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RESEARCH ARTICLE

A case–control study of autonomic function tests in male cigarette smokers and healthy control subjects

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ABSTRACT

Background: Use of cigarette is a great cause of preventable morbidity and mortality. The blood vessel system effects of cigarette smoke are mediated by nicotine (alkaloid). Alkaloid increases heart rate and the myocardial pump activity. **Aims and Objectives:** This study aims to detect and compare autonomic function tests in male cigarette smoker and non-smoker healthy control subjects. **Materials and Methods:** The study was conducted in the Department of Physiology, Sawai Man Singh Medical (SMS) College and Hospital, Jaipur, Rajasthan, on 30 male cigarette smokers between the age group of 20 and 40 years, selected among employees of SMS Medical College, Jaipur, from various departments along with 30 healthy age-matched non-smokers. **Results:** Heart rate response to deep breathing (30:15 ratio), expiration/inspiration ratio, and Valsalva ratio were significantly decreased in smokers. Cigarette users have increase in systolic blood pressure (BP) and diastolic BP, but no significance difference was found in our study, BP response to standing shows decrease in systolic BP and sustained handgrip test (SHG) response is also decrease in diastolic BP in cigarette users than the control healthy subjects. **Conclusion:** Our study results can be concluded that cigarette smoking causes increase sympathetic and reduced parasympathetic activity when compared with control healthy subjects.

KEY WORDS: Autonomic Function Test; Smokers; Non-smokers; Diastolic Blood Pressure; Systolic Blood Pressure; Orthostatic Fall; Sustained Hand Grip Test

INTRODUCTION

The blood-related effects of cigarette smoking are mediated by alkaloid. Alkaloid increases the cardiac output by increasing heart rate and the myocardial contractility.[1]

Abuse of drugs is one of the biggest curses. Out of the various drugs abuse, the most widely distributed and commonly used drug in the world is "Tobacco."[2]

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Cigarette smoking affects an estimated 5 million people annually worldwide. By the early 2030, tobacco-related deaths would reach to about 10 million in a year.[3] The World Health Organization reports on global status of non-communicable diseases (2010) stated that cigarette causes an increase in lung cancer deaths, chronic respiratory diseases, and nearly 10% of the cardiovascular diseases, communicable diseases tuberculosis, and lower respiratory infections.[4]

Cigarette smoking on leukocyte count reflects inflammatory activity, exposures to oxidants, or vulnerability of the host toward inflammatory conditions, inflammatory response elicited by cigarette is due to protein degrading enzymes, released by the neutrophil.[5]

Cigarette smoking leads all phases of atherosclerosis from endothelial dysfunction, later causes thrombosis. All types

(active and passive) of cigarette smoke exposure predisposes to cardiovascular diseases. Cigarette smoking causes inflammation, thrombosis, and oxidation of low-density lipoprotein (LDL) cholesterol.[6]

The blood pressure (BP) and heart rate increasing effects of cigarette smoking are due to increase catecholamine blood levels that are dependent on the adrenergic stimulation.[7]

Cigarette smoking also impacts the baroreceptors sensitivity in humans, which may increase in the BP and the heart rate as well as to the concomitant changes in their variability. The cigarette causes the downregulation of the beta-adrenergic receptors in chronic smokers.[8]

Cardiovascular system is influenced by the interplay of sympathetic and parasympathetic autonomic nervous system.[9,10]

MATERIALS AND METHODS

Our study aims at finding out sympathovagal balance which would help in early detection of comorbid conditions. This type of study has not been undertaken at our institute, the study was conducted in the Department of Physiology, SMS Medical College and Hospital, Jaipur, Rajasthan, on 30 male cigarette smokers between the age group of 20 and 40 years, among employees of various departments of SMS Medical College, Jaipur, along with 30 healthy age-matched non-smokers. Permission was obtained by the Research Review Board and Ethical Committee of the Institute.

Inclusion Criteria for Cigarette Users

The following criteria were included in the study:
1. Cigarette smokers who use cigarette for more than 5 years, subjects will be categorized according to smoking index as light smoker (1–100), moderate smoker (101–200), and heavy smoker (>201)[11]
2. Age group between 20 and 40 years
3. Subjects who gave informed written consent.

Inclusion Criteria for Control Group

The following criteria were included in the study:
1. Non-cigarette smokers and non-tobacco consumers in any form
2. Age- and sex-matched healthy individuals
3. Subjects who are cooperative and given informed written consent.

Exclusion Criteria for Cigarette User

The following criteria were excluded from the study:
1. Any acute illness
2. Hypertension, diabetes, cardiac, renal, liver, and other chronic diseases
3. Subjects on medications known to affect autonomic functions.

Subjects were instructed to avoid tea, coffee, and food at least 2 h before start of the recording. The recording was taken between 9.00 AM and 12.00 Noon. All the participants were subjected to anthropological measurements; include height, weight, hip circumference, and waist circumference. Detailed history and general physical examinations were conducted to rule out any disease.

The various non-invasive autonomic function tests were performed by a Windows based Cardiac Autonomic Neuropathy (CAN Win) Analysis System version 1.0 with interpretation. CAN Win detects CAN Win based on Ewing's battery tests. BP was recorded with automated digital device to avoid manual error.

Autonomic Function Tests by CAN Win[12]

Basal heart rate

The basal heart rate was recorded in supine position by CAN Win based on electrocardiogram after 15 min of rest.

Immediate heart rate response to standing (30:15 ratio)

The ratio of longest R-R interval of the 30th beat and shortest R-R interval of 15th beat after standing of subject was measured by CAN Win. The related heart rate response was expressed by 30:15 R-R ratio (which is normal if >1.04; borderline between 1.01 and 1.03 and abnormal if < 1.00).[13]

Heart rate response to deep breathing (expiration/inspiration [E/I] ratio)

The ratio of longest R-R interval in expiration and shortest R-R interval in inspiration was measured as E/I ratio. The average of three successive breathing cycles gives the E/I ratio of individual.

Valsalva maneuver

Valsalva ratio was ratio of maximum R-R interval after the strain to ratio of shortest R-R interval during the strain.

BP response to standing

BP changes were recorded on standing (immediate and after 60 s of motionless standing). After standing a substantial amount of blood is redistributed to blood vessels of the lower extremities, which decreases venous return and cardiac output. To maintain hemodynamic parameters, the human body initiates a physiological compensatory reaction as vasoconstriction, tachycardia, and increased cardiac output. These compensatory mechanisms are triggered by a decrease in BP and mediated by the carotid and aortic body reflex. Decreased pressure in the carotid and aortic sinus decreases the rate of discharge from the baroreceptor to the nucleus

tractus solitarius. This decreases vagal activity and raises sympathetic activity, which results return of BP to normal.

BP falls immediately on standing. After 15–30 s, systolic pressure returns to normal (or remain slightly elevated), but diastolic pressure remains elevated (increased peripheral resistance due to vasoconstriction) and tachycardia persists.

BP response to sustained handgrip test

This test assesses BP response to an isometric handgrip exercise. Subjects are instructed to perform three maximum possible contractions on handgrip dynamometer. The average force generated in all three contractions was calculated. The subject was instructed to maintain the handgrip at 30% of the maximum force while simultaneously recording BP in non-dominant hand. Resting BP was measured using a CAN Win Analysis System based on NiBP in supine position. The BP was recorded each minute as soon as red light indicator turned up on prompt panel. The diastolic BP rises because of increased muscle contraction activity.[14]

Statistical Analysis

The information was entered into windows 10 Microsoft Excel. The data were expressed as mean ± SD. Student's unpaired "*t*-test" applies to calculate the level of significance. The level of significance was assigned at $P < 0.05$.

RESULTS

The findings of the present study are depicted in Tables 1-3.

DISCUSSION

Cigarette smoking raises inflammation, thrombosis, and oxidation of LDL cholesterol.[7] All types of smoke use increase heart rate and BP due to effect of nicotine, which is a cardioactive substance. Coronary artery disease is a major cause of premature death and disability due to cigarette smoking in world.

In our study, we obtained significant increase in resting heart rate in cigarette users and significantly lower 30:15 ratio, E/I ratio in cigarette users while there was no significant difference which were found in Valsalva maneuver of cigarette users and control subjects.

In sympathetic function tests systolic and diastolic BP was increase but could not found significantly different, orthostatic hypotension value was lower among cigarette users than controls and results of sustained handgrip test was also lower in smokers and significant difference occurs in diastolic BP values.

Table 1: Comparison of anthropometric parameters in cigarette users and control subjects

Parameters	Cigarette user (mean±SD)	Control (mean±SD)	*P*-value
Age (years)	31.0±5.48	30.8±3.31	0.86 (NS)
BMI (kg/m^2)	21.28±2.29	21.48±1.71	0.71 (NS)

NS: Not significant

Table 2: Comparison of parasympathetic function tests in cigarette user and control subjects

Parameters	Cigarette user (mean±SD)	Control (mean ±SD)	*P*-value
Supine heart rate (beats/min)	84.37±9.46	69.80±5.79	0.00 (HS)
Heart rate response to standing (30:15 ratio)	0.97±0.13	1.35±0.25	0.00 (HS)
Heart rate response to deep breathing (E/I ratio)	1.32±0.16	1.43±0.23	0.03 (S)
Valsalva ratio	1.35±0.34	1.39±0.15	0.63 (NS)

HS: Highly significant, S: Significant, NS: Not significant

Table 3: Comparison of sympathetic function tests in cigarette user and control subjects

Parameters	Cigarette user (mean±SD)	Control (mean±SD)	*P*-value
Supine SBP (mmHg)	124.37±9.57	121.03±7.76	0.14 (NS)
Supine DBP (mmHg)	71.80±8.57	71.87±7.92	0.98 (NS)
Orthostatic fall in SBP (mmHg) supine to standing	4.03±6.34	5.77±4.59	0.23 (NS)
Rise in DBP (mmHg) SHG test	6.30±2.17	11.70±4.48	0.00 (HS)

HS: Highly significant, S: Significant, NS: Not significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure

The resting heart rate was higher in smokers as compared to control subjects [Table 3] ($P = 0.000$). The results of Marshall *et al*. (1969), Grassi (1994), Lucini *et al*. (1996), Sharma (2008), and Ferdousi *et al*. (2014) are concordant with the present study results.

The 30:15 ratio was decrease in cigarette users as compared to the controls and the difference was statistically significant [Table 2 and $P < 0.000$].

Our study results are consistent with the study conducted by Behera *et al*. (2010), Swathi *et al*. (2015), Mallikarajuna *et al*. (2015), Ohta *et al*. (2016), and Kaur *et al*. (2017).

The heart rate response to deep breathing (E/I ratio) was also lower in cigarette user as compared to control [Table 1 and $P < 0.05$]. Our study results are similar with the study conducted by Malge (2015) and Kavitha *et al*. (2015).

Valsalva ratio value among cigarette users was lower than the control group [Table 2 and $P > 0.05$]. The study done by Tayade *et al*. (2014) and Birajdar *et al*. (2016) has similar findings.

Control of normal BP is a complex process. Arterial BP is a result of cardiac output and peripheral vascular resistance.

Systolic BP in supine position in cigarette user was higher than mean supine systolic BP in control subjects. Supine diastolic BP was higher in cigarette user as compared in the control subjects [Table 3 and $P > 0.05$].

A sudden change from supine to standing position leads to peripheral pooling of blood in the dependent parts. The decreased venous return to the heart was leading fall in end-diastolic volume and therefore BP decrease. In our study, mean orthostatic fall in systolic BP (after 60 s) in cigarette user was lower, as compared to control subjects [Table 3 and $P > 0.05$].

In SHG test, muscle contraction increases diastolic BP and heart rate. This is because of increased peripheral resistance due to vasoconstriction. Rise in diastolic BP will be small if there is extensive peripheral sympathetic abnormality. Efferent fibers conduct impulse to the muscle and heart, resulting in increased cardiac output, BP, and heart rate. Change in diastolic BP to sustained handgrip in cigarette user was found to be lower as compared of control subjects [Table 3 and $P < 0.000$].

Cigarette smoking provokes a complex pattern of acute autonomic changes. Smoking reduces baseline level of sympathetic activity in muscle and vagal cardiac nerve activity. This resets baroreflex responses in heart and augments sympathetically mediated baroreflex responses in muscles.

Cigarette reflects inflammatory activity on leukocyte count, exposures to oxidants toward inflammatory agents. The inflammatory response elicited by smoke of cigarette is due to protein degrading enzymes, which released by the neutrophils.[5]

Apart from chronic inflammation, smoking may lead to hyperplasia which further leads to dysplasia and in due course of time frank malignancies of oral cavity, oropharynx, gastrointestinal tract, respiratory tract, urogenital tract, etc.

Imbalance of sympathovagal interplay may lead to cerebrovascular accident, myocardial infarction, hypertension, dyslipidemia, and arrhythmias, which may prove fatal.

Autonomic function testing should be a part of the routine clinical evaluation in smokers and can be used as a biomarker for early detection and subsequent management of cardiovascular morbidity and mortality.

Limitations

- In the present study, nicotine (alkaloid) or the epinephrine levels were not measured in blood and correlation between these parameters with autonomic changes was also not analyzed
- The acute effect of cigarette on autonomic functions was not assessed.

CONCLUSION

From our study, we concluded that cigarette smoking increases sympathetic activity and reduced parasympathetic activity when compared with non-smoker healthy subjects. Thus, the present study signifies the importance of non invasive methods for screening of autonomic function tests among cigarette smokers. The early detection is important for prevention and timely management of arrhythmias, cardiovascular diseases, and sudden death.

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