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Original Article

Autonomic dysfunction in patients with bronchial asthma

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ABSTRACT

Aim: Any abnormality in autonomic regulation of the airways, may lead to bronchospasm, airway edema and excessive mucous secretion, which are the event that take place in pathogenesis of airway obstruction in bronchial asthma. The present study was aimed to explore and validate status of sympathetic and parasympathetic division of autonomic nervous system in asthmatic patients by using battery of simplest and non-invasive tests. Methods: The study involved 100 subjects (age group 30-60 years) out of which 50 were asthmatics and 50 were healthy volunteers. In all the study subjects six different non-invasive,simple,standardized autonomic function tests were done. Result: The values in the tests assessing parasympathetic division were significantly lower in asthmatic patients as compared to control subjects (P<0.001). All the tests assessing sympathetic division also showed significant difference between asthmatic and control subjects. The rise in diastolic blood pressure (DBP) at 2 minute after sustained hand grip test and with cold pressor test after 1 minute in asthmatic was significantly lower as compared to rise in DBP in controls. (P<0.001) whereas the fall in systolic blood pressure (SBP) on standing from supine position (after 1 minute) was significantly higher in asthmatic subjects as compared to controls (P<0.001).Conclusion: The results suggest that there is good evidence about autonomic dysfunction in asthmatic patients. Though, both sympathetic and parasympathetic nervous system was found to be affected, more affection was of parasympathetic division.

1. Introduction

The autonomic nervous system controls several aspect of airway function [1]. Any abnormality in autonomic regulation of the airways, therefore, may lead to bronchospasm, airway edema and excessive mucous secretion, which are the event that take place in 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 common central origin of cardiovascular and respiratory autonomic efferent fibers [4]. Therefore to evaluate autonomic functions in asthmatics, different non-invasive, safe and easily reproducible cardiovascular autonomic reflex function tests are used. Enhanced parasympathetic activity is considered as an important factor in pathogenesis of bronchial hyperactivity [5]. This hyperactivity is generally co-existent with airway inflammation and is associated with altered sensory neuronal activity [6]. β-adrenoceptor blockade in asthmatics, develops severe broncho-constriction ,whereas in normal people no significant effect on airway caliber was observed [7, 8]. The mechanism underlying β-adrenoceptor blockade induced bronchoconstriction in asthmatics has not been identified yet. Despite the widespread measurement of circulating plasma concentration under various conditions, the role and importance of adrenaline in control of airway caliber in asthma remains uncertain [9-10]. Previous studies have also reported insignificant sympathetic hyperactivity in asthmatics to combat bronchoconstriction [8, 11]. In present study we have tried to explore and validate status of sympathetic and parasympathetic division of autonomic nervous system in asthmatic patients by using battery of simplest and non-invasive tests.

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2. Materials and Methods

The study involved 100 subjects (age group 30-60 years) out of which 50 were asthmatics and 50 were healthy volunteers after their written informed consent was obtained. All the patients had history and clinical feature of bronchial asthma as defined by American thoracic Society [12]. The criteria followed while selecting the patient were: duration of asthma more than 2 years, with at least two asthmatic exacerbations in any year; patient's age between 30-60 years; should not be taking any drug which is known to cause alteration in blood pressure and heart rate. Subjects with a history of diabetes, scleroderma, ischemic heart disease, cardiac arrhythmia, hypertension, chronic bronchitis, central or peripheral nervous system disorders, alcoholics, smokers, those practicing yoga or other physical training or any other disease that is known to produce autonomic neuropathy were excluded. Those subjects were also excluded who had an asthmatic attack within two weeks of the study. The autonomic function tests included three tests evaluating the para-sympathetic division and three tests evaluating the sympathetic division. All the tests were non-invasive,simple,standardized and widely used. All the subjects were made familiar with all maneuvers by prior trials.

2.1.Tests evaluating parasympathetic division:

1) The respiratory sinus arrhythmia was recorded as a mean variation in heart rate in beats per minute (bpm) during deep breathing at the rate of six breaths per minute [13].
2) The heart rate response to valsalva maneuver was recorded as the difference between maximum and minimum heart rates during and after the standard valsalva maneuver in bpm[14].
3) Immediate heart rate response to standing was expressed as the maximum rise in heart rate over the basal rate in bpm[15].

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

2.2.Tests evaluating sympathetic division:

1) The blood pressure response to standing was taken as a fall in systolic pressure within 1 minute of standing [17].

2) The blood pressure response to sustained hand grip was taken as the rise in diastolic pressure on 2 minute sustained handgrip at one third of maximal voluntary contraction [18].

3) The blood pressure response to cold pressor test was taken as the increase in diastolic blood pressure on immersing a hand in ice water (1-40C) up to wrist for at least one minute [19].

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

2.3.Statistical analysis:

All the values were presented as mean ± SD. The data were statistically analyzed by using unpaired t test and chi-square test. A 'P' value of less than 0.05 was considered to be significant.

3.Results

The mean age of asthmatic patients was 41.44 ± 6.71 years and that of control subjects, 41.42 ± 7.20 years. Age group did not show significant difference between patients and controls. The male and female ratio in asthmatics was 1.17:1 while in control it was 1.08:1.Gender distribution also did not show a significant difference between asthmatics and controls. Baseline cardiovascular parameters in control as well as in asthmatics are shown in table I. Heart rate was significantly higher in asthmatics as compared to controls.

Table 1. General subject's profile

Parameters	Control (n=50)	Asthmatic (n=50)	P-value
Age (years)	41.42 ± 7.20	41.44 ± 6.71	0.99(NS)
Heart rate(bpm)	80.66±7.02	84.98±10.72*	0.019
Systolic blood pressure(mm Hg)	113.88±6.98	116.48±9.22	0.115(NS)
Diastolic blood pressure(mm Hg)	76.9±6.75	78.12±7.15	0.382(NS)

Values expressed as mean ± SD; bpm: beats per minute
*P<0.05

3.1.Autonomic function tests for sympathetic and parasympathetic division

Results of different autonomic function tests for sympathetic and parasympathetic division are shown in table II. 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 heart rate response to standing (P<0.001). The values in these three tests were lower in asthmatic patients as compared to control subjects [Table II]. On comparing the sympathetic function tests results, all the three tests showed significant difference between asthmatic and control subjects. The rise in diastolic blood pressure(DBP) at 2 minute after sustained hand grip test and with cold pressor test after 1 minute in asthmatic was significantly lower as compared to rise in DBP in controls.(P<0.001). Fall in systolic blood pressure (SBP) on standing from supine position (after 1 minute) was significantly higher in asthmatic subjects as compared to controls (P<0.001).

Table 2: Autonomic function tests for sympathetic and parasympathetic division

Parameters	Control (n=50)	Asthmatic (n=50)	P-value
Mean variation in heart rate (HR) in deep breathing test (bpm)	17.7 ± 2.58	8.28±4.90*	< 0.001
Valsalva ratio	1.26±0.05	1.15±0.16*	< 0.001
Immediate HR response to standing (30:15 ratio)	1.09±0.05	1.08±0.28*	< 0.001
Fall in SBP on standing (mm Hg) [after 1 minute]	6.22±3.22	15.84±10.52*	< 0.001
Rise in DBP on sustained hand grip(mm Hg) [after 2 minute]	19.98±3.30	12.48±5.47*	< 0.001
Rise in DBP with cold pressor test (mmHg) [after 1 minute]	15.72±3.30	11.92±4.04*	< 0.001

4.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 autonomic nervous system (ANS) – sympathetic and parasympathetic division [20]. This study was carried out to evaluate the status of ANS in asthmatics. Basal heart rate was found to be significantly higher in asthmatics as compared to controls(P< 0.05).Our findings are coexistent with Garrard CS et al[21] and in contrast to Magnus et al [22] who found an alteration in the resting heart rate towards bradycardia in asthmatics in the preview of vagal hypertonia. These data suggest that variation in heart rate at rest are mediated by combined effect of cardiac, vagal and sympathetic nerves acting on sino-atrial node[23]. The mean basal systolic and diastolic blood pressure was insignificantly higher in asthmatics as compared to controls. This may be due to α adrenergic hyperresponsiveness in asthmatics [24].

In our study, asthmatics showed statistically significant lower heart rate variation to deep breathing test when compared to controls. 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 heart rate variation to deep breathing in our study reflects parasympathetic hyperactivity in asthmatics. We observed significantly (P<0.05) lower value for heart rate response to valsalva maneuver in asthmatics when compared to controls. This finding was similar to the study of Prabhat KD et al [11]. This finding might be due to increased vagal response in asthmatics compared to control subjects. However,some authors[26] reported higher values of heart rate response to valsalva maneuver in asthmatics. So, it can be concluded that valsalva maneuver is a reflection of both sympathetic and parasympathetic activity and significant variation in the heart rate in asthmatic may be due to parasympathetic hyperactivity. 30:15 ratio(immediate heart rate response to standing) was slightly but significantly lower in asthmatics in comparison with controls. Our findings are coexistent with Kallenbach JM et al [27]. DJ Ewing et al [28] showed that the initial heart rate response to standing is under vagal control, with an immediate vagal withdrawl which increases the heart rate 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 significant change in asthmatics.

In our study, in asthmatics the rise in diastolic blood pressure was significantly lower as compared to controls with sustained hand grip (SHG) test an cold pressor test (CPT) whereas fall in systolic blood pressure was found to be statistically significant(P<0.05) with supine to standing test (Orthostatic test). CPT is considered as index of vascular (vasoconstrictor) reactivity which depends on sympathetic outflow and orthostatic hypotension in asthmatics probably indicates damage to baroreflex arc and sympathetic vasoconstrictor fibers. Moreover, significantly lower rise of diastolic blood pressure (DBP) in asthmatics on SHG test suggest sympathetic nervous system affection. So, overall, we observed sympathetic dysfunction in asthmatics. Manoj Kumar et al [29] observed significant rise and Prabhat KD et al [11] reported non-significant rise in DBP with SHG test, CPT and supine to standing test as compared to controls. They attributed this rise to increased adrenergic drive (sympathetic hyperactivity) in asthmatics to combat parasympathetic hyperactivity.

5.Conclusion

It appears from our studies that there is good evidence about autonomic dysfunction in asthmatic patients. Though, both sympathetic and parasympathetic nervous system was found to be affected, more affection was of parasympathetic division. However, longer follow up of asthmatic patients is required for analyzing the true morbidity and mortality of autonomic involvement in asthmatic patients. Therefore further studies will be necessary to establish whether the association of asthma and autonomic dysfunction has any prognostic implications.

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