Original Article

Impact of smoking status on autonomic functions assessed by spectral analysis of heart rate variability

Sultana Ferdousi, Mehboba Ferdous, Md. Saiful Islam

Department of Physiology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Abstract

Background and Aim: Increased sympathetic activity associated with cigarette smoking has been recognized as a major independent risk factor for cardiac morbidity and mortality. This study was aimed to assess and to differentiate cardiac autonomic activity by analysis of heart rate variability (HRV) in apparently healthy male regular light, moderate and heavy cigarette smokers.

Methods: This comparative analytical study conducted in apparently healthy male regular cigarette smokers with age between 20 to 55 years. They were divided into light, moderate and heavy smokers (n=40 in each group) according to the cumulative effect of smoking calculated by pack-years. For comparison, 70 apparently healthy male non-smoker subjects were studied as control. HRV data was recorded in a controlled laboratory environment by a multichannel polyrite. Statistical analysis of data among the groups was performed by one-way Analysis of variance (ANOVA). Association of different variables with a ratio of low-frequency to high-frequency power (LF-HF ratio) was done by Pearson correlation and multivariate regression analysis was used to assess the independent contribution of smoking status to LF-HF ratio.

Results: Resting heart rate (HR) ($P < 0.001$), systolic blood pressure ($P < 0.01$), diastolic blood pressure (DBP) ($P < 0.001$) and rate pressure product (RPP) were found to be significantly high in all groups of smokers. Low frequency (LF) component, LF power expressed in normalized unit (LFnu) and LF-HF ratio were significantly ($P < 0.001$) higher in all smokers than non-smokers and were also significantly high ($P < 0.05$) in heavy smokers compared to light smokers. Total power, high frequency (HF) component and HF power expressed in normalized unit (HFnu) were found significantly ($P < 0.001$) less in all smokers compared to control and were also significantly ($P < 0.05$) low in heavy smokers compared to light smokers. HR and RPP in moderate smokers and DBP in light smokers showed a significant correlation with LF/HF ratio. LF/HF ratio showed significant and independent contribution to RPP in moderate smokers.

Conclusion: Results of this study suggest cardiac autonomic dysfunction characterized by increased sympathetic activity with attenuated cardiac vagal modulation and shift of sympathovagal balance towards strong sympathetic dominance in regular cigarette smokers, that are more prominent in heavy smokers. Significant dose-response association between cumulative smoking exposure, deranged cardiac autonomic function and increased cardiovascular stress were found in smokers.

Key words: Cigarette smoker, heart rate variability, high-frequency, low-frequency, nicotine

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INTRODUCTION

It has been reported that cigarette smoking is the strongest risk for cardiovascular (CV) disease including coronary artery disease (CAD), stroke, sudden death, peripheral artery disease and aortic aneurysm.[1] Smoking has also been termed as major independent risk factor for CAD.[2] Among several physiological mechanisms proposed for CV events due to smoking, increased sympathetic activity is the most important one.[2] In addition, strong relationship between cigarette smoking and decreased cardiac vagal activity with increased cardiac death has been reported.[3] Moreover, decreased cardiac vagal activity and consequent increased sympathetic activity have also been observed as short-term effect of cigarette smoking.[4]

In several studies, changes in cardiac autonomic nerve function were attributed to cigarette smoking of varying intensity.[5-7] In clinical practice, heart rate variability (HRV)

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Address for correspondence: Dr. Sultana Ferdousi, Department of Physiology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. E-mail: sferdousiratna@gmail.com

has been used as a valuable non-invasive tool to assess autonomic CV dysfunctions.[8] In HRV analysis, total power (TP), high-frequency (HF) component, HF power expressed in normalized unit (HFnu) reflect parasympathetic or cardiac vagal activity, whereas low-frequency (LF) component, LF power expressed in normalized unit (LFnu) depict sympathetic activity and ratio of LF to HF power (LF-HF ratio) represents sympathovagal balance (SVB).[8-11] HRV analysis has been used for assessing autonomic dysfunctions in smokers.[4,6,12]

Recently, rate pressure product (RPP) that assesses cardiac work load has been proposed as a marker of CV risk.[13-16] The RPP is an index of myocardial oxygen consumption.[13,15] RPP is the product of heart rate (HR) and systolic blood pressure (SBP), which measures the stress put on cardiac muscle requiring energy for myocardium depicting cardiac work.[14] In previous studies change in RPP was correlated with change in myocardial blood flow.[13-15] Thus, RPP has been used as a non-invasive method for assessing myocardial work load and stress.

It was observed that HRV was lower in smokers who smoke more than 10 cigarettes/day compared to smokers who smoke less than 10 cigarettes/day.[17] Most of the reports on comparison of autonomic function between heavy smoker and non-smoker have found a significant increase in LF power, LFnu and LF-HF ratio in heavy smokers compared with the controls.[6,7,18] However, published data on the cumulative effect of smoking assessed by pack-years on HRV in light, moderate and heavy smokers is lacking. Further, the reports on the degree of autonomic imbalance and the CV risks in these three categories of smokers are inadequate. Therefore, this study was designed to find out the relative impact of cumulative cigarette smoking exposure on cardiac autonomic function and CV risks among light, moderate and heavy cigarette smokers.

MATERIALS AND METHODS

This comparative analytical study was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from July 2011 to June 2012. The protocol of this study was approved by the institutional review board of BSMMU. A total of 120 apparently healthy male current regular cigarette smokers as described earlier,[19,20] aged 20-55 years were enrolled for this study by simple random sampling. On the basis of information about smoking habit and cumulative effects of smoking exposure (pack-years) and after matching the age and body mass index (BMI), study group subjects were divided into light smoker consisting of 40 smokers between 0.1 and 20 pack-years, moderate smoker consisting of 40 smokers between 20.1 and 40 pack-years, and heavy smoker consisting of 40 smokers with >40 pack-years.[21] Pack-years was calculated by the following formula:[22]

$$\text{No. of pack-years} = \frac{\text{No. of cig. smoked per day} \times \text{no. of years smoked}}{20}$$

Totally 70 healthy male non-smoker subjects served as control group. Subjects were selected from hospital staff, patient's attendants, motor vehicle drivers, medical college staff from BSMMU campus. Smokers with history of CAD, active respiratory infection, diabetes mellitus, consumption of other tobacco products, thyroid disorder, renal or hepatic dysfunction, taking drugs affecting autonomic nervous system or any psychiatric illness were excluded from the study.

Selected subjects were informed about the aim, benefit and risk of the study before enrollment and an informed written consent was obtained from the volunteers. All the subjects were asked to report to the Department of Physiology, BSMMU at about 9 am. For recording HRV parameters, subjects were advised to finish their meal by 9:00 pm on the previous night, to be free from any physical or mental stress, refrain from smoking at least 12 h before the study, not to take any sedatives or drugs known to affect nervous system and to have a sound sleep at night. On the test day, the subjects had a light breakfast without tea or coffee. All examinations were carried out in the autonomic function testing laboratory in the Department of Physiology, BSMMU between 9:00 am and 2:00 pm in a controlled laboratory environment. On arrival, personal and medical history was collected and a through clinical examination of all subjects was done and all the information were recorded in a prefixed data schedule. Height and weight were measured and BMI was calculated. Before recording HRV data, BP was recorded in supine position after 15-20 min rest, using sphygmomanometer (Alrk-2, Tokyo, Japan) on 3 occasions 5 min apart and the average values of SBP, diastolic blood pressure (DBP) were recorded and mean arterial pressure was calculated. Thereafter, 5 min lead II electrocardiogram was recorded for short-term HRV analysis, as per the recommendation of task force[8] by a multichannel Recorder and Medicare Systems digitized polygraph (Polyrite D version 2.2; RMS Pvt. Ltd., Chandigarh, India). The value of mean HR, the power spectral measures of HRV was obtained from the automated software. RPP were calculated as SBP × HR/100.[13,23]

Statistical analysis

All data were expressed as mean ± standard errors of the mean and were evaluated by Statistical Package for Social Sciences (SPSS) version 12 (SPSS Software Inc, Chicago, IL, USA). For statistical analysis, one-way

Analysis of variance (ANOVA) and *post-hoc* Tukey was used to compare means between the groups. The association of LF/HF ratio with age, BMI, BP and RPP was tested by Pearson correlation coefficient test. Multivariate linear regression analysis assessed the independent contribution of LF/HF ratio to RRP in different groups and also odds ratio (OR) was calculated in different groups to assess the strength of association between sympathovagal imbalance (SVI) and cigarette smoking status. $P < 0.05$ was considered to be statistically significant.

RESULTS

The demographic, anthropometric, CV and power spectral HRV data obtained in non-smokers and difference degree of smokers are summarized in Table 1.

No significant differences were observed for age and BMI among different groups of smokers and non-smokers as well as within the smoker groups [Table 1]. All CV parameters were significantly increased in all categories of smokers in comparison to non-smokers. However, these CV variables were not statistically significant when compared within the light, moderate and heavy smoker groups except for HR and RPP that were significantly increased in heavy smokers compared to light smokers [Table 1].

Among the HRV parameters, TP, HF and HFnu were significantly reduced and LF, LFnu and LF/HF ratio were significantly increased in all smoker groups compared to the control group. Furthermore, TP, HF and HFnu were found significantly lower and the LF, LFnu and LF/HF were significantly increased in heavy smokers compared to light smokers. Moreover, LF/HF ratio was found significantly increased in heavy smokers than that of moderate smoker group. No statistically significant difference was found when data were compared between light and moderate or moderate and heavy smokers, except the LF/HF ratio, which was more in heavy smokers compared to light and moderate smokers [Table 1].

Results of Pearson correlation analysis exploring the relationship of SVB with age, BMI, HR, SBP, DBP and RPP are presented in Table 2. Only the HR and RPP in moderate smokers and DBP in light smokers showed significant correlation with LF/HF ratio. Results of multiple regression analysis demonstrated significant and independent contribution of LF/HF ratio to RPP in moderate smokers [Table 3]. OR was calculated to assess the risk association between SVI and smoking status and the results showed significant and consistently increased CV risk association in different degree of smokers, which was maximum in heavy smokers [Table 4].

DISCUSSION

The current study evaluated cardiac autonomic status by analyzing HRV and CV risks in apparently healthy light, moderate and heavy current regular male cigarette smokers. Decreased vagal tone and HRV suggested by lower HF, HFnu, TP and increased cardiac sympathetic drive reflected by higher LF, LFnu and also SVI evidenced by significantly higher LF/HF ratio were noted in all smoker groups,[9] that are in agreement with other studies that reported only in heavy smokers.[5-7,18] The novelty of the present work is that we have compared autonomic dysfunctions and CV risks in different grades of smokers, which has not been studied by others. In

Table 1: Age, BMI, HR, BP, RPP and HRV parameters in different groups of smokers expressed in mean (±SEM)

Parameters	Control (*n*=70)	Light (*n*=40)	Moderate (*n*=40)	Heavy (*n*=40)
Age (years)	32.3±0.97	31.9±1.25	32.25±1.16	33.5±1.18
BMI (kg/m^2)	26.67±0.43	26.54±0.57	26.19±0.5	26.06±0.45
HR (beats/min)	72.83±0.66	77.13±1.81**	78.3±1.92**	82.7±1.85***#
SBP (mmHg)	112±0.98	119.12±1.73*	122.5±1.66*	123.33±1.77**
DBP (mmHg)	70±0.91	74.4±1.55*	75.05±1.11**	76.6±1.01***
MAP (mmHg)	84±0.94	89.31±1.64*	90.87±1.38***	92.84±1.39***
RPP (mmHg/min)	78.50±1.9	91.96±2.9***	95.71±2.9***	101.93±2.9***##
HRV parameters				
TP (ms^2)	3347.97±101.03	2950.3±157.34*	2867.3±142.4*	2505.76 ± 128.82***#
LF (ms^2)	671.70±38.36	792.42±50.15	840.97±46.77	977.32 ± 59.0***#
HF (ms^2)	584.46±29.42	495.68±35.36*	467.57±31.03**	392.91 ± 29.6***#
LFnu	54.4±0.96	70.87±1.39***	73.15±1.16***	74.97 ± 1.21***#
HFnu	45.60±0.96	29.13±1.39***	26.85±1.16***	25.03 ± 1.21***#
LF/HF ratio	1.22±0.05	1.72±0.1***	1.99±0.12***	2.70 ± 0.14******###††

P>0.05 *The depicts comparison with control group, **P*<0.05, ***P*<0.01, ****P*<0.001, #The depicts comparison with light smoker, #*P*<0.05, ##*P*<0.01, ###*P*<0.001, †The depicts comparison with moderate smoker, †*P*<0.05, ††*P*<0.01. Statistical analysis was done by ANOVA followed by post-hoc Tukeys test among 4 groups. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, RPP: Rate pressure product, BMI: Body mass index, BP: Blood pressure, HRV: Heart rate variability, SEM: Standard errors of the mean, TP: Total power, LF: Low-frequency, HF: High-frequency, LFnu: Normalized low-frequency power, HFnu: Normalized high-frequency power, LF/HF ratio: Low and high-frequency components

Table 2: Correlation of LF/HF ratio with age, BMI, HR, SBP, DBP and RPP among non-smokers and different groups of smokers

Parameters	Control		Light		Moderate		Heavy	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age (year)	−0.000	0.99	0.151	0.42	0.04	0.79	−0.02	0.91
BMI (kg/m^2)	0.091	0.46	−0.13	0.49	−0.081	0.67	0.081	0.67
HR (bpm)	−0.06	0.62	0.30	0.10	0.381*	0.03	0.20	0.28
SBP (mmHg)	0.18	0.12	−0.06	0.72	0.17	0.36	−0.35	0.05
DBP (mmHg)	0.04	0.71	−0.44*	0.01	−0.20	0.28	0.24	0.19
RPP (mmHg/min)	0.08	0.51	0.22	0.23	0.441*	0.01	−0.01	0.94

*P<0.05 was considered significant. LF/HF ratio: Low and high-frequency components, BMI: Body mass index, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RPP: Rate pressure product

Table 3: Multiple regression of LF/HF ratio (independent variable) with rate pressure product (dependent variable) in controls and smoker groups

Parameters	Regression coefficient β	95% confidence interval		*P* value
		Lower limit	Upper limit	
Control	−0.126	−1214.052	388.992	0.308
Light	0.222	−4.413	17.302	0.238
Moderate	0.441	2.026	17.030	0.015*
Heavy	−0.014	−7.513	7.005	0.943

*P<0.05 considered significant. LF/HF ratio: Low and high-frequency components

Table 4: Multivariate logisistic regression analysis for prediction of sympathovagal imbalance (LF/HF ratio) by smoking status in different groups of smokers adjusted for age, gender and BMI

Smoking status	OR	95% confidence interval		*P* value
		Lower limit	Upper limit	
Light	1.7	1.3	5.3	0.038
Moderate	3.2	1.6	7.4	0.002
Heavy	5.6	1.9	11.5	<0.001

P<0.05 was considered significant. LF/HF ratio: Low and high-frequency components, BMI: Body mass index, OR: Odds ratio

the present study, these significant autonomic changes were more pronounced in heavy smokers compared to light smokers. The reliability of these cardiac autonomic dysfunctions in different categories of smokers based on packs per year is further supported by the increased trend of BP in all smokers and significant increase in HR and RPP in heavy smokers compared to light smokers. The characteristic autonomic changes in cigarette smokers have been suggested to be resulting from the effect of consumption of nicotine and other substances contained in cigarette smoke.[3,5-7,18,22] The cumulative effect of smoking exposure was obvious from the magnitude of changes in HRV and CV parameters in heavy smokers in comparison to light smokers who were chronically exposed to higher dose of nicotine and other tobacco components of cigarettes; and the changes were less evident in light smokers, which could suggest the possibility of a dose-response relationship between smoking habit and autonomic dysfunction.[21]

LF/HF ratio has been used as an index of SVB which characterizes autonomic state resulting from the interaction of sympathetic and vagal influences on sinoarterial node.[24,25] Increased value of LF/HF ratio representing SVI in prehypertensives has been reported to be closely linked to CV risk in patients suffering from even non-cardiac disease.[16,26] Autonomic imbalance in smokers can be linked to the effect of nicotine-mediated stimulation of autonomic ganglia and adrenal medulla resulting in increased discharge in cardiac sympathetic fibers, increased release of catecholamine, muscle sympathetic nerve excitation and increased peripheral chemoreceptor sensitivity.[6,27-29] This enhanced sympathetic activity increases HR, BP and myocardial contractility by acting on β_1 adrenergic receptor and also increases coronary vasomotor tone by acting on α_2 adrenoceptor.[27-30] In chronic nicotine abuse, baroreflex centers are directly affected in the brainstem that reduces afferent baroreceptor sensitivity and results in elevated sympathetic tone.[31]

In the present study, in addition to the presence of SVI, there was increased CV risk in all categories of smokers as there was increase in RPP in all the three smoker groups. Further, increase in LF-HF ratio was associated with an increase in RPP in moderate smoker group [Table 3] suggesting a direct link of SVI with CV risk in moderate smoker. As this association was not significant in heavy smokers, it appears that some other factors contribute to increased RPP (cardiac stress) in heavy smokers. Nevertheless, the degree of smoking status was associated with the severity of SVI as OR used for prediction of smoking status to LF-HF ratio was progressively more from light to heavy smokers [Table 4]. Smoking causes impaired SVB due to high nicotine concentration that impairs baroreceptor sensitivity, which is also a known CV risk. In addition to the direct nicotinic effect, the increased release of neuropeptide Y as a part of physiological adjustment for autonomic balance might cause suppression of cardiac vagal tone contributing to the reduced vagal modulation in smokers.[31]

The association of CV risk parameters such as increased HR, BP and RPP with decreased HRV has been assessed in this work in different group of smokers, which is the novelty of this study. Furthermore, results of logistic regression analysis indicate significant association of SVI with smoking status, which indirectly reflects the dose-response relationship of smoking with SVI. Increased RPP is a known predictor of CV risk,[14-16] that reflects increased myocardial oxygen demand and

stress.[14] The increased RPP in smokers could explain the nicotine-induced sympathetic overactivity causing increased coronary vasomotor tone by acting on α_2 adrenoceptors.[28] It is noteworthy that significant rise of RPP in all smoker and its significant contribution to SVI indicates CV risk is high in smokers especially in moderate smoker group. Thus, the results of the present study suggest impaired CV neural regulation and increased myocardial work stress in smokers, which could herald the danger of adverse CV events.

Limitations of the study

We have not studied the CV autonomic reactivity tests and direct myocardial stress assessed by cardiac imaging system. Furthermore, we have not assessed the association of plasma nicotine with SVI in different group of smokers.

CONCLUSION

Cardiac autonomic dysfunction characterized by increased sympathetic activity with concomitant suppression of cardiac vagal modulation was evident in all the three groups of regular cigarette smokers. Significant association between cumulative smoking exposure and deranged cardiac autonomic function with increased CV stress were found in these smokers, which was more marked in heavy smokers. Considering public health and high prevalence of cigarette smoking, vigorous efforts of tobacco control program may be required in reducing the incidence of CV morbidity in smokers.

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