0.013). **Conclusion:** Poor asthma control is associated with lower HRV, depressed sympathetic and enhanced parasympathetic modulations especially in those with longer asthma duration.

KEY WORDS: Asthma control test, asthma, autonomic, heart rate variability

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INTRODUCTION

Heart rate variability (HRV) assesses the differences of the periods between consecutive heartbeats, which vary under autonomic control. HRV can be measured by the time domain method, the frequency domain method and others.[1] In the time domain method, mean heart rate (MHR), the square root of variance of RR intervals (SDNN) and square root of the mean squared differences of successive RR intervals (RMSSD) can be calculated. On the other hand, frequency domain parameters include total power (TP), very low frequency (VLF), low frequency (LF), high frequency (HF), normalized low frequency (LF Norm), normalized high frequency (HF Norm) and LF/HF ratio.

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SDNN reflects all cyclic components of the variability in recorded series of RR intervals.[1-3] RMSSD is an estimate of high-frequency variations in short-term RR recordings and therefore reflects parasympathetic regulation of the heart.[1-3] TP reflects overall autonomic activity. The physiological explanation of the VLF component is less defined.[4] The LF power is modulated by both sympathetic and parasympathetic outflows as well as by other factors, including baroreceptor activity.[4,5]

The advantage of the normalized low frequency (LF Norm) and the normalized high frequency (HF Norm) is that they minimize the effect of changes in very low frequency power and emphasizes changes in sympathetic and parasympathetic regulation respectively.[2] LF Norm is the ratio between absolute value of the low frequency and difference between total power and very low frequency. HF Norm is the ratio between absolute value of the high frequency and difference between total power and very

low frequency.[2] LF/HF ratio signifies the overall balance between sympathetic and parasympathetic systems.[1-3]

Although enhanced cholinergic activity of asthmatics has been established at least four decades ago,[6,7] little HRV studies were done on asthma patients.[8-11] Moreover, the results of these studies are not reproducible, probably due to inter-individual differences of autonomic balance in test groups or inadequacy of methods.

Almost all previous researches on HRV of asthmatics considered asthma severity at the time of the studies without special concern for the disease control. Moreover, all these studies were based on 24-hour HRV recordings. Although long-term HRV looks more attractive, it may be less effective in determining the relation between autonomic modulations and asthma activity. This is because asthma activity is extremely labile and can change throughout the day.[12,13] Other determinants of heart rhythm are similarly not constant during the day, e.g., respiratory rate[14] and blood pressures.[15-17] Therefore, it seems more logical to study short-term HRV under similar conditions where these parameters are less likely to change significantly. Several studies confirm that short-term correlate very well with long-term HRV.[18] Desok *et al*. demonstrate that fifteen to thirty second heartbeat measurements were long enough to produce reliable long-term patterns of HRV features. Thus, short and intermittent recordings of heartbeats could be used to detect long-term HRV patterns.[19] This is especially true for power spectral measures of RR variability calculated from short (2 to 15 minutes) ECG recordings.[20] Another advantage of short-term HRV is that it is more practical and less expensive when needed for the purpose of follow-up in outpatient clinics.

This study aims to evaluate the pattern of autonomic modulations in asthmatic patients based on short-term HRV studies. The present study has considered asthma activity over the last month prior to patients' evaluations using internationally valid and reliable test, namely Asthma Control Test (ACT).[21-23] The relation between autonomic modulation and the duration of bronchial asthma was also appraised.

MATERIALS AND METHODS

The study involved one hundred patients with past medical history of bronchial asthma (at least for two years) selected from chest clinics of teaching hospitals in Khartoum state – Sudan. Patients with past medical history suggestive of other chronic respiratory diseases, diabetes mellitus, hypertension, heart diseases or any illness that may alter heart rate were excluded from the study. The ages range between 20-40 years.

Volunteers arrived at the physiology laboratory between 09.00 and 12.00 am. Asthma history and drug therapy was recorded to assess asthma activity at the time of examination as well as over the last month prior to patients' evaluation using asthma control test (ACT).[24,25] The ACT is a 5-item patient-administered survey for assessing asthma control. Each of the five questions is given a score from 1 to 5. Responses from the ACT are summated to yield a score that ranges from 5 (no control) to 25 (complete control).[22] A score of 20 or higher was used as discriminating cut-off to define totally from poorly controlled patients while a score of 15 or lower was used as discriminating cut-off to define asthma that was not controlled at all.[21-25] Allflow Spirometer (Version 5.18 - Clement Clarke International Limited – U. K) was used for assessing pulmonary function according to ATS/ERS[26] standards. Biocom 3000 ECG recorder (Heart Rhythm Scanner - Version 2.0 - Biocom Technologies – U.S.A) was used for studying HRV.

Statistical evaluation was performed using the Microsoft Office Excel (Microsoft Office Excel for Windows; 2003) and SPSS (version 19). Screening studied variables for significant correlation between measurements of asthma severity and HRV indices were performed using bivariate correlation. In physiological studies comparing HRV in different well-defined groups, the differences between underlying heart rate should also be properly noted.[2] Therefore, heart rate (MHR) was introduced as a covariate in the statistical analysis of HRV using partial correlations. $P < 0.05$ was considered significant.

RESULTS

According to ACT, seventeen subjects (17%) of the studied patient were suffering from well controlled asthma, twenty-seven (27%) were poorly controlled, and fifty-six (56%) were uncontrolled. The means (M) and standard deviations (SD) of age and other physical characteristics of studied asthmatic patients are summarized in Table 1. Table 2 demonstrates the M ± SD of the time and the frequency domains HRV indices of studied asthmatic patients when classified according to ACT. Figures 1 and 2 compare LF Norm, HF Norm, and LF/HF between different classes of asthma patients. The significances of the correlations between ACT state and HRV indices are given in Table 3.

Following adjustment for MHR and anti-asthma medications, ACT score correlates positively with both LF Norm (CC = 0.302, $P = 0.002$) and LF/HF (CC = 0.212, $P = 0.036$) and negatively with HF Norm (CC = -0.317, $P = 0.001$).

Table 1: Characteristics of studied asthmatic patients

	M ± SD
Age (Years)	29.5 ± 5.3
Asthma Duration (Years)	11.6 ± 8.7
Body Mass Index (Kg/m^2)	24.2 ± 5.3
Mean Arterial Blood Pressure (mmHg)	92.1 ± 10.0
Random Blood glucose Concentration (mg/dl)	102.8 ± 10.9
FEV_1 (L)	2.3 ± 0.8
FVC (L)	3.2 ± 1.0
FEV_1%	71.7 ± 14.3
PEFR (L/sec)	4.9 ± 1.9

All studied asthma classes, namely well controlled, poorly controlled, and uncontrolled asthmatic patients, had long-standing history of asthma (M ± SD = 17.88 ± 10.55, 8.93 ± 6.97 and 10.93 ± 8.14 years, respectively). However, asthma duration was significantly higher in well controlled compared with both poorly controlled and uncontrolled asthmatic patients ($P = 0.000$ for both). Duration of asthma correlates positively with HF Norm (CC = 0.235, $P = 0.020$) and negatively with LF Norm (CC= -0.250, $P = 0.013$). High FEV_1 is associated with higher HF component of the power spectral density (CC = 0.200, $P = 0.049$). High FVC is associated with improved HRV as indicated by SDNN (CC = 0.275, $P = 0.006$), RMSSD (CC = 0.294, $P = 0.003$), TP (CC = 0.271, $P = 0.007$), LF (CC = 0.248, $P = 0.014$), and HF (CC = 0.271, $P = 0.07$). Neither FEV_1% nor PEFR show significant correlations with HRV indices.

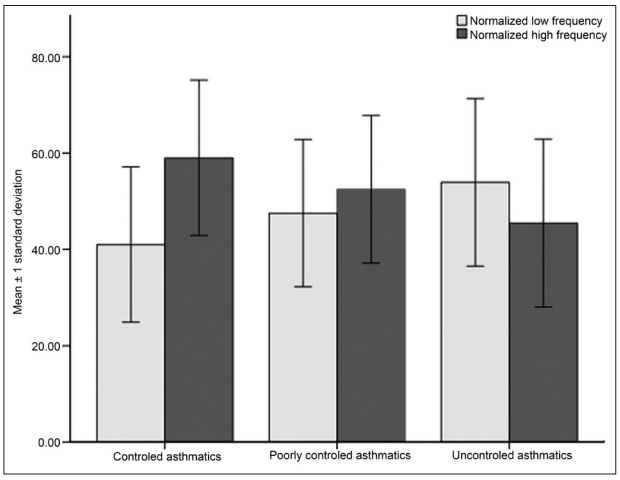

Figure 1: LF Norm and HF Norm of studied asthmatic patients

DISCUSSION

It is evident from the results that higher level of asthma control is associated with improved sympathetic (LF Norm and LF/HF) and depressed parasympathetic (HF Norm) modulations. Moreover, asthmatic patients with better ventilatory functions have the benefit of enhanced HRV as indicated by the significant positive correlations between FVC and SDNN, RMSSD, TP, LF, HF. These results are comparable with the earlier HRV researches in asthmatic patients, although previous studies were mostly in children and based on smaller sample size.[8-11] Almost

Table 2: M ± SD of HRV indices in studied asthmatic patients

	Controlled Asthmatic Patients ($N = 17$) (M ± SD)	Poorly Controlled Asthmatic Patients ($N = 27$) (M ± SD)	Uncontrolled Asthmatic Patients ($N = 56$) (M ± SD)
MHR	91.4 ± 10.9	88.1 ± 10.0	88.6 ± 11.8
SDNN	110.2 ± 68.9	121.2 ± 79.4	88.7 ± 75.9
RMSSD	128.5 ± 98.0	133.2 ± 97.6	92.6 ± 89.4
TP	3148.2 ± 3494. 7	4316.4 ± 5330.8	2171.0 ± 3392.0
VLF	491.3 ± 378.4	729.8 ± 938.3	681.3 ± 1397.7
LF	921.5 ± 1110.6	1408.6 ± 1730.1	633.9 ± 959.4
HF	1676.6 ± 2118.9	2178.0 ± 2861.9	856.4 ± 1496.0
LF Norm	41.0 ± 16.1	47.5 ± 15.3	53.9 ± 17.4
HF Norm	59.0 ± 16.1	52.5 ± 15.3	45.5 ± 17.4
LF/HF	0.9 ± 1.1	1.2 ± 1.2	2.0 ± 2.7

CC: Correlation coefficient, P = Significance

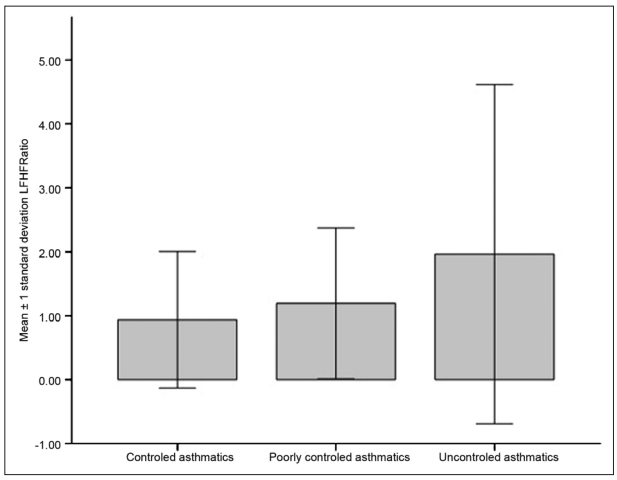

Figure 2: LF/HF Norm of studied asthmatic patients

Table 3: The correlations between ACT state and HRV indices

	Correlations between ACT state and HRV parameters		Correlations between ACT state and HRV parameters following adjustment for MHR		Correlations between ACT state and HRV parameters following adjustment for MHR and anti-asthma medications	
	CC	P	CC	P	CC	P
MHR	-0.074	0.467			0.098	0.335
SDNN	-0.147	0.143	-0.141	0.164	-0.141	0.167
RMSSD	-0.179	0.075	-0.169	0.095	-0.165	0.104
TP	-0.148	0.142	-0.138	0.172	-0.136	0.181
VLF	0.045	0.654	0.047	0.643	0.040	0.699
LF	-0.156	0.121	-0.147	0.147	-0.143	0.160
HF	-0.208	0.037*	-0.198	0.050	-0.193	0.057
LF Norm	0.286	0.004*	0.294	0.003*	0.302	0.002*
HF Norm	-0.301	0.002*	-0.311	0.002*	-0.317	0.001*
LF/HF	0.199	0.048*	0.206	0.041*	0.212	0.036*

all previous studies were designed to compare healthy controls with different classes of asthma severity and none of them was able to demonstrate significant correlations between parameters of asthma severity and HRV indices. For example, Garrard *et al*. evaluated ten healthy controls, nine asymptomatic, untreated asthmatic subjects, and ten asthmatic patients during treatment for acute asthma, by measurement of the variation in resting heart rate using frequency spectrum analysis.[9] Spectral density of the beat-to-beat heart rate was measured with the LF and HF. Sympathetically mediated heart rate variability (LF Norm) was significantly lower in both asymptomatic and acute asthma subjects compared to the controls. However, the study failed to prove dominance of parasympathetic modulations (HF Norm) in asthmatic groups. 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.[8]

Kazuma *et al*. analyzed the 24-hour HRV in asthmatic children (ages 5-15 years). These subjects were divided into groups according to the severity of their asthma.[10] The autonomic nervous function (ANF) of asthma subjects was lower in comparison to the normal group. SDNN, LF, and HF were lowest in the severe asthma group. One year later, Kazuma and his group examined the circadian rhythm of parasympathetic nervous function in asthmatic children.[11] Circadian rhythm disappeared in 11.25% of asthmatic children and was observed in all the individuals in the healthy children. Moreover, the parasympathetic nervous function was low during periods of remission.

The current results also showed that asthma duration correlates positively with HF Norm and negatively with LF Norm. One major difference between mild and severe asthma is the duration of contact of small airways to inflammatory mediators.[27] This is especially true if one consider inadequate clearance of inflammatory mediators secondary to arterial luminal narrowing observed in bronchial circulation of uncontrolled/persistent asthma patients.[28] The attenuated sympathetic activity (as indicated by LF Norm) in those with longer asthma duration offers a good choice for vasodilatation of the already narrowed blood vessels by the effect of remodeling and hence better washout of the inflammatory mediators. However, this hypothesis remains to be investigated by further study. Alternatively, the enhanced parasympathetic activity (as indicated by HF Norm) in those with longer asthma duration will further aggravate bronchoconstriction and worsen asthma symptoms.

The current results also showed that all studied asthma classes, namely well controlled, poorly controlled, and uncontrolled asthmatic patients, had long-standing history of asthma. However, asthma duration was significantly higher in well controlled compared with both poorly controlled and uncontrolled asthmatic patients. Although asthma duration was significantly higher in well controlled compared with both poorly controlled and uncontrolled asthmatic patients, it seems that there was enough time for inflammatory mediators to act in both controlled and uncontrolled asthmatic patients (M ± SD of asthma duration = 17.88 ± 10.55 and 10.93 ± 8.14 year, respectively). Moreover, longer asthma duration in well controlled patients could be explained by the fact that asthmatics with longer history of the disease became more knowledgeable in dealing with asthma, e.g., avoidance of triggers, compliance with treatment protocols, and therefore, release of less quantity of inflammatory mediators.

CONCLUSION

In conclusion, previous studies examining the pattern of autonomic modulations in asthmatic patients report mixed findings possibly due to inadequacy of methods. In the present study, all diseases that may affect HRV were excluded in studied subjects; statistical analysis has considered variations due the differences in MHR and anti-asthma medications among asthmatic patients; and HRV was studied over a short duration to safeguard against the labile activity of asthma. All these considerations make the effects of possible confounding factors on autonomic modulation unlikely in this study. Results were interesting and revealed that poor asthma control is associated with depressed sympathetic and enhanced parasympathetic modulations especially in those with longer asthma duration. Moreover, asthmatic patients with better ventilatory functions have the benefit of better HRV.

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Announcement

Respiratory Update, Goa 2012

Baroda Chest Group under the aegis of the Western chapter Indian Chest Society is organizing a respiratory update at the Radisson Blu Hotel, Cavelossim, Goa from 27-29 July 2012. The faculty includes Dr. Ron duBois, Dr. Luke Howard, Prof. Henry Tezalaar, Dr. A. A. Mahashur, Dr. Zarir Udwadia, Prof. Dheeraj Gupta, Prof. D. J. Christopher, Prof. G. C. Khilnani, Dr. Raja Bose, Dr. Ravindra Mehta and others.

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