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ORIGINAL ARTICLE

A STUDY OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN ASTHMATIC PATIENTS AND DETERMINE ITS CORRELATION WITH SEVERITY

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ABSTRACT: CONTEXT Bronchial asthma is a chronic inflammatory disorder of the airways affecting people of all ages. It is manifested physiologically by a wide spread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy and clinically by paroxysms of dyspnea, cough and wheezing. Airways are richly innervated by autonomic nervous system which plays a part in the control and their secretion. They regulate many aspects of airways' physiology such as smooth muscle, mucus secretions, blood flow, micro vascular permeability and the migration and release of inflammatory cells. These effects are due to the release of neurotransmitters from autonomic nerves. **MATERIAL AND METHODS:** The present work was undertaken in 50 cases of bronchial asthma attending medical OPD and indoor and they were randomly selected without any bias of age and sex. Criteria for grading of severity of asthma were determined by clinical & Peak expiratory Flow Rate [PEFR]. A complete general and systemic examination was carried out and they were specifically examined in detail for signs of autonomic dysfunction employing the standard "Ewing-Clarke" battery of five tests for cardiovascular autonomic functions. Three tests were used for parasympathetic function- 1.Heart rate response to Valsalva maneuver 2. Heart rate variation during deep breathing 3. Immediate Heart rate response to standing. And two tests were used for sympathetic function- 1. Blood pressure response to standing 2.Blood pressure response to sustained handgrip. **OBSERVATIONS:** In the present study, 32 patients (64%) were tested positive for autonomic dysfunction out of 50 cases. Maximum number of cases 17(94.44%) out of 18 with autonomic dysfunction had severe asthma. 15(46.87%) out of 32 cases with autonomic dysfunction had mild-moderate asthma. Thus there was an increase in autonomic dysfunction with increased severity of asthma ($p<0.001$ highly significant). **CONCLUSION**: The severity of asthma also increases the incidence of autonomic dysfunction. Thus it can be concluded that the incidence of autonomic dysfunction present in asthmatic patients increases with increasing severity of the disease emphasizing the role of autonomic nervous system in its pathophysiology.

KEYWORDS: Bronchial asthma, Autonomic Function Test, Cardiovascular Autonomic dysfunction,

INTRODUCTION: Bronchial asthma is a chronic inflammatory disorder of the airways, [1] affecting people of all ages. At present there is no known cure, but it can be treated & controlled. There is a general trend of increase deaths and hospitalization from asthma recorded in all the industrialized countries in the world.

Asthma is now one of the world's most common long term conditions, according to the global burden of asthma report. WHO estimates that 235 million people currently suffer from asthma.[2] Its

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prevalence is predicted to continue increasing in coming years. An absolute 2% increase in the prevalence of asthma in India would result in an additional 20 million people with the disease.

The disease is characterized by increased responses of the tracheobronchial tree to a multiple stimuli. It is manifested physiologically by a wide spread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy and clinically by paroxysms of dyspnea, cough and wheezing.[3]

Airways are richly innervated by 4 components of autonomic nervous system which play a part in the control and their secretion - adrenergic, cholinergic, inhibitory non-adrenergic non-cholinergic and excitatory non-adrenergic non-cholinergic.[4] They regulate many aspects of airways' physiology such as airway smooth muscle tone, submucosal gland secretion, epithelial cell function, bronchial vascular tone and permeability, and probably secretion from mast cells and other inflammatory cells.[5] These effects are due to the release of neurotransmitters from autonomic nerves. These are often but not always neuropeptides.

The cholinergic nervous system is the predominant neural bronchoconstrictor pathway in humans. Airways inflammation results in exaggerated acetylcholine release from cholinergic nerves via dysfunction of the autoreceptor, muscarinic M2, which is possibly caused by a major basic protein or IgE. Inhibitory noradrenergic non-cholinergic (NANC) nerves, containing vasoactive intestinal peptide and nitric oxide, may be the only neural bronchodilator pathways in human.[6] The effect of VIP and NO are diminished after allergic reaction by inflammatory cell mediated tryptase and reactive O2 species. Thus in asthmatics, the inflammatory change mediated neural imbalance which may result in airway hyper-responsiveness.

E-NANC nerves, which release tachykinins, [7] have a variety of actions including airways' smooth muscle constrictor, mucus secretion, vascular leakage and neutrophil attachment and they may be involved in the pathogenesis of asthma, since tachykinin receptor antagonists are effective for bradykinins' and/or exercise induced bronchoconstriction in asthmatic patients.

Thus airway and pulmonary vascular tone may be determined by a complex interplay between different components of the autonomic nervous system.

The object of the present study is to evaluate the autonomic dysfunction in bronchial asthma and determine its correlation with severity as a knowledge of an early autonomic dysfunction can encourage the physician to use therapies such as anticholinergics proven to be effective in bronchial asthma and improve the quality of life of these patients.

MATERIAL AND METHODS: The present work was undertaken in 50 cases of bronchial asthma attending medical OPD and indoor of the Department of Medicine, G R Medical College and J.A. Group of Hospitals, Gwalior (M.P.) and they were randomly selected without any bias of age and sex. 50 healthy volunteers were served as controls and their age & sex were matched with cases.

Diagnostic Criteria: Criteria for grading of severity of asthma by clinical & Peak expiratory Flow Rate [PEFR].

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	MILD	MODERATE	SEVERE
SYMPTOMS	• Intermittent & brief nocturnal symptoms <2 times / month • Asymptomatic b/w exacerbations • Infrequent episodes <1 attack / 2 months	• More frequent exacerbation • Nocturnal symptomatic > 2 times / month • Symptomatic daily. • Requiring B2 agonist for relief.	• Very frequent exacerbation frequent nocturnal symptoms • Continuous symptomatic • Physical exercise limited • Chronic persistent.
Lung function (PEFR)	• PEF >80% • PEF Variability <20% • PEF normal after bronchodilator	• PEF 60-80 % Predicted • PEF Variability 20-30 % • PEF normal after bronchodilator	• PEF < 60 % Predicted • PEF Variability >30 % • PEF below normal dispute therapy.

Exclusion Criteria:

1. Patient with history suggestive of heart disease, renal disease, liver disease, diabetes mellitus, significant anemia, electrolyte imbalance or resting abnormal ECG was excluded from the study.
2 All medications that can cause orthostatic hypotension or interfere with autonomic function tests e.g. diuretics, antihypertensives, Ca channel blockers, B blockers, TCA, barbiturates, antipsychotics narcotics etc. should be avoided 24 hrs. prior to the tests.

METHODS: Those persons selected for the study were subjected to a standardized protocol of history, examination and investigations. A thorough history was recorded with special emphasis on symptoms of autonomic dysfunction.

A complete general and systemic examination was carried out and they were specifically examined in detail for signs of autonomic dysfunction employing the standard “Ewing-Clarke” battery of tests for cardiovascular autonomic functions.

Apart from routine investigations of blood hemoglobin, total and differential leukocyte counts, Spirometry (PEFR) was also done.

Precautions required before performing the autonomic function tests:

1. Eat only easily digestible foods on the day of testing and avoid all foods 3hrs prior to testing.
2. Avoid products, which contain caffeine -coffee, tea; some sodas; tobacco (smoked and/or chewed) or alcohol for at least 3hrs.prior to the tests.
3. All medications that can cause orthostatic hypotension or interfere with autonomic testing results i.e. diuretics, antihypertensives, Ca channel blockers, β blockers, TCA, barbiturates, antipsychotics, narcotics etc. should be avoided 24 hours prior to the test.

All the subjects will be well-informed regarding the above precautions that need to be taken before performing the tests.

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1. Tests for parasympathetic function

(a) **Heart rate response to valsalva Maneuver:** The test was performed by the patient blowing into a mouthpiece connected to a sphygmomanometer maintaining a pressure of 40mm Hg for 15secs while a continuous lead II ECG was recorded. The reflex response in healthy subjects includes tachycardia and peripheral vasoconstriction during the strain, followed by an overshoot in blood pressure and bradycardia after release of strain.

The result was expressed as "Valsalva Ratio" which is the ratio of longest R-R interval after the maneuver (reflecting the bradycardia following the release) to the shortest R-R interval during the maneuver (reflecting tachycardia as a result of strain). The normal ratio is >1.21 and a ratio of <1.10 is considered abnormal.

(b) **Heart rate variation during deep breathing:** The patient was asked to sit quietly and breathe deeply at the rate of 6cycles/min and lead II surface electrocardiogram is recorded throughout the period. The maximum and minimum R-R intervals during each breathing cycle were measured and these were converted into beats/minute.

The HRV >15 bpm is considered normal & that <10 bpm is abnormal.

(c) **Immediate Heart rate response to standing:** The test was performed with the patient lying quietly while the heart rate was recorded continuously on an electrocardiograph. The patient was then asked to stand unaided and the point of standing was marked on the electrocardiograph (lead II). Normally an immediate increase in heart rate which is maximal at about 15th beat after starting to stand occurs and it is followed by gradual bradycardia maximal at about 30^{th} beat. This is expressed as 30:15 beat ratio (R-R interval) and is normally >1.04. A value of <1.01 is taken as definite evidence of autonomic dysfunction.

2. Tests of sympathetic function:

(a) **Blood pressure response to standing:** The blood pressure was measured by a sphygmomanometer while patient was lying down and again immediately after and at 1st and 3rd minutes after standing up. A difference in systolic blood pressure of 30mm Hg is more or less a definite sign of postural hypotension while a fall of 16-29mm Hg is taken as borderline.

(b) **Blood pressure response to sustained handgrip:** The patient was asked to sit in a chair and his resting blood pressure was recorded. He was then asked to maintain 30% of maximum tension on a dynameter for 5 minute. The blood pressure was again recorded before the release of handgrip. The difference in diastolic blood pressure normally is >16mmHg while a rise of <10mmHg is taken as abnormal.

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Tests	Normal	Borderline	Abnormal
Test for parasympathetic functions			
Heart rate response to valsalva maneuver (Valsalva ratio)	>1.21	1.11-1.20	<1.10
Heart rate variation (R-R interval) during deep breathing (max-minimum heart rate)	> 15 beats/min	11-14 beats/min	< 10 beats/min
Immediate heart rate response to standing (30:15 ratio)	> 1.04	1.01-1.03	< 1.0
Test for sympathetic function			
BP response to standing (fall in systolic blood pressure)	< 10 mmHg	11-29 mmHg	> 30 mmHg
BP response to sustained handgrip (increase in diastolic BP)	> 16 mmHg	11-15 mmHg	< 10 mmHg

Tests of autonomic function[8]

The subjects were categorized as:

1. Normal: all five tests normal or one borderline.
2. Early involvement: one of the three heart rate tests abnormal or two borderline.
3. Definite involvement: two or more of the heart rate tests abnormal.
4. Severe involvement: two or more of the heart rate tests abnormal plus one or both blood pressure tests abnormal or both borderline.

OBSERVATIONS:

Grade of asthma	Total cases	Grade of autonomic dysfunction			*Total cases with Autonomic dysfunction	Percentage (%)
		Early	Definite	Severe		
Mild - Moderate	32	10	3	2	15	46.87%
Severe	18	5	8	4	17	94.44%
Total	50	15	11	6	32	64%

Table No. 1: Relation of autonomic dysfunction with severity of asthma

*Prevalence with severity of asthma: χ^2=11.29, d.f. = 1; p<0.001, highly significant

Table shows that maximum number of cases 17(94.44%) out of 18 with autonomic dysfunction had severity of asthma. 15(46.87%) out of 32 cases with autonomic dysfunction had mild-moderate asthma. Thus there was an increase in autonomic dysfunction with increased severity of asthma (p<0.001 highly significant)

DISCUSSION: Bronchial smooth muscle constriction plays a major role in asthma and recent studies implicate autonomic nervous system in it. Parasympathetic system may affect the airways via reflexes involving bronchial smooth muscle or via increased mediator release locally. Adrenergic innervation appears less potent. B-adrenergic blockade has little or no effect in healthy subject but causes bronchoconstriction in asthmatic patients. Therefore bronchial hyper-reactivity occurring in asthma

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apart from hyperplasia of smooth muscle may be due to abnormalities of parasympathetic or sympathetic nervous system functions.

The present work has been carried out with a view to evaluate the status of autonomic functions pertaining to cardiovascular system in randomly selected 50 non-cardiac, non-diabetic asthmatic subjects reporting medical out patients and wards of G.R. Medical College and J.A. Group of Hospitals, Gwalior (M.P.). 50 randomly selected healthy volunteers known to be non-asthmatic served as controls. The cases and controls were thoroughly examined and subjected to tests after a detailed history. The findings are discussed below:-

Prevalence of Autonomic dysfunction: The prevalence of autonomic dysfunction in the asthmatic population studied was found to be 64%. The prevalence rate in this study is comparable with studies of others.

Sharma B et al (2003) found autonomic dysfunction in 22(73.33%) asthmatic patients out of 30 asthmatic patients.[9]

Kaliner M. et al (1982) and Shah P. K.D. et al (1990) also observed significant prevalence of autonomic dysfunction in asthmatic patient.[10]

Relation of autonomic dysfunction with severity of asthma: In the present study, it was observed that with the increasing severity of the disease, there was a significant increase in the incidence of autonomic dysfunction ($p<0.01$, highly significant). As compared to 46.87% cases in mild-moderate group there was rise to 94.44% cases in severe group.

This is in confirmation with the findings of Sharma B et al (2003) who showed that as the severity of asthma increases, the incidence of autonomic dysfunction also increases. In his study severe asthma was present in 16 patients out of which 15 patients had demonstrable autonomic dysfunction.

Shah P.K.D. et al (1990) observed significant autonomic dysfunction with the increasing severity of disease ($p<0.001$).

Thus, in the wake of these observations, it becomes imperative to evaluate autonomic function tests in every asthmatic for any evidence of autonomic involvement. Hopefully, the observations of the present study will add up to our existing knowledge of the disease and will go a long way to help a physician improve the quality of life of his patients.

CONCLUSION: The literature and the present study show that asthmatics display definite autonomic dysfunction compared to controls. Although both the autonomic systems; the parasympathetic and the sympathetic may play a role in pathophysiology of asthma. There is no significant increase in the frequency of autonomic dysfunction in various age groups and different sex of the asthmatics.

The severity of asthma also increases the incidence of autonomic dysfunction. Thus it can be concluded that the incidence of autonomic dysfunction present in asthmatic patients increases with both increasing duration as well as increasing severity of the disease emphasizing the role of autonomic nervous system in its pathophysiology.

Hence, every physician should make an effort to evaluate the autonomic nervous system in every asthmatic as an early knowledge of the same can encourage the physician to use therapies such

as anticholinergics proven to be effective in bronchial asthma and improve the quality of life of his patients.

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