Original Article

Alteration of autonomic function is associated with disease severity in patients with bronchial asthma

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Abstract

Background and Aim: Abnormality in the autonomic regulation of the airway results in airway obstruction in bronchial asthma. However, autonomic abnormality in asthmatic patients is generalized and is not confined to airway only. Therefore, the present study was conducted to assess the abnormality of autonomic nervous system (ANS) and its association with disease severity in bronchial asthma patients.

Methods: Sixty patients of bronchial asthma aged between 15 and 50 years were included in the study. After taking informed consent, the duration of asthma was noted in each of these patients and six noninvasive ANS testing namely deep breathing test, orthostatic test, 30:15 ratio, sustained hand grip test, valsalva manoeuvre and cold pressure test was performed.

Results: The study population consisted of 60 bronchial asthma patients (34 males and 26 females) and 60 controls (32 males and 28 females). It was found that out of 60 patients, 46 patients had abnormal autonomic function test values ($P < 0.001$). Patients who depicted more than one abnormal autonomic function test, had bronchial asthma for more than 5 years. Similarly, 32 patients having severe asthma and 28 patients having moderate asthma showed evidence of autonomic dysfunction ($P < 0.001$). About 48% patients had only parasympathetic dysfunction.

Conclusion: Bronchial asthma patients displayed definitive dysfunction of ANS as compared with age and sex-matched controls. With severity and chronicity of asthma, the autonomic function was proportionately attenuated. Parasympathetic overactivity appears to be closely linked to the severity of bronchial asthma.

Key words: Autonomic dysfunction, autonomic function test, bronchial asthma

Received: 8th June, 2015; *Revised:* 24th June, 2015; *Accepted:* 29th June, 2015

INTRODUCTION

The autonomic nervous system (ANS) controls several aspect of airway function.[1] Any abnormality in the autonomic regulation of the airways may lead to bronchospasm, airway edema, and excessive mucous secretion, which are involved in the pathogenesis of airway obstruction in bronchial asthma.[2,3] Autonomic abnormality in asthmatic patients is however, generalized and is not confined to airway only. Altered cardiovascular and respiratory responses reflecting autonomic abnormality is due to the common central origin of cardiovascular and respiratory autonomic efferent fibers.[4]

Access this article online	
Quick Response Code:	Website: www.ijcep.org
	DOI: 10.4103/2348-8093.161535

This system comprises different type of afferent and efferent pathways mediated through cholinergic, adrenergic and nonadrenergic noncholinergic (NANC) mechanisms which may be excitatory, that is, broncho-constricting (e-NANC) or inhibitory, that is, broncho-dialating (i-NANC). Airway inflammation associated with asthma may affect neuronal activity at several points along the neural reflex pathway, including the functions of the primary afferent (sensory) nerves, integration within the central nervous system, synaptic transmission within autonomic ganglia, and transmission at the level of the postganglionic neuroeffector junction.[5] The cholinergic nervous system is more important in the regulation of airway tone as it has direct innervations of airway smooth muscle while

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adrenergic system is important in regulation of airway blood flow and glandular secretion, but it does not innervate airway smooth muscle. It may be that the i-NANC is the only neural bronchodilatory pathway present in human airways.[6-9] However, β2-adrenergic receptors are abundantly expressed on human airway smooth muscle. Activation of these receptors causes bronchodilation.[10]

Evaluation of autonomic function in asthmatics is performed using different invasive and noninvasive, safe and easily reproducible cardiovascular autonomic reflex function tests. Enhanced parasympathetic activity is considered as an important factor in the pathogenesis of bronchial hyperactivity.[11] In the present study, we have tried to explore and validate the status of sympathetic and parasympathetic division of ANS by using invasive and noninvasive tests, and to assess its association with the disease severity in asthmatic patients.

MATERIALS AND METHODS

The study was conducted in the department of Physiology during the period January 2014 to March 2014. Sixty asthmatic patients and 60 nonallergic healthy volunteers were studied. Ethical clearance was obtained from Institutional Ethical Committee. Written informed consent was taken from all the subjects after explaining them in details about the study. All the patients had history and clinical features of bronchial asthma as defined by the American Thoracic Society.[12] The severity of bronchial asthma was defined on the basis of symptoms, number of hospitalization, number of exacerbation, daily use of B2 agonists, peak expiratory flow (PEF) variability and best PEF.[12] The following criteria were followed while selecting the patients: Duration of asthma for more than 5 years, with at least two asthmatic exacerbations in any year; patient's age between 15 and 50 years; should not be on medications that may alter their heart rate (HR) or blood pressure. Those subjects who had an asthmatic attack within 2 weeks of the study were also excluded. Asthmatic drugs that are known to affect the autonomic function was discontinued. Oral theophylline and oral β2-adrenergic agents were with held for at least 72 h; inhaled short-acting β-agonists and ipratropium bromide were stopped for at least 8 h prior to the study. Subject with a history of scleroderma, diabetes, ischemic heart disease, cardiac arrhythmia, hypertension, chronic bronchitis, central or peripheral nervous system disease or any other disease that is known to produce autonomic neuropathy were excluded. The following manoeuvres and recording or responses were carried out in asthmatic patients and control subjects.

Tests evaluating parasympathetic division

- Deep breathing test: The respiratory sinus arrhythmia was recorded as a mean variation in HR in beats per minute (bpm) during deep breathing at the rate of six breaths per minute[13]
- Valsalva manoeuvre: The HR response to valsalva manoeuvre was recorded as the difference between maximum and minimum HRs during and after the standard valsalva manoeuvre in bpm[14]
- 30:15 ratio: Immediate HR response to standing was expressed as the maximum rise in HR over the basal rate in bpm.[15,16]

$$30:15 \text{ ratio} = \frac{\text{R – R interval between } 15^{th} \text{ and } 16^{th} \text{ beat}}{\text{R – R interval between } 30^{th} \text{ and } 31^{st} \text{ beat}}$$

Tests evaluating sympathetic division

- Orthostatic test: The blood pressure response to standing was taken as a fall in systolic pressure within 1 min of standing[17]
- Sustained hand grip (SHG) test: The blood pressure response to SHG was taken as the rise in diastolic pressure on 2 min sustained handgrip at one-third of maximal voluntary contraction[18]
- Cold pressure test (CPT): The blood pressure response to CPT was taken as the increase in diastolic blood pressure (DBP) on immersing a hand in ice water (1–4°C) up to wrist for at least 1 min.[19]

Tests were performed after an overnight fast. Calm and relaxed environment was provided while carrying out the manoeuvres. Subjects were connected to electrocardiography (ECG) machine for HR and ECG recording. Blood pressure was recorded by sphygmomanometer with a standard cuff at a set interval. After resting period of at least 30 min, autonomic function tests were performed.

Statistical analysis of data

Data were presented as mean ± standard deviation and were statistically analyzed using unpaired *t*-test and Chi-square test. A P value < 0.05 was considered to be significant. SPSS 16 (SPSS Software Inc. Chicago, USA) statistical software was used for statistical analysis of data.

RESULTS

The mean age of asthmatic patients was 41.44 ± 6.71 years and that of control subjects was 41.42 ± 7.20 years. The male and female ratio in asthmatics was 1.17:1 while in control it was 1.08:1. Baseline cardiovascular parameters in control, as well as in asthmatics are depicted in Table 1. HR was significantly higher in asthmatics as compared with controls.

Results of different autonomic function tests for sympathetic and parasympathetic division are depicted in

Table 2. The parasympathetic test results, which showed significant difference between the control and asthmatic subjects were respiratory sinus arrhythmia ($P < 0.001$); valsalva response ($P < 0.001$) and immediate HR response to standing ($P < 0.001$) [Table 2]. On comparing the sympathetic function test results, all the three tests showed a significant difference between asthmatic and control subjects. The rise in DBP at 2 min after SHG test and with CPT after 1 min in asthmatic was significantly lower as compared with controls ($P < 0.001$). Fall in systolic blood pressure (SBP) on standing from a supine position (after 1 min) was significantly higher in asthmatic subjects as compared with controls ($P < 0.05$).

To represent the clinical severity of bronchial asthma in the study population ($n = 60$) the subject were divided in two groups, group 1 mild to moderate asthma ($n = 28$) and group 2 severe asthma ($n = 32$) based on defined criteria. Of these 32 patients, classified as severe, only 8 had a normal autonomic function, and the remaining 24 had autonomic dysfunction. Of 28 patients classified as mild to moderate asthma, only 14 had evidence of autonomic dysfunction ($P < 0.01$) [Table 3]. Analyzing the association between severity of bronchial asthma and parameters of autonomic function as independent variables, the odds ratio (with 95% confidence interval) was found to be >1.0 with $P < 0.05$ in all parameters [Table 4].

Further on comparing duration of asthma and number of patients with abnormal autonomic function. Twelve patients had duration of asthma <5 years, out of which 3 patients had an abnormal test, the remaining 11 had normal tests. Whereas, 46 patients had bronchial asthma for more than 5 years, out of these 36 had abnormal tests, and 10 patients had a normal test ($P < 0.001$).

Table 1: General characteristics of study subjects

Parameters	Control (*n*=60)	Asthmatic (*n*=60)	*P*
Age (years)	41.44±6.71	41.42±7.20	0.0967
HR (bpm)	72.60±7.01	82.28±9.27	0.0152*
SBP (mm Hg)	118.27±7.16	122.34±9.11	0.0682
DBP (mm Hg)	72.9±7.01	76.01±7.96	0.0984

Values expressed as mean±SD. *P<0.05 was considered statistically significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SD: Standard deviation, bpm: Beats per minute, mm Hg: Millimeter of mercury

DISCUSSION

The role of sympathetic and parasympathetic system in regulation of airway smooth muscle in asthmatics is crucial.[1] Bronchial hyperactivity occurring in asthma apart from hyperplasia of smooth muscle may be due to abnormalities of ANS – sympathetic and parasympathetic division.[20] Our findings are inagreement with Garrard *et al*.[21] and in contrast to Nordin and Fagius[22] who found an alteration in the resting HR towards tachycardia in asthmatics in the preview of vagal hypertonia. These data suggest that variation in HR at rest are mediated by the combined effect of cardiac, vagal and sympathetic nerves acting on the sinoatrial node.[23] The mean basal SBP and DBP were not significantly higher in asthmatics as compared to controls. This may be due to α-adrenergic hyperresponsiveness

Table 2: Comparision of autonomic function tests for sympathetic and parasympathetic divisions between control and asthmatic patients

Parameters	Control (*n*=60)	Asthmatic (*n*=60)	*P*
Mean variation in HR in deep breathing test (bpm)	18.2±2.98	8.01±4.1	0.0002*
Valsalva ratio (valsalva maneuver)	1.06±0.05	1.66±0.16	0.0022*
Immediate HR response to standing (30:15 ratio)	1.08±0.05	1.05±0.28	0.0152*
Fall in SBP on standing (mm Hg) (after 1 min) (orthostatic test)	05.88±2.72	16.24±9.25	0.0002*
Rise in DBP on sustained hand grip (mm Hg) test (after 2 min)	18.29±2.90	12.28±3.487	0.0044*
Rise in DBP with cold pressor test (mm Hg) (after 1 min)	14.56±3.60	10.67±3.90	0.0063*

Values expressed as mean±SD. *P<0.05 was considered statistically significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SD: Standard deviation, bpm: Beats per minute, mm Hg: Millimeter of mercury

Table 3: Comparision of asthma severity in group 1 and group 2 with autonomic dysfunction in patients with bronchial asthma

Parameters	Group 1 mild to moderate (*n*=28)	Group 2 severe asthma (*n*=32)	*P*
Mean variation in HR in deep breathing test (bpm)	8.95±4.0	12.84±5.1	0.002*
Valsalva ratio (valsalva maneuver)	1.51±0.012	1.98±0.18	0.016*
Immediate HR response to standing (30:15 ratio)	0.98±0.18	1.65±0.28	0.001*
Fall in SBP on standing (mm Hg) (after 1 min) (orthostatic test)	12.18±4.3	18.78±8.2	0.002*
Rise in DBP on sustained hand grip (mm Hg) test (after 2 min)	14.34±3.84	9.77±2.84	0.009*
Rise in DBP with cold pressor test (mm Hg) (after 1 min)	12.25±2.61	8.76±2.98	0.008*

Values expressed as mean±SD. *P<0.05 was considered statistically significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SD: Standard deviation, bpm: Beats per minute, mm Hg: Millimeter of mercury

Table 4: Bivariate regression of autonomic dysfunction with disease severity status in patients with bronchial asthma

Parameters	Severity status (*n*=60)	
	OR (95% CI)	*P*
Mean variation in HR in deep breathing test (bpm)	1.89 (1.680-2.100)	0.001**
Valsalva ratio (valsalva maneuver)	1.63 (1.460-1.810)	0.004**
Immediate HR response to standing (30:15 ratio)	2.03 (1.801-2.260)	0.001**
Fall in SBP on standing (mm Hg) (after 1 min) (orthostatic test)	1.42 (1.275-1.565)	0.002**
Rise in DBP on sustained hand grip (mm Hg) test (after 2 min)	1.80 (1.605-2.050)	0.001**
Rise in DBP with cold pressor test (mm Hg) (after 1 min)	1.74 (1.501-1.916)	0.001**

**P<0.01 was considered statistically significant. Statistical analysis was done by either Pearson correlation. OR: Odds ratio, CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, bpm: Beats per minute, mm Hg: Millimeter of mercury

in asthmatics.[24] The R-R interval variation during deep breathing is under vagal control (efferent)[25] and the abnormality could be due to impaired afferent, central or efferent vagal mechanism.[23] Therefore, lower HR variation to deep breathing in our study reflects parasympathetic hyperactivity in asthmatics. We observed significantly ($P < 0.05$) lower value for HR response to valsalva manoeuvre in asthmatics when compared to controls. This finding was similar to the study of Prabhat *et al*.[26] However, some authors[27] reported higher values of HR response to valsalva manoeuvre in asthmatics. Hence, it can be suggested that valsalva manoeuvre is a reflection of both sympathetic and parasympathetic activity and significant variation in the HR in asthmatic could be due to parasympathetic hyperactivity. 30:15 ratio (immediate HR response to standing) was significantly lower in asthmatics in comparison with controls. Our findings are inconcordance with Kallenbach *et al*.[28] Ewing *et al*.[29] showed that the initial HR response to standing is under vagal control, with an immediate vagal withdrawl, which increases the HR over first 10–15 beats. This is followed by a vagal reactivation that slows the heart and gives a characteristic bradycardia. The 30:15 ratio, thus, represents parasympathetic vagal control and, therefore, showed a significant change in asthmatics.

In asthmatics, the rise in DBP was significantly lower as compared to controls with SHG test. A CPT and fall in SBP was found to be significant ($P < 0.05$) with supine to standing test (orthostatic test), all these may be due to sympathetic dysfunction.

Kumar *et al*.[30] observed the significant rise and Prabhat *et al*.[26] reported a nonsignificant rise in DBP with SHG test, CPT and supine to standing the test as compared to controls. They attributed this rise to increased adrenergic drive (sympathetic hyperactivity) in asthmatics to combat parasympathetic hyperactivity.

Severity and chronicity of any disease has its own effects on the morbidity pattern and outcome of the disease. Hence in our study, comparing the severity of bronchial asthma with autonomic parameters, significant autonomic dysfunction was observed in severe asthmatics as compared to milder ones, and it was more in parasympathetic indices. On bivariate analysis, it was observed that there is a significant association between autonomic dysfunction and severity of bronchial asthma. Furthermore, patients with duration of asthma for more than 5 years had significant autonomic dysfunction. These findings show that both severity and duration of asthma have effect on the autonomic functions of patients.

Limitations of the study

Moderate sample size in each group, and the interindividual difference in the autonomic dysfunctions among the study participants are the limitations of the study.

CONCLUSION

It appears from this study that there is good evidence of autonomic dysfunction in asthmatic patients when compared with age-sex matched controls. Though both sympathetic and the parasympathetic nervous systems were found to be affected, parasympathetic division was found to be predominately affected. Parasympathetic overactivity appears to be closely linked to severity of bronchial asthma. Hence, future studies on the role of anticholinergics in the treatment of asthma are vital. Autonomic dysfunction is observed to be increase with chronicity, as well as with the severity of bronchial asthma. Bronchial asthma patients display definitive dysfunction of ANS as compared with age and sex-matched controls. However, further studies with a larger sample size will be necessary to establish whether the association of asthma and autonomic dysfunction has any prognostic implications, and as well as on the morbidity pattern of disease.

ACKNOWLEDGMENTS

We acknowledge Mr. Ravishankar Kannouje who helped in typing the manuscript and preparation of tables. We are also thankful for the patients who had participated in the study.

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How to cite this article: Verma AR, Khodiar PK. Alteration of autonomic function is associated with disease severity in patients with bronchial asthma. Int J Clin Exp Physiol 2015;2:110-4.

Source of Support: Nil, **Conflict of Interest:** Nil.