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SYMPATHETIC HYPERACTIVITY IN PATIENTS OF BRONCHIAL ASTHMA

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Abstract : The bronchoconstricting and bronchodilating divisions of the autonomic nervous system control airway caliber of lungs. Parasympathetic hyperactivity in asthmatics eventuates in broncho-constriction. Sympathetic activity increases to combat this but fails to control bronchoconstriction due to negligible innervations of the airway smooth muscles although it causes vasoconstriction of blood vessels.

In this study the effects of autonomic function test for sympathetic division were seen on selected patients and controls. Our results indicate sympathetic hyperactivity or an increased α-adrenergic input in asthmatics.

Key words : bronchial asthma autonomic dysfunction autonomic function test

INTRODUCTION

The airway caliber of lungs involves various airway functions like smooth muscle tone, epithelial cell function, mucous secretion, blood flow, micro vascular permeability and inflammatory mediator release under normal circumstances, which are all controlled by the autonomic nervous system. This system comprises different types of afferent and efferent pathways mediated through cholinergic, adrenergic and non-adrenergic non-cholinergic mechanisms which may be excitatory i.e. bronchoconstricting (e-NANC) or inhibitory i.e. bronchodialating (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 (1).

The cholinergic nervous system is more important in the regulation of airway tone as it has direct innervations of airway smooth muscle, while 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

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bronchodilatory pathway present in human airways (2, 3, 4, 5). However, β_2-adrenergic receptors are abundantly expressed on human airway smooth muscle. Activation of these receptors causes bronchodilation (6).

Bronchial obstruction in asthma occurs due to impaired function of the pre-junctional auto inhibitory M_2-cholinoceptor that causes an increased and uncontrolled release of acetylcholine. In vitro findings show that the number of NPY immunoreative nerves is significantly reduced in asthmatics suggesting an increased cholinergic input in asthma, as NPY can inhibit the release of acetylcholine (7). Damage in the airway epithelium which occurs in asthma causes exposure of afferent endings leading to increased sensitivity to the inhaled irritant as well as to enhance mediator release under baseline conditions.

In asthmatics, β-adrenoceptor blockade develops severe bronchoconstriction, whereas in normal people no significant effect on airway caliber can be observed (8, 9). The mechanism underlying β-adrenoceptor blockade induced bronchoconstriction in asthmatics has not been identified yet. However, it is observed that in asthmatics β-adrenoceptor blockade bronchoconstriction can be inhibited by the anticholinergic pretreatment (10), and an indirect effect of anticholinergic drug has been postulated. On the one hand, this observation might support an increased cholinergic input in patient with asthma (whereby the blockade of the subsequently up regulated adrenergic system would cause bronchoconstriction); on the other hand it suggests a *per se* enhanced adrenergic stimulation in asthmatic patients, for example an increased plasma adrenaline level. Despite widespread measurement of circulating plasma concentration under various conditions (11-14), the role and importance of adrenaline in control of airway caliber in asthma remains uncertain.

The cardiovascular and respiratory autonomic efferent fibers have common central origin (15) and hence the altered cardiovascular and respiratory responses may reflect the abnormalities of the autonomic nervous system. Therefore, to evaluate the autonomic functions in asthmatics, different non invasive, safe and easily reproducible cardiovascular autonomic reflex function tests are used. In the present study we have assessed the sympathetic division of autonomic nervous system by using a battery of three tests in which we have observed changes in blood pressure after stimulation of sympathetic part.

Earlier studies have also reported insignificant sympathetic hyperactivity in asthmatics to combat bronchoconstriction (9, 16, 17).

METHODS

Thirty asthmatic patients and twenty non allergic healthy volunteers were studied after obtaining their written consent. All the patients had history and clinical features of bronchial asthma as defined by the American Thoracic Society (18).

The following criteria were followed while selecting the patients: duration of asthma more than five year, with at least two asthmatic exacerbation in any year;

patient's age between 20 to 40 years; should not be taking medications that may alter their heart rate or blood pressure but not limited to digoxin, calcium channel blockers, β-blockers, theophylline, or oral β-agonists during the study period. Those subjects were also excluded who had an asthmatic attack within 2 weeks of the study. Treatment with that asthma medication which could affect the autonomic function was discontinued. Oral theophylline and oral β_2-adrenergic agents were withheld for at least 72 h; inhaled short-acting β-agonists and ipratropium bromide were held 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.

All the healthy subjects and patients had to undergo baseline Spiro metric testing in which forced vital capacity (FVC); forced expiratory volume in 1 second (FEV_1); FEV_1 as percentage of FVC (FEV_1%) and peak expiratory flow rate (PEFR) were recorded. The tests performed for examining the sympathetic division of autonomic nervous system were:

1. Blood pressure response to sustained hand grip.
2. Blood pressure response to cold pressor test.
3. Blood pressure response to standing from the supine posture.

The maneuver and recording of responses was carried out as follows.

The blood pressure response to sustained hand grip (19) – The subjects were asked to grip the dynamometer with their dominant hand and maintain the pressure on dynamometer for 2 min at 30% of maximal voluntary contraction (MVC) and the blood pressure was recorded from the non-exercising arm before the test, one minute after onset of hand grip and just prior to release of hand grip at 2 minutes.

The blood pressure response to cold pressor test – Subjects were asked to immerse both feet in ice water (1–4°C) for 1 min (20). The blood pressure was recorded just before the test and at 1 min, after the immersion of feet in the water. The systolic and diastolic pressure difference at 1 min from the baseline was calculated.

The blood pressure response to standing from the supine posture – The subjects were asked to stand up quickly from supine posture and keep standing quietly for 2 minutes (21). The blood pressure was recorded at 0 min (in lying position) and 0.5th, 1st and 2nd min of standing up. The difference in systolic and diastolic pressure at half, 1st and 2nd minute of standing from that of supine (baseline; 0 min.) pressure was calculated.

Study Design

Subjects were presented after an overnight fast. Special precautions were taken to provide a calm and relaxed environment for autonomic function testing and to avoid any thing that might modify autonomic responses by inducing fear

or anxiety. Subjects were connected to ECG machine for recording of heart rate and ECG. BP was measured by sphygmomanometer with a standard cuff at set interval. After a resting period of at least 30 min, autonomic function test for sympathetic division were performed.

Statistical Analysis

Statistical Analysis was done by using student's t test. Values are shown as means ± S.D.

RESULTS

The age of asthmatic subjects varied from 20–40 (29.27±6.25) years, while that of control subjects varied from 23 to 35 (28.45±3.52) years. The male and female ratio in asthmatics was 2:5 while in controls it was 1:10. Baseline cardiovascular and ventilatory functions of asthmatics as well as of controls are shown in Table I. The forced expiratory volume in one second, forced vital capacity and peak expiratory flow rate were significantly lower in asthmatics as compared to controls.

TABLE I: General subjects' profile.

Parameters	*Asthmatics*	*Controls*	*P Value*
Age (yrs)	29.27±6.25	28.45±3.52	
Heart Rate (bpm)	79.47±8.80	83.65±7.07	>0.05
Systolic Blood Pressure (mm Hg)	123.33±12.60	121.8±7.45	>0.05
Diastolic Blood Pressure (mm Hg)	82.47±11.65	80.0±5.41	>0.05
FEV1 (ml)	2261.33±504.61	3445.30±581.07	<0.01
FEV1 : FVC (%)	58.83±11.50	78.52±4.52	<0.01
FVC (ml)	3843.0±389.65	4389.45±682.65	<0.01
PEFR (L/min)	326.33±46.42	512.5±45.87	<0.01

Values expressed as mean and standard deviation.

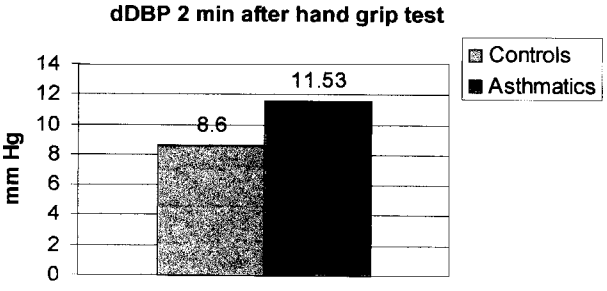
TABLE II: Vascular response after various autonomic function tests.

Parameters	*Asthmatics*	*Controls*	*P Values*
dDBP with Sustained Hand grip test (after 2 min)	11.53±5.06	8.6±3.25	<0.05
dDBP with Cold Pressure Test (after 1 min)	5.75±2.86	3.9±1.89	<0.01
dDBP with Supine to Standing Test (after 1 min)	3.73±2.21	2.1±2.0	<0.01

Values expressed as mean and standard deviation.

Vascular response to autonomic function tests for sympathetic division – Results of different autonomic function tests for sympathetic division are shown in Table II.

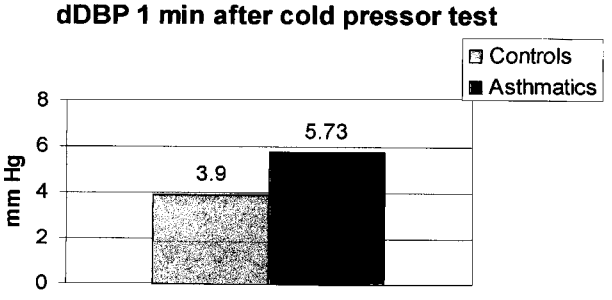
As shown in Fig. 1, the rise in diastolic blood pressure at 2 min after sustained hand grip test in asthmatics was significantly higher as compared to rise in diastolic blood pressure in controls (P<0.05).



Mean values of dDBP in controls and asthmatics

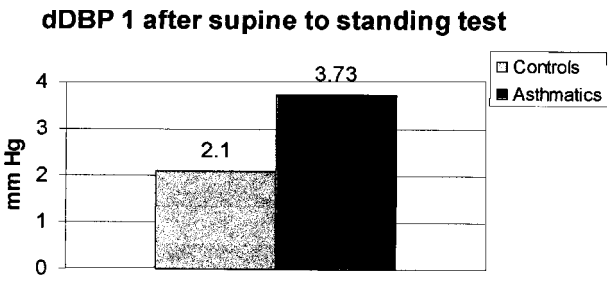
Fig. 1

Figures 2 and 3 show significant rise in diastolic blood pressure in cold pressor test (after 1 min) and supine to standing test (after 1 min) in asthmatics, as compared to the rise in controls (P<0.01).



Mean values of dDBP in controls and asthmatics

Fig. 2



Mean values of dDBP in controls and asthmatics

Fig. 3

DISCUSSION

Autonomic function tests for sympathetic division which were carried out in this study have been extensively used in the past. They are all standard, non invasive, safe and easily reproducible.

Basal diastolic blood pressure was insignificantly higher in asthmatics as compared to controls while basal heart rate was insignificantly lower in asthmatics as compared to controls. These data suggest higher parasympathetic tone and α-adrenergic hyper responsiveness in asthmatics (22). The ventilatory responses also suggest a higher basal parasympathetic airway tone in asthmatics.

In our study asthmatic subjects showed significant rise in diastolic blood pressure with sustained hand grip test, cold pressor test and supine to standing test as compared to controls. The rise in diastolic blood pressure in these tests is a measure of sympathetic efferent vasoconstrictor function mediated via α-adrenergic receptor (23). In asthma, where α-adrenergic hyper responsiveness has been proposed (22), there should be an exaggerated blood pressure response with these tests.

Prabhat et al. (16) and Gupta and Dolwani (17) have also found greater rise in diastolic blood pressure in asthmatics after sustained hand grip test but their results are not significant. Results of these tests demonstrate the function of sympathetic efferent on the blood vessels, but the sympathetic system can not be directly correlated with bronchial hyperactivity as airway α- and β-receptor stimulation is under control of circulating adrenaline and noradrenaline and direct innervations of human airways smooth muscle is negligible (24, 25, 26).

This increased adrenergic drive to combat parasympathetic hyperactivity causing bronchoconstriction is also supported by the fact that in asthmatics β-receptor blockade causes severe bronchoconstrictions, whereas in normal subjects no significant effect on airway caliber occurs (8, 9). This bronchocostriction can be inhibited by the anticholinergic pretreatment (10). From this observation it is concluded that there is increased cholinergic input in asthmatics causing up regulation of the adrenergic system. When this is blocked therapeutically it results in bronchoconstriction.

It appears from our studies that sympathetic hyperactivity develops in asthmatic patients to combat the bronchoconstriction caused by

parasympathetic hyperactivity. It, however, fails in this objective because direct innervation of human lung with sympathetic division of the autonomic nervous system is negligible. In view of this we recommend a circumspect use of sympathomimetic drugs in the treatment of bronchial asthma as they tend to increase the sympathetic hyperactivity.

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