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Physiology

CARDIOVASCULAR AUTONOMIC FUNCTION IN ASTHMA: A STUDY IN EASTERN INDIA

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ABSTRACT

Introduction: Any abnormality in the autonomic control of the airway can result in bronchospasm, airway edema and excessive mucous secretion, which are characteristic of bronchial asthma. There is scarcity of literatures on cardiovascular autonomic dysfunction in asthma. Some of the studies have suggested increased vagal drive while others have reported sympathetic dominance to the heart.

Aims: Evaluation of cardiovascular autonomic function in asthma by simple non-invasive tests

Methods: A case control study was carried out involving 18-50 yrs old previously diagnosed asthma patients and same number of age and sex-matched controls. Electrocardiogram (ECG) and blood pressure were obtained from multi-parameter monitor (BPL Excello). Parasympathetic function was evaluated by heart rate response to Valsalva maneuver (Valsalva ratio), heart rate response to deep breathing for 1 minute and heart rate response to standing (30:15 ratio). Sympathetic function was assessed by blood pressure response to standing and sustained hand-grip test (HGT). HGT was performed using a handgrip dynamometer (Inco, Ambala, India, 0-60 kg). Mann Whitney test and Spearman's test were used for data analysis. P value less than 0.05 was considered significant.

Results: Out of 39 patients, 17 were female. Asthma patients had significantly higher systolic and diastolic blood pressure (DBP). 30:15 ratio and DBP change in response to HGT were significantly lower in patients compared to controls. Twenty three patients (59%) had at least one abnormal or two borderline test results indicating autonomic impairment.

Conclusion: Autonomic dysfunction is common in asthma with affection of both parasympathetic and sympathetic components.

KEYWORDS : : cardiovascular autonomic dysfunction; asthma; valsalva maneuver;

Introduction:

Asthma is a chronic inflammatory syndrome characterized by variable bronchoconstriction with airway hyperresponsiveness to a variety of trigger. The autonomic nervous system plays a pivotal role in the regulation of bronchial tone, submucosal glandular secretion, bronchial capillary permeability and release of inflammatory mediators in the airway [1]. Bronchospasm, airway edema and excessive mucous secretion, which are characteristic of bronchial asthma, may thus result from abnormality in autonomic regulation of the airways [2,3].

Anticholinergic treatment inhibits basal bronchial tone and hyperresponsiveness of airway suggesting the role of enhanced parasympathetic activity in the pathogenesis of asthma [4]. Previous studies have also reported compensatory sympathetic hyperactivity in asthmatics as evidenced by severe bronchoconstriction in response to beta-adrenoceptor blockade and increased plasma catecholamine level [5, 6]. There is paucity of literatures on cardiovascular autonomic profile in asthma. Some studies suggest increased vagal drive to the heart while others have reported sympathetic dominance [7, 8]. Sympathetic overactivity which predisposes to sudden cardiac death in asthma may be a compensatory phenomenon or may be due to the use of beta-agonists [9].

Autonomic functions can be evaluated by simple, non-invasive, safe and easily reproducible cardiovascular autonomic function tests [10]. The objective of this study is to evaluate whether there is any alteration of cardiovascular autonomic function in asthma patients and its relation with duration.

Materials and Methods:

This case control study was carried out in a tertiary care centre in eastern India after approval from the Institutional Ethics Committee. Cases were previously diagnosed 18-50 yr-old asthma patients of more than 2 years durations attending the outpatient department of chest medicine. Subjects with a history of diabetes, connective tissue disease, ischemic heart disease, cardiac arrhythmia, chronic bronchitis, central or peripheral nervous system disorders, renal diseases or any other disease that is known to produce autonomic neuropathy were excluded. Alcoholics, smokers and those practicing yoga or other physical training were also excluded. Those having acute asthmatic attack within two weeks of the study were excluded. Age and sex matched healthy volunteers who did not have any autonomic symptom and did not use any medication served as the control group. An age difference of up to 5 years was the age-matching criterion for each matched pair.

Informed consent was taken from all subjects before their inclusion in the study. Patients were interrogated for symptoms and signs suggestive of autonomic dysfunction like perspiration, palpitation, orthostatic hypotension (lightheadedness, blurred vision, sensation of weakness and unsteadiness, fainting or syncope upon standing) and Raynaud's phenomenon. Laboratory investigations included complete blood count, fasting and post-prandial plasma glucose, serum TSH, urea, creatinine, 24-hr urinary protein, albumin-creatinine ratio, X-ray chest. The procedure of spirometry was explained and demonstrated to the subjects. American Thoracic Society (ATS) criteria for acceptability and repeatability of spirometry were strictly followed [11]. Out of minimum three maneuvers, that with largest sum of FVC and FEV1 was taken for spirometry values. Control level of Asthma severity was done according to American Thoracic Society (ATS) criteria [12].

Autonomic function tests were done in the morning at a temperature of 22-25°C. Tobacco and caffeinated drinks were withheld for about 3 hours and alcohol was not allowed 8 hours before tests [13].

Electrocardiogram (ECG) and blood pressure were obtained from multi-parameter monitor (BPL Excello). Minimum resting heart rate (RHR) was recorded and three readings of blood pressure were taken at 2 minutes intervals after the period of 15 minute of rest in supine position. Resting systolic blood pressure (RSBP) and resting diastolic blood pressure (RDBP) were calculated by averaging the readings. Autonomic function were assessed using battery of cardiovascular reflex tests as devised by Ewing [10,14,15]. Parasympathetic function was evaluated by heart rate response to Valsalva maneuver, heart rate response to deep breathing and immediate heart rate response to standing. Sympathetic function was assessed by blood pressure response to standing and sustained hand-grip test (HGT). The order of the tests performed was as follows: immediate heart rate and blood pressure response to standing, heart rate response to Valsalva, heart rate response to deep breathing followed by blood pressure response to HGT. Valsalva maneuver, deep breathing and sustained handgrip tests were executed in sitting posture.

1. Immediate heart rate response to standing: The subjects were asked to stand up from supine position within 5 seconds and to remain motionless [15]. 30:15 ratio was calculated as ratio of longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.

2. Heart rate response to Valsalva: Each subject blew forcibly into a mouthpiece connected to the open end of an aneroid manometer so as to raise the pressure upto 40 mm Hg and maintained at that level for 15 seconds. The maneuver was performed thrice at intervals of one minute. Valsalva ratio (VR) was calculated as the ratio of longest RR intervals after the maneuver to the shortest RR interval during straining. The mean of the three Valsalva ratios were used for analysis.
3. Heart rate variation during deep breathing: Subjects breathed deeply and regularly at 6 breaths per minute upto a period of 1 minute. HR variation during deep breathing (HR_var) was calculated from ECG as mean of the differences between maximum HR during inspiration and minimum HR during expiration for 6 cycles. Expiratory: Inspiratory (E:I) ratio was also calculated as mean of the maximum RR during expirations divided by mean of minimum RR during inspirations [16].
4. Blood pressure response to standing: Blood pressure was recorded at 30 seconds, 1, 2 and 3 minutes after standing from supine position. Difference between resting SBP and minimum of four readings of SBP upon standing were expressed as postural change in SBP (cSBP_PT). Similar procedure was used for measuring change of DBP with posture (cDBP_PT).

5. Sustained handgrip test (HGT): Subjects forcefully compressed a handgrip dynamometer (Inco, Ambala, India, 0-60 kg) and the maximum force that was attained during handgrip was noted from the pointer on the scale. Each subject maintained force at 30% of this value for upto a maximum of three minutes without undue discomfort during which blood pressure was measured at 30 seconds intervals. Difference of resting SBP and DBP and maximum of those readings were expressed as blood pressure response to handgrip (cSBP_HGT and cDBP_HGT).

The five test parameters viz. VR, HR_var., 30:15 ratio, cSBP_PT and cDBP_HGT were scored using reference values from Ewing et al giving 0 for a normal result, 0.5 for a borderline result, and 1 for an abnormal result, thus giving a score of 0-5 for each subject who underwent the standard battery of all five tests [14]. Autonomic dysfunction was considered to be present if any patient had score 1 or more.
GraphPad Prism version 5 (San Diego, CA: GraphPad Software Inc., 2007) was used for statistical analysis. Data were analyzed by Mann Whitney test. Spearman's test was used to determine correlation between two parameters. P value less than 0.05 was considered significant.

Result:
Out of 48 patients initially enrolled for the study, 9 had to be excluded following exclusion criteria. Of the remaining 39 patients, 17 were female. Median age of the patients was 38.54 years with an age range of 18-50 years. Median disease duration was 4.59 years (range 2-20 yrs). All of them had normal plasma glucose, urea and creatinine. ECG and ultrasonography of abdomen were normal in all. 12 patients had well controlled asthma while 9 were poorly controlled. Controls included 39 apparently healthy matched volunteers. Everyone used beta-2 agonist.

Autonomic function test parameters of cases and controls have been compared in table 1. Asthma patients had significantly higher resting systolic and diastolic blood pressure compared to controls. 30:15 ratio and diastolic blood pressure response to handgrip test were significantly reduced in asthmatics. They also had increased heart rate, decreased heart rate variation with deep breathing, decreased EI ratio and decreased valsalva ratio but they didn't reach level of significance.

Table 1: Autonomic function test (AFT) parameters of cases and control

Parameters	Cases (n=39) Mean (SD)	Control (n=39) Mean (SD)	P value
RSBP	119.7 (14.77)	112.3 (9.11)	0.0101*
RDBP	76.4 (8.674)	71.4 (8.96)	0.0141*
Minimum RHR	83.3 (14.55)	79.9 (10.79)	0.2541
HR_var	15.8 (7.55)	18.4 (7.91)	0.1408
E:I ratio	1.205 (0.104)	1.247 (0.122)	0.0833
VR	1.392 (0.223)	1.477 (0.235)	0.1014
30:15R	1.178 (0.189)	1.300 (0.202)	0.0071*
cSBP_HGT	19.48 (12.02)	21.18 (10.17)	0.498
cDBP_HGT	16.19 (7.778)	22.22 (7.52)	0.0008*
cSBP_PT	0.1624 (9.166)	-1.583 (6.393)	0.328
cDBP_PT	-3.368 (5.311)	-5.492 (5.320)	0.0797

p value obtained by Unpaired t test; negative values indicate increase in BP on standing; RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; RHR, resting heart rate; HR_var, heart rate variation with deep breathing; E:I, expiratory: inspiratory; VR, Valsalva ratio; cSBP_HGT, change in systolic blood pressure with sustained handgrip; cDBP_HGT, change in diastolic blood pressure with sustained handgrip; cSBP_PT, change in systolic blood pressure on standing; cDBP_PT, change in diastolic blood pressure on standing;

Table 2: Frequency of impairment of different autonomic function test (AFT) parameters in cases and controls

Parameters		Normal	Borderline	Abnormal
Valsalva ratio	Case	31 (79.49%)	5 (12.82%)	3 (7.69%)
	Control	36 (92.30%)	2 (5.13%)	1 (2.56%)
30:15 ratio	Case	34 (87.18%)	2 (5.13)	3 (7.69%)
	Control	38 (97.43%)	0 (0%)	1 (2.56%)
Heart rate variation with deep breathing	Case	19 (48.72%)	10 (25.64%)	10 (25.64%)
	Control	30 (76.92%)	4 (10.26%)	5 (12.82%)
DBP response to HGT	Case	19 (48.72%)	10 (25.64%)	10 (25.64%)
	Control	32 (82.05%)	7 (17.95%)	0 (0%)
SBP response to standing	Case	37 (94.87%)	1 (2.56%)	1 (2.56%)
	Control	39 (100%)	0 (0%)	0 (0%)

Table 2 shows the number of cases and controls with normal, borderline and abnormal results for five AFT parameters. Heart rate variation with deep breathing and DBP response to HGT were most commonly affected in asthma patients.

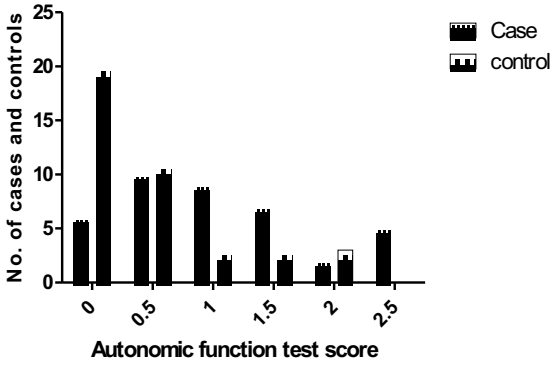

Fig 1: Score-wise distribution of cases and controls

Score wise distribution of cases and controls has been shown in fig 1.AFT score was zero in 6 (15%) patients and 20 (51%) controls while 10 (26%) patients and 11 (28%) controls had AFT score being 0.5. 23 (59%) patients had autonomic dysfunction with AFT score being 1 or more. Out of these 6 had only sympathetic dysfunction, 7 had only parasympathetic dysfunction while remaining 10 patients had mixed abnormality. There was no significant correlation between disease duration and AFT score (Spearman's r =0.2652, P = 0.1027) as shown in fig 2.

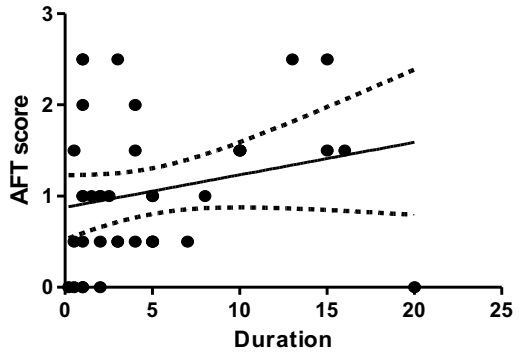

Fig 2: Scatter plot of disease duration vs autonomic function test score

Discussion

In our study, increased heart rate and significantly increased blood pressure indicate higher resting sympathetic tone in asthmatics. Decreased diastolic blood pressure response to handgrip test probably implies failure to increase the already increased sympathetic drive. Decreases in 30:15 ratio and other parasympathetic parameters are indicative of parasympathetic dysfunction. 59% of patients showed altered autonomic function. There was no relation of autonomic parameters with disease duration.

There are several reports of increased heart rate in asthmatics compared to controls [8, 17]. This is due to sympathetic over activity and increased plasma catecholamine levels [18]. There is parallel increase in parasympathetic drive to the heart and airways in asthmatics [7]. Previous studies have found increased values of parasympathetic test parameters in asthma [7,17,19]. Reduced value of parasympathetic parameters in this study unlike others, may be due to altered sympatho-vagal balance toward sympathetic dominance. Both parasympathetic and sympathetic innervation have some role in all five tests although a division into parasympathetic and sympathetic tests is of clinically convenience [10]. DBP response to HGT was increased in asthmatics in several studies unlike ours [17,20]. However decrease in parasympathetic and sympathetic parameters was found in one study [21].

Small sample size is a limitation of this study. A larger sample size could have allowed the comparison of autonomic parameters among poorly controlled, partially controlled and well-controlled groups of asthma.

To conclude, autonomic impairment is common in asthma with involvement of both parasympathetic and sympathetic components.

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