Influence of Heavy Cigarette Smoking on Heart Rate Variability and Heart Rate Turbulence Parameters

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Background: Cigarette smoking increases the risk of cardiovascular events related with several mechanisms. The most suggested mechanism is increased activity of sympathetic nervous system. Heart rate variability (HRV) and heart rate turbulence (HRT) has been shown to be independent and powerful predictors of mortality in a specific group of cardiac patients. The goal of this study was to assess the effect of heavy cigarette smoking on cardiac autonomic function using HRV and HRT analyses.

Methods: Heavy cigarette smoking was defined as more than 20 cigarettes smoked per day. Heavy cigarette smokers, 69 subjects and nonsmokers 74 subjects (control group) were enrolled in this study. HRV and HRT analyses [turbulence onset (TO) and turbulence slope (TS)] were assessed from 24-hour Holter recordings.

Results: The values of TO were significantly higher in heavy cigarette smokers than control group (-1.150 ± 4.007 vs -2.454 ± 2.796, $P = 0.025$, respectively), but values of TS were not statistically different between two groups (10.352 ± 7.670 vs 9.613 ± 7.245, $P = 0.555$, respectively). Also, the number of patients who had abnormal TO was significantly higher in heavy cigarette smokers than control group (23 vs 10, $P = 0.006$). TO was correlated with the number of cigarettes smoked per day ($r = 0.235$, $P = 0.004$). While LF and LF/HF ratio were significantly higher, standard deviation of all NN intervals (SDNN), standard deviation of the 5-minute mean RR intervals (SDANN), root mean square of successive differences (RMSSD), and high-frequency (HF) values were significantly lower in heavy smokers. While, there was significant correlation between TO and SDNN, SDANN, RMSSD, LF, and high frequency (HF), only HF was correlated with TS.

Conclusion: Heavy cigarette smoking has negative effect on autonomic function. HRT is an appropriate noninvasive method to evaluate the effect of cigarette on autonomic function. Simultaneous abnormal HRT and HRV values may explain increased cardiovascular event risk in heavy cigarette smokers.

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heart rate turbulence; cigarette

INTRODUCTION

Cigarette smoking is a major cardiovascular risk factor. Smoking may lead to myocardial infarction, stroke, and sudden death by several mechanisms.[1] Smoking increases sudden death risk more than tenfold in men and fivefold in women.[2] Increased sympathetic nervous system activity is one of the factors suggested to be responsible for the effects of smoking.[3] However, previous studies that used heart rate variability (HRV) showed conflicting results about the effect of cigarette on autonomic nervous system.[4,5] Heart rate turbulence (HRT) is a novel noninvasive method to assess autonomic function. HRT has been shown to be a greater predictive power than HRV on mortality.[6] No studies have previously evaluated HRT analysis in heavy cigarette smokers. Therefore, the goal of this study

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was to assess the effect of heavy cigarette smoking on cardiac autonomic function using HRV and HRT analyses and to determine the association between HRT and HRV parameters.

MATERIAL AND METHODS

Study Group

This study was performed in Ministry of Health Diskapi Yildirim Beyazit Research and Educational Hospital and Yuksek Ihtisas Heart-Education and Research Hospital from June 2007 to May 2008. A total of 4875 Holter recordings were evaluated for ventricular premature beat presence. For the measurement of HRT parameters during echocardiography, recordings having at least 500 ventricular premature complex (VPCs)/day were chosen for the evaluation. However, after removal of patients with exclusion criteria, only 143 subjects were included in the study. Therefore, 69 healthy long-term heavy smokers (41 females, 28 males, with mean age of 42.36 ± 7.84 years) and age- and sex-matched 74 nonsmokers (50 females, 28 males, with age of 41.38 ± 8.65 years) were enrolled in the study. Heavy cigarette smoking was defined as more than 20 cigarettes smoked per day.

The subjects who had hypertension, diabetes mellitus, coronary artery disease, valvular heart diseases or other structural heart disease, lung diseases and/or pulmonary HT, renal diseases, collagen diseases, rhythms other than sinus, abnormal thyroid function, or serum electrolyte values were excluded from the study. In addition, subjects who had not any VPC to measure HRT were excluded from the study. Also, the subjects who use drugs that may influence HRT parameters were excluded from the study. All subjects were not allowed to drink alcohol and any caffeinated beverages during the study.

Transthoracic echocardiography was performed using Vingmed Vivid 3 (Horten, Norway) echocardiograph and a 2.5 MHz transducer to determine underlying structural heart disease before the study.

A written consent was obtained from all patients and our local ethical committee approved the study.

HRT Analysis

All subjects underwent 24-hour Holter monitoring. Holter ECGs were carefully analyzed by expert cardiologists blinded to the study using DMS CardioScan Holter system (DM Soft-ware., Inc., Stateline, NV, USA). HRT parameters were calculated using an algorithm adapted from the web page popularizing noncommercial use of HRT (http://www.h-r-t.org). In HRT analysis, two numerical descriptors were estimated: TO and TS. TO is the amount of sinus acceleration following a VPC, TS is the rate of sinus deceleration that follows the sinus acceleration. TO is expressed as a percentage and is calculated with the following formula: $TO\ (\%) = 100 \times [(RR_1 + RR_2) - (RR_{-1} + RR_{-2})]/(RR_{-1} + RR_{-2})$, where RR_1 and RR_2 are the first and second sinus RR intervals after the VPC, and RR_{-1} and RR_{-2} are the first and second sinus intervals preceding the VPC. TS was calculated as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after a VPC. TS was calculated based on the averaged tachogram. Filtering algorithms were used to eliminate inappropriate RR intervals and VPCs with overly long coupling intervals or overly short compensatory pauses. Filtering algorithms excluded from the HRT calculation RR intervals with the following characteristics: <300 ms, >2000 ms, >200 ms difference to the preceding sinus interval, and $>20\%$ difference to the reference interval (mean of the five last sinus intervals). In addition, these algorithms limit the HRT calculation to VPCs with a minimum prematurity of 20% and a postextrasystole interval that is at least 20% longer than the reference interval (mean of last five sinus RR intervals). TO $\geq 0\%$ and TS ≤ 2.5 ms/beat are described as abnormal.

HRV Analysis

The HRV analysis was assessed over a 24-hour period. The time- and frequency-domain analyses of HRV were performed according to the recommendation of the task force.[7] For the time domain, standard deviation of all NN intervals (SDNN), standard deviation of the 5-minute mean RR intervals (SDANN), and root mean square of successive differences (RMSSD) were measured. For the frequency domain, analysis power spectral analysis based on the Fast Fourier transformation algorithm was used. Three components of power spectrum were computed following bandwidths: HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), and the LF/HF ratio.

Table 1. Clinical Characteristics of the Study Subjects

	Heavy Smokers Group	Control Group	P Value
Age (years)	42.36 ± 7.84	41.38 ± 8.65	0.468
Men, n (%)	28 (37.8%)	24 (32.4%)	0.491
Body mass index (kg/m^2)	25.27 ± 2.54	24.73 ± 2.20	0.169
Systolic BP (mmHg)	128.24 ± 16.85	126.35 ± 14.00	0.459
Diastolic BP (mmHg)	79.53 ± 9.62	78.31 ± 5.63	0.350
Cigarettes/day	22.40 ± 2.94	–	
Duration of smoking (years)	8.80 ± 2.93	–	
Left ventricular EF (%)	64.41 ± 6.75	64.08 ± 4.98	0.740
Mean heart rate (beats/min)	77.76 ± 7.17	76.01 ± 9.02	0.195
Ventricular premature contraction/day	782.03 ± 1827.41	808.46 ± 1323.58	0.920

BP = blood pressure; EF = ejection fraction.

Statistical Analysis

Results were reported as mean ± standard deviation and percentages. Continuous variables were analyzed with Student's *t*-test. Categorical variables were compared by using chi-square test. The relation between the number of years of smoking and the number of cigarettes smoked per day and HRT parameters were assessed by Pearson's correlation coefficient. Also, association between HRV and HRT parameters were assessed by Pearson's correlation coefficient. A value of $P < 0.05$ was considered statistically significant. SPSS-15.0 for Windows statistical software package program (SPSS Inc, Chicago, IL, USA) was used for statistical analyses.

RESULTS

Clinical characteristics of two groups were shown in Table 1. Age, sex, body mass index, systolic and diastolic blood pressures, left ventricular ejection fraction, mean heart rate, and mean ventricular premature contraction were not significantly different between two groups. The results of the HRT parameters were shown in Table 2. The values of TO were significantly higher in heavy smokers group than control group (-1.150 ± 4.007 vs -2.454 ± 2.796, $P = 0.025$, respectively), but values of turbulence (TS) were not statistically different between two groups (10.352 ± 7.670 vs 9.613 ± 7.245, $P = 0.555$, respectively). When value >0% for TO and <2.5 ms/beat for TS, proposed by Schmidt et al.,[6] was used as abnormal HRT values, the number of subjects who had abnormal TO was significantly higher in heavy smokers group than control group (23 vs 10, $P = 0.006$). However, the number of subjects who had abnormal TS was not different in both groups. Correlation analyses revealed a significant association between TO and the number of cigarettes smoked per day ($r = 0.235$, $P = 0.004$) (Fig. 1). But, there was no correlation between TS and the number of cigarettes smoked per day (Fig. 2). Also, no correlation was found between the duration of cigarette smoking and each HRT parameters.

The results of the HRV parameters were shown in Table 3. While LF and LF/HF ratio were significantly higher, SDNN, SDANN, RMSSD and HF values were significantly lower in heavy smokers. While, there was significant correlation between TO and SDNN, SDANN, RMSSD, LF, and HF, only HF was correlated with TS. (Table 4, Fig. 3).

DISCUSSION

To our knowledge, this is the first study to evaluate the effect of cigarette smoking on cardiac autonomic function by HRT analyses. In our study, we found that mean TO values and the number of subjects who had abnormal TO were significantly

Table 2. Results of Heart Rate Turbulence (HRT) Analyses

	Heavy Smokers Group	Control Group	P Value
TO (%)	−1.15 ± 4.01	−2.45 ± 2.80	0.025
TS (ms/beat)	10.35 ± 7.67	9.61 ± 7.24	0.555
Abnormal TO, n (%)	23 (33)	10 (14)	0.006
Abnormal TS, n (%)	12 (17)	10 (14)	0.521

TO = turbulence onset; TS = turbulence slope.

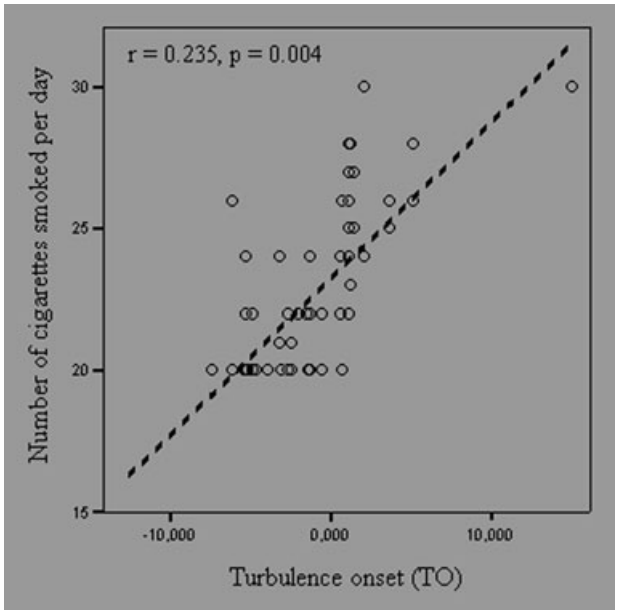

Figure 1. Correlation between turbulence onset (TO) and the number of cigarette smoked per day.

different in heavy smoker subjects from controls. The numbers of cigarettes smoked per day were positively correlated with TO values. In addition, cigarette smoking causes an increase in LF and LF/HF ratio, while a decrease in SDNN, SDANN,

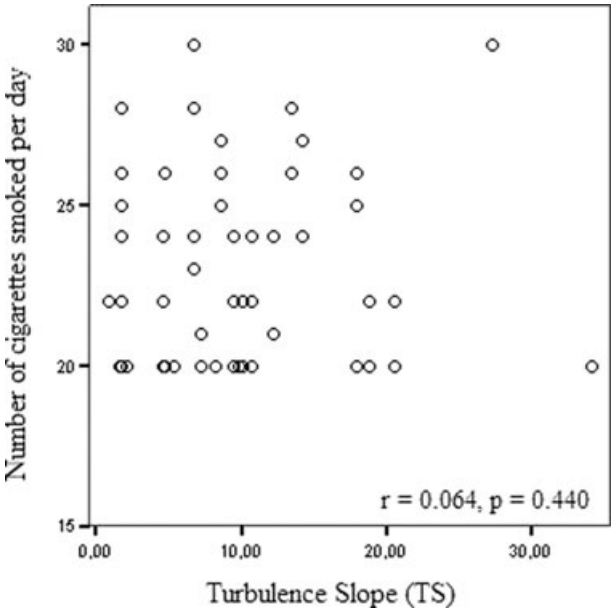

Figure 2. Correlation between turbulence slope and the number of cigarette smoked per day.

Table 3. Results of Heart Rate Variability (HRV) Parameters

	Heavy Smokers Group	Control Group	P Value
SDNN (ms)	108.7 ± 22.5	133.4 ± 24.2	<0.001
SDANN (ms)	99.2 ± 20.3	121.4 ± 23.5	<0.001
RMSSD (ms)	28.4 ± 16.3	42.4 ± 14.2	<0.001
LF (ms^2)	691.0 ± 362.0	441.5 ± 310.1	<0.001
HF (ms^2)	140.2 ± 95.4	261.0 ± 223.3	<0.001
LF/HF	5.5 ± 1.9	1.9 ± 0.6	<0.001

SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the 5-minute mean RR intervals; RMSSD = root mean square of successive differences; LF = low frequency; HF = high frequency.

RMSSD, and HF. Also, it was observed that, TO was significantly correlated with SDNN, SDANN, RMSSD, LF and HF, but only HF was correlated with TS.

Cigarette smoking is an important risk factor for cardiovascular disease. There are several mechanisms suggested about hazardous effects of smoking on cardiovascular events. One of these suggested mechanisms is a smoking-initiated activation of the sympathetic nervous system.[3] Hayano et al. have demonstrated that smoking causes an acute and transient decrease in vagal cardiac control, and that heavy smoking causes long-term reduction in vagal cardiac control and blunted postural responses in autonomic cardiac regulation.[8] Alyan et al. have showed that smoking causes a significant increase in sympathetic activity and impairs sympathovagal balance.[9] Previous studies that evaluated the effect of smoking on cardiac autonomic function, usually used HRV analysis.[4,5,9–11] Conflicting results have been reported in these studies.[4,5] Kageyama et al. showed that smoking was not associated with HRV parameters.[4] In contrast, Eryonucu et al. found that HRV parameters were significantly lower in smokers than in nonsmokers.[5] Therefore, we used HRT analysis to investigate the effect of smoking on autonomic function.

HRT is a marker of autonomic function, defined as initial acceleration and a subsequent deceleration of sinus rhythm following a ventricular premature complex. HRT is relatively new noninvasive test and is considered to reflect increased sympathetic tone and abnormal baroreflex sensitivity.[12,13] First in 1999, Schmidt et al. introduced HRT, since than HRT has been used to assess

Table 4. Correlation between HRT and HRV Parameters

HRV Parameters	Turbulence Onset	Turbulence Slope
SDNN	r = −0.691, P < 0.001	r = 0.090, P = 0.285
SDANN	r = −0.658, P < 0.001	r = 0.100, P = 0.235
RMSSD	r = −0.220, P = 0.008	r = 0.027, P = 0.746
LF	r = 0.721, P < 0.001	r = −0.118, P = 0.161
HF	r = −0.436, P < 0.001	r = 0.241, P = 0.004

SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the 5-minute mean RR intervals; RMSSD = root mean square of successive differences; LF = low frequency; HF = high frequency.

autonomic function and to predict sudden death in different patient groups.[14–19] Barthel et al. demonstrated that HRT was a strong predictor of subsequent death in postinfarction patients of the reperfusion era.[14] Also, HRT has been shown to be an independent and powerful predictor of mortality after myocardial infarction, with greater predictive power than HRV.[6] Jeron et al. showed that HRT was blunted in diabetic patients with autonomic dysfunction.[15] Cryer et al. have reported that plasma catecholamine levels increase within 1 minute after smoking.[20] Also, in a previous study in which HRV was used, LF/HF ratio significantly increased immediately after smoking.[21] In our study, there was a significant positive correlation between TO values and the number of cigarettes smoked per day. This finding could show acute effect of smoking on autonomic cardiac function.

In the present study, impaired HRV was also demonstrated in heavy smokers. This data suggests that sympathetic activation during cigarette smoking may be result of increased catecholamine in plasma or impaired baroreflex function. Previous studies showed that, there was a correlation between HRT and HRV parameters in a different group of cardiac patients.[13,22,23] Lindgren et al. demonstrated that TO and TS correlated with baroreflex sensitivity. In that study, TS correlated with SDNN, while only LF/HF was correlated with TS.[22] Koyoma et al. showed that, TO and TS significantly correlated with SDNN in chronic heart failure patients.[23] Also, in patients with coronary heart disease, the significant correlation between HRT and HRV parameters was observed.[13] Similarly, in our study, there was significant correlation between TO and HRV parameters. The results of this study indicate that HRT is not only related with abnormal baroreflex sensitivity, also is related with autonomic tone.

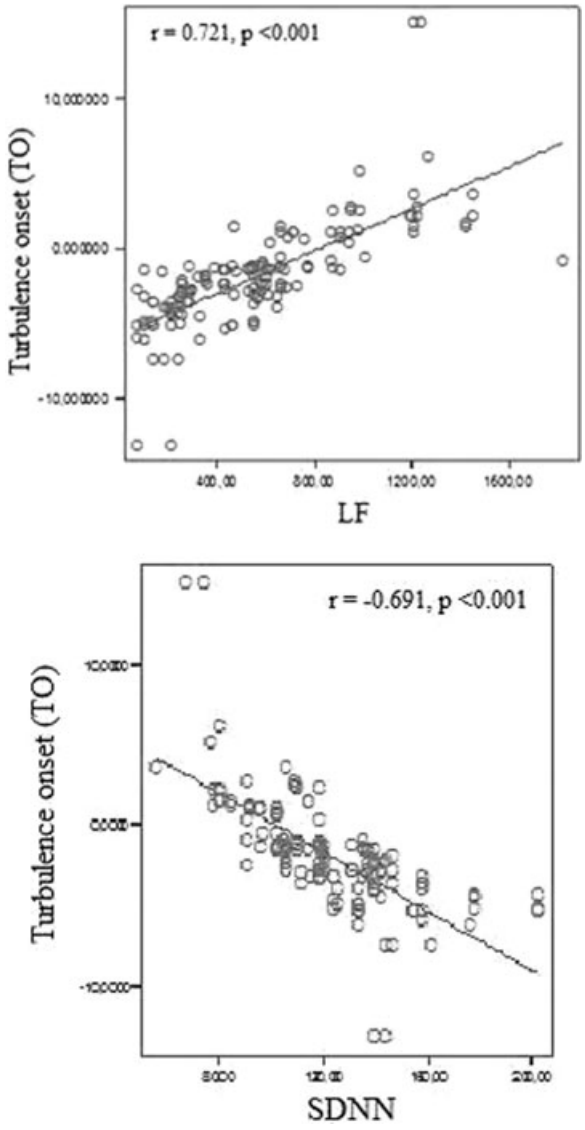

Figure 3. Relationship between TO and LF (upper panel) and SDNN (lower panel).

Study Limitations

These preliminary findings require confirmation in larger number of heavy cigarette smokers. HRT cannot be measured in subjects without VPCs, as a minimum of 15–20 sinus beats after each VPC and 3–5 beats before the VPC are required for accurate calculation of HRT.[6] Therefore, we had to exclude the subjects, who did not have any VPC, in this study. Circadian variation can influence HRT results. We could not examine circadian pattern of HRT values and mean RR intervals. In addition, it is difficult to accept that these subjects represent fully healthy cohort. Therefore generalization of our results to entire healthy population is a difficult concern.

CONCLUSION

In conclusion, heavy cigarette smoking has negative effect on autonomic function. HRT is an appropriate noninvasive method to evaluate effect of cigarette on autonomic function. Simultaneous abnormal HRT and HRV values may explain increased cardiovascular event risk in heavy cigarette smokers.

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