Original Research Paper

Volume-9 | Issue-8 | August - 2019 | PRINT ISSN No. 2249 - 555X

Physiology

PATTERNS OF CARDIAC AUTONOMIC MODULATIONS IN ASTHMATIC PATIENTS

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ABSTRACT The present study was aimed to explore and validate the status of sympathetic and parasympathetic divisions of autonomic nervous system in asthmatic patients by using battery of simple and non-invasive tests. 80 asthmatic patients and 80 age matched healthy controls were subjected to 6 standardized tests to evaluate their autonomic status. Due care was taken to remove factors which could interfere with results. Tests requiring stimulation of parasympathetic system i.e. deep breathing test, immediate heart rate response to standing, and heart rate response to Valsalva maneuver were significantly lower in asthmatics as compared to controls (p value<0.001). Tests assessing the sympathetic division i.e. postural fall of blood pressure, sustained hand grip test and cold pressor test showed significant difference between asthmatics and controls (p value<0.001). The rise in diastolic blood pressure (DBP) at 2 mins after SHG test and at 1 min after CPT in asthmatics was significantly lower as compared to rise in DBP in controls, whereas, fall in systolic blood pressure (SBP) on standing from supine position (after 1 min) was significantly higher in asthmatics as compared to controls. These results suggest that there is a good evidence of autonomic dysfunction in asthmatics with affection of both sympathetic and parasympathetic nervous system and that the hyperresponsiveness of the parasympathetic system is an important factor in producing bronchial spasm in asthmatic patients.

KEYWORDS : Bronchial asthma, Autonomic nervous system, Autonomic function tests

INTRODUCTION

The autonomic nervous system controls many aspects of airway function[1]. In addition to regulation of airway smooth muscle tone, autonomic nerves may influence mucus secretion from sub mucosal glands, transport of fluid across epithelium, permeability and blood flow in the bronchial circulation and release of mediators from the mast cells and other inflammatory cells[2]. Any abnormality in the autonomic regulation of the airways, hence, may lead to bronchospasm, airway edema, and excessive mucus secretion[3], the events that take place in the pathogenesis of airway obstruction in bronchial asthma[4].

The postulated autonomic abnormality in asthma is an imbalance of autonomic control, with excitatory mechanisms (cholinergic; alpha1-adrenergic or noncholinergic excitatory [substance P]) superimposed upon the inhibitory mechanisms (beta-adrenergic or non-adrenergic inhibitory [vasoactive intestinal peptide] mechanisms). The cholinergic nervous system is more important in the regulation of airway tone as it has direct innervations of airway smooth muscle while adrenergic nervous system is important in regulation of airway blood flow and glandular secretion, but it does not innervate airway smooth muscles. It may be that i-NANC is the only neural bronchodilator pathway present in human airways. However, B2-adrenergic receptors are abundantly expressed on human airway smooth muscle. Activation of these receptors causes bronchodilation.
The autonomic abnormalities in asthmatic patients are generalized and not limited to airways only. The cardiovascular and respiratory autonomic efferent fibers have a common central origin[5], and hence, the altered cardiovascular and respiratory responses may reflect these abnormalities. It has therefore been suggested that there might be an intrinsic relationship between cardiac and bronchial autonomic control, and that this relationship might be altered in asthmatic individuals[6]. However, vagal regulation of resting bronchomotor tone depends on reflexes initiated in irritant airway receptors[7,8], whilst vagal activity to the heart occurs in response to arterial baroreceptors[9,10]. This apparent independence of vagal control suggests that bronchial and cardiac vagal activities would be unrelated. Therefore in the present study, different non-invasive, safe and easily reproducible cardiovascular autonomic reflex function tests were used to explore and validate status of sympathetic and parasympathetic division of autonomic nervous system in asthmatic patients.

SUBJECTS AND METHODS

The study included 80 patients with bronchial asthma and 80 healthy age matched controls after their written consent was obtained. All the patients had history and clinical features of bronchial asthma as defined by the American Thoracic society[11].

The criteria followed while selecting the patient were: Duration of asthma more than 2 years with at least 2 asthmatic exacerbations in any year, patients age between 20-40 years, should not be taking any drug which is known to cause alteration in blood pressure and heart rate for the preceding 2 weeks (except β-agonist aerosols in the event of exacerbation preferably at least 6hrs prior to the test), non-smokers. Patients with concurrent respiratory infections, COPD, bronchitis, history of diabetes, scleroderma, ischemic heart disease, cardiac arrhythmias, hypertension, 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 or alter the heart rate were excluded from the study. The autonomic function tests used were non-invasive, simple, standardized and widely used.

Tests evaluating parasympathetic division:

Heart rate response to deep breathing was recorded as a mean variation in heart rate in beats per minute (bpm) during deep breathing at the rate of 6 breaths/min[12].

Heart rate response to valsalva maneuver was recorded as the difference between maximum and minimum heart rates during and after the standard valsalva maneuvers in bpm[13].

Heart rate response to standing was expressed as the maximum rise in heart rate over the basal rate in bpm[14].

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

Tests evaluating sympathetic division:

Blood pressure response to standing (Orthostatic test) was taken as a fall in systolic BP within 1minute of standing[16].

Blood pressure response to Sustained Hand Grip was taken as rise in the DBP on 2 minutes sustained hand grip at one third of MVC[17].

Blood pressure response to Cold Pressor Test was taken as the rise in DBP on immersing hand in ice water (1-4 ^{0} C) up to wrist for at least 1minute[18].

Tests were done after an overnight fast. Calm and relaxed environment

was provided while carrying out the maneuvers. Patients were made familiar with all the maneuver's by prior trials. Subjects were connected to Medicaid Students Physiopac for heart rate and ECG recording. BP was recorded using sphygmomanometer with a standard cuff at set interval. After a resting period of at least 30 mins, autonomic function tests were performed.

All the values were presented as mean±standard deviation. The data was statistically analyzed using unpaired t test. P value of less than 0.05 was considered to be statistically significant.

RESULTS

The mean age of asthmatic patients was 28.86±5.791 years and that of control subjects, 30.26±5.69 years, thus excluding the variables in autonomic tone occurring with age. Heart rate was significantly higher in asthmatics as compared to controls. The baseline cardiovascular parameters in controls as well as in asthmatics are as given in table1.

Table no 1: Baseline Cardiovascular parameters in Asthmatics and Controls

Parameter	Asthmatics (n=80, 44M/36F)	Controls (n=80, 46M/34F)	P-value
Age	28.86±5.79	30.26±5.69	0.12(NS)
Heart rate(bpm)	82.75±5.44	72.57±3.96	<0.001*
Systolic blood pressure (mmhg)	115.98±3.56	115.28±3.78	0.23(NS)
Diastolic blood pressure (mmhg)	75.45±2.66	74.60±3.71	0.09(NS)

Footnote: *significant; p-value<0.05 is considered significant; NS-not significant; unpaired T-test applied

The results of different Autonomic function test for sympathetic and parasympathetic division are shown in Table II

Table no 2: Autonomic function tests for Parasympathetic and sympathetic division

Parameters	Asthmatics	Controls	P-value
Mean variation in Heart rate (HR) in Deep Breathing Test (DBT) (bpm)	9.47±1.64	17.57±2.22	<0.001*
Valsalva Ratio	1.12±0.025	1.27±0.040	<0.001*
Immediate Heart rate (HR) response to standing (30:15 ratio)	0.78±0.02	0.89±0.01	<0.001*
Decrease in Systolic Blood Pressure (SBP) on standing (mmHg) [after 1 minute]	15.71±2.18	6.08±1.46	<0.001*
Increase in Diastolic BP on Sustained Hand Grip (mmHg) [after 2 minutes]	11.22±2.00	18±2.52	<0.001*
Increase in Diastolic BP on Cold Pressor Test (mmHg) [after 1 minutes]	11.22±2.00	12.62±1.90	<0.001*

Footnote: *significant; p-value<0.05 is considered significant; NS-not significant; unpaired T-test applied

The parasympathetic test results were significantly lower (p value<0.001) in asthmatics as compared to controls. The sympathetic test results showed significant difference between asthmatics and control subjects (p value<0.001). The rise in diastolic blood pressure (DBP) at 2 mins after SHG test and at 1 min after CPT in asthmatics was significantly lower as compared to rise in DBP in controls, whereas, fall in systolic blood pressure (SBP) on standing from supine position (after 1 min) was significantly higher in asthmatics as compared to controls.

DISCUSSION

The study was conducted to evaluate the sympathetic, parasympathetic activity and their interplay in asymptomatic bronchial asthma patients; and to compare it with age matched controls, by measurements of variations in various autonomic function tests. Basal resting HR was found to be significantly higher in asthmatics as compared to controls. The mean basal systolic and diastolic BP was insignificantly higher in asthmatics as compared to controls. This may be due to α-adrenergic hyper-responsiveness in asthmatics[19]. Our findings are consistent with Garrard CS et al.[20] and in contrast to Magnus et al.[21] who found an alteration in the resting HR towards bradycardia in asthmatics in the preview of vagal hypertonia. Seidler et al.[22] also recorded higher resting HR in asthmatic subjects. Variations in HR at rest are mediated by combined effects of cardiac, vagal and sympathetic nerves acting on sino-atrial node, rate of discharge of which is under vagal control. Hence, the possibility exists that an alteration in autonomic control in airway caliber may be reflected by a parallel change in the control of heart rate.

In our study, asthmatics showed statistically significant lower heart rate variation to DBT when compared to controls. Our findings are in contrast to Kallenbach et al.[6] and Shah et al.[23] who found a significantly greater magnitude of respiratory sinus arrhythmia in the asthmatics than in the controls. The R-R interval variation during deep breathing is under vagal control (efferent)[24]. Moreover, several physiologic mechanisms may contribute to respiratory heart rate variations, including reflexes involving pulmonary and atrial stretch receptors and baroreceptors. There may also be direct interaction between the respiratory and cardiovascular centers in the brainstem[25].The degree of contribution of each of these components is related to the frequency and amplitude of the respiratory signal, the mean level of vagal and sympathetic activity, and the mechanical state of the airways, indicating that the respiratory sinus arrhythmia is the quantitative measurement of mean cardiac vagal efferent activity[25].
Mean valsalva ratio in our study showed significantly lower value in asthmatics when compared to controls. Our findings are similar to those of Shah et al.[23] and Samadhan et al.[26]. Valsalva maneuver elicits complex scale of hemodynamic events that results in the activation of sympathetic and parasympathetic neurons. Valsalva ratio reflects parasympathetic activity, whereas alterations in blood pressure are a measure of sympathetic function. Thus, the Valsalva maneuver is reflection of both sympathetic and parasympathetic activity.

Immediate heart rate response to standing was slightly but significantly lower in asthmatics in comparison with controls. Our findings are coexistent with Kallenbach et al.[6] and Samadhan et al.[26]. Changing posture from lying to standing produces an integrated reflex response of the cardiovascular system, which includes alterations in heart rate and blood pressure. DJ Ewing et al.[14] showed that the initial heart rate response to standing is under vagal control, with an immediate vagal withdrawal 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 increase in diastolic blood pressure was significantly lower as compared to controls with Sustained hand grip (SHG) test and Cold pressor test (CPT), whereas decrease in systolic blood pressure was found to be statistically significant with supine to standing test (Orthostatic test). Manoj Kumar et al.[27] observed significant rise and Shah PKD et al.[23] 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. Samadhan et al.[26] observed a significantly lower rise in diastolic blood pressure in asthmatics as compared to controls with sustained hand grip (SHG) test and cold pressor test (CPT) whereas a significant fall in systolic blood pressure with supine to standing test (Orthostatic test). It is necessary here to be cautious in interpreting the results of these tests, as they demonstrate the function of sympathetic efferent's on the vessels. Thus, it cannot be directly equated with bronchial hyper-reactivity, as the airway α and β-receptor stimulation is under the influence of circulating adrenaline and nor-adrenaline. Direct sympathetic innervation of human airways smooth muscle is negligible. CPT is considered as index of vascular (vasoconstrictor) reactivity which depends on sympathetic outflow. Orthostatic hypotension in asthmatics probably indicates damage to baroreflex arc and sympathetic vasoconstrictor fibers. Moreover, significantly lower increase in diastolic blood pressure (DBP) in asthmatics on SHG test suggest sympathetic nervous system affection. So, overall, sympathetic dysfunction in asthmatics was observed in our study.

CONCLUSIONS

The present study delineated a raised central parasympathetic outflow

and a concomitant low central sympathetic outflow in asthmatic subjects as compared to that observed in the control group. This deranged sympatho-vagal interplay with vagal dominance at the expense of a decreased sympathetic outflow could be a plausible pathophysiologic mechanism leading to airway obstruction, the hallmark of Bronchial Asthma.

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.

REFERENCES:

[1] Nadel JA, Barnes PJ. Autonomic regulation of the airways. Ann Re v Med 1984; 35:451-67

[2] Hira HS, Kulpate DDS. Autonomic innervation of human airways: its clinical significance. J Asso Phy Ind 1988 ; 36:216-18

[3] Ingram Jr RH . Site and mechanism of obstruction and hyper responsiveness in asthma. Am Rev Respir Dis 1987; 136:562-64

[4] Kaliner M, Shelhamer J, Davis PB, Smith LJ, Venter JC. Autonomic nervous system abnormalities and allergy. Ann Intern Med 1982; 96:349-57

[5] Richardson JB. Nerve supply to the lungs. Am Rev Respir Dis 1979; 119 :785-802

[6] Kallenbach JM, Webster T, Dowdeswell R, Reinach SG, Scott Milar RN, Zwi S. Reflex heart rate control in asthma: evidence of parasympathetic overactivity. Chest 1985;87(5):644–8.

[7] Jammes Y, Mei N. Assessment of the pulmonary origin of bronchoconstrictor vagal tone. J Physiol 1979;291:305–16.

[8] Nadel JA, Widdicombe JG. Reflex effects of upper airway irritation on total lung resistance and blood pressure. J Appl Physiol 1962;17:861–5.

[9] Spyer KM. Central nervous integration of cardiovascular control. J Exp Biol 1982;100:109–28.

[10] Kollai M, Jokkel G, Bonyhay I, Tomcsanyi J, Naszlady A. Relation between baroreflex sensitivity and cardiac vagal tone in humans. Am J Physiol 1994;266(1 Pt 2):H21–7.

[11] American Thoracic Society. Statement on chronic bronchitis, asthma and pulmonary emphysema. Am Rev Respir Dis 1962;85:762-69.

[12] Sundkwist G,Almer LO,Lilja B.Respiratory influence on heart rate in diabetes mellitus.Br Med J 1979;1:924-25.

[13] Levin AB. A simple test of cardiac function based upon the heart rate changes induced by valsalva maneuver.Am J Cardiol 1966; 18:90-9.

[14] Ewing DJ,Cambell IW,Murray A,Neilson JM,Clarks BF. Immediate heart rate response to standing- a simple test for autonomic neuroapathy in diabetes.Br Med J 1978; 1:145-47.

[15] Bannister Roger, Autonomic failure: A textbook of clinical disorder of Autonomic .nervous system. Oxford University Press 1983; 371-436.

[16] Tarazi RC,Found FN.Circulatory dynamics in progressive autonomic failure.In: Bannister R ed.Autonomic failure – A textbook of clinical disorders of autonomic nervous system,1983.Oxford : Oxford University Press; 96-114.

[17] D J Ewing, J B Irving,Kerr F,Wildsmith JAW,Clarke BF. Cardiovascular responses to sustained hand grip in normal subjects and patients with diabetes mellitus- A test for autonomic function. Clin Sci Mol Med 1974; 46:295-306.

[18] God John O. Godden, Grace M. Roth. The changes in the intraarterial pressure during immersion of the hand in ice-cold water. Circulation. 1955 ; Vol XII:963-973

[19] Barnes PJ, Dollery CT, MacDermot J. Increased pulmonary alpha-adrenergic and reduced beta-adrenergic receptors in experimental asthma. Nature 1980; 285(5766):569–71

[20] Garrard CS, Seidler A, McKibben A, McAlpine LE, Gordon D. Spectral analysis of heart rate variability in bronchial asthma. Clin Autonom Research 1992; 2:105–11

[21] Nordin Magnus, Fagius J. Effect of noxious stimulation on sympathetic vasoconstrictor outflow to human muscles. Jour. of Physi.1995; 489(3):885-894

[22] Seidler A, Gerrad CS, Me Alpine L, Gordon D. Autonomic nervous system responses to inhaled histamine in normal subjects and asthmatics. Am Rev Respir Dis 1987; 135:A 478

[23] Shah PKD, Lakhotia M, Mehta S, Jain SK, Gupta GL. Clinical dysautonomia in patients with bronchial asthma. Chest 1990; 98(6):1408–13

[24] Iain AD O'Brien, Paul O'Hare. Heart ate variability in healthy subjects: effect of age and the deviation of normal ranges for tests of autonomic function. British heart Journal 1986; 55: 348-354

[25] Katona PG, 1ih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol1975; 5:801-05

[26] Samadhan P. Mitkari, Pushpa A., Sachin M. Autonomic dysfunction in patients with bronchial asthma. Int J Biol Med Res. 2011; 2(4): 852-855

[27] Manoj Kumar, NS Verma, S Tiwari, US Pande. Sympathetic hyperactivity in patients of bronchial asthma. Indian J Physiol Pharmacol 2005; 49(1):89-94