ABSTRACT

Introduction: Smoking has been known to cause various adverse cardiovascular reactions. Our study was conducted to demonstrate the chronic effects of smoking on baroregulatory function by using heart rate turbulence (HRT) parameters among asymptomatic smokers.

Materials and Methods: Sixty four smokers with histories of incessant smoking for at least one year (group 1) and 30 non-smokers (group 2) were enrolled in this study. Addiction of smoking was graded according to the modified Fagerström test for nicotine dependence (m-FNDT). Each smoker was conferred a nicotine dependence index (NDI) according to the m-FNDT. The values of HRT (TO: Turbulence onset, TS: Turbulence slope) were compared between two groups along with basic clinical, echocardiographic and Holter parameters. And the relationship between HRT and m-FDT was analyzed.

Results: There was no significant difference the basic clinical and echocardiographic features (p> 0.05). The mean value of TO was higher significantly (p< 0.05) in group 1 than group 2, the mean values of TS was not different significantly between the two groups. The value of NDI was positively correlated with the value of TO (p< 0.05).

Conclusion: Smoking impaired baroregulatory function especially in TO, even in asymptomatic smokers.

Key Words: Smoking; heart rate; nicotine; tobacco use disorder.

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The Effect of Smoking on the Baroregulatory System; Heart Rate Turbulence

Sigara Alışkanlığının Baroregülatuvar Sisteme Olan Etkisi; Kalp Hızı Türbülansı
INTRODUCTION
Cigarette smoking is an important and independent risk factor for cardiovascular morbidity and mortality\(^1\). Some studies suggest that smokers have a sympathetic hyperactivity compared with non-smokers\(^2,3\). Smoking increases plasma catecholamines and cardiac norepinephrine spillover and results in an increase in blood pressure, heart rate, ventricular preystole (VPC) and sympathetic outflow that all of them are potentially arrhythmogenic\(^4\). Several studies indicate an association between smoking and autonomic dysfunction\(^5,6\). Also these studies suggested that baroreflex function is impaired in normal person with smoking. Impaired cardiac autonomic function has been associated with cardiac vulnerability and may represent an important pathophysiologic mechanism linking cigarette smoking and risk of cardiac mortality. It has been shown that smoking as an independent risk factor for recurrence of sudden cardiac death (SCD)\(^7\). SCD from arrhythmia is a major cause of mortality.

Risk stratification for ventricular arrhythmias and sudden cardiac death (SCD) is enormous importance for the health care community. The major problem in risk stratification is the relative low positive predictive value of most tests such as heart rate variability parameters, QT dispersion, late potentials or programmed stimulation. Heart rate turbulence (HRT) is a relatively new parameter used as a tool for evaluating cardiac autonomic tone. Abnormal HRT reflects increased sympathetic tone and abnormal baroreflex sensitivity, both facilitate ventricular arrhythmias\(^8,9\). Also these studies showed that HRT is a valuable tool in the setting of risk stratification. Furthermore, it is easy to perform without the need for additional time-consuming tests or procedures\(^10\). Our study was conducted to demonstrate the chronic effects of smoking on baroregulatory function by using HRT parameters among asymptomatic smokers.

MATERIALS and METHODS
Patients
Sixty four smokers with histories of incessant smoking for at least 1 year (group 1, 35 males and 29 females; mean age, 29.9 ± 6.6 years) and thirty non-smokers (group 2, hospital staff; 16 males and 14 females; mean age, 29.0 ± 6.1 years) were enrolled in this study. A complete physical and echocardiographic examination was performed before the study. Routine 12-lead electrocardiography (ECG) of the patients was also evaluated prior to the ambulatory rhythm monitoring. All study subjects were free from the other risk factors for coronary artery disease (hypertension, diabetes mellitus, etc.), and no subject was receiving any medication. Informed consent was obtained from all patients and the protocol was approved by the ethics committee. All participants were asked to refrain from alcohol and caffeine-containing beverages and strenuous exercise for 24 hours prior to study and during 24 hours holter recording. All smokers were also asked not to smoke cigarettes for at least 8 hours before the study and during holter recording.

Fagerström Test for Nicotine Dependence
Addiction of smoking was graded according to the modified Fagerström test for nicotine dependence (m-FNNDT)\(^11\). Each smoker was conferred a nicotine dependence index (NDI) according to the m-FNNDT.

Measurement of Heart Rate Turbulence
24-hour Holter recordings of all patients were analyzed to obtain the HRT parameters of TO and TS. Recordings
were performed with a GE Marquette SEER system digitizing at 125 samples per second (GE Marquette, Milwaukee, WI). QRS detection, morphology classification (normal, aberrant, premature aberrant) and measurement of the RR interval were automatically performed by the system. All Holter files were reviewed and manually corrected.

HRT analysis was performed on sequences of sinus RR intervals after VPB. The evaluated sinus rhythm immediately before and after the VPB was free from any arrhythmia or other artifacts. HRT after a VPB comprises two parameters: TO, which represents the initial acceleration (shortening of R-R intervals); and TS, which represents the subsequent deceleration (prolongation of R-R intervals)\(^{(12)}\). In mathematical terms, TO (\(\%\)) (normal < 0) is the difference between the sum of the first two R-R intervals after the compensatory pause following a VPB and the sum of the last two R-R intervals preceding the VPB, divided by the sum of the last two R-R intervals preceding the VPB. TS (normal > 2.5 ms/R-R interval number) was accepted as the steepest regression line between the R-R interval count and the duration. The average of HRT values measured for all convenient VPBs was accepted as the final HRT value to characterize the patient.

For the risk stratification HRT values are classified into three categories:

1. Category 0; TO and TS are normal,
2. Category 1; 1 of TO or TS is abnormal,
3. Category 2; both TO and TS are abnormal.

If HRT cannot be calculated because no or too few suitable VPC tachograms are found in the recording, patients who are otherwise in sinus rhythm are classified as HRT category 0\(^{(9,10,13)}\).

The presence of potential causes of impaired HRT including CHF, moderate or severe degrees of any valvular regurgitation or co-existent valvular stenosis, previous MI, angina or angina-like symptoms, diabetes mellitus and obstructive sleep apnea, were accepted as exclusion criteria. Those patients with pacemaker rhythm, atrial fibrillation (AF), left bundle branch block, right bundle branch block, any sign of ischemia on the initial ECG and echocardiographic evidence of LV hypertrophy, systolic dysfunction, wall motion abnormalities or pericardial disease were also excluded from the study.

**Statistical Analysis**

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using student t-test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson correlation coefficients examined the degree of association between examined variables. \(p\) value < 0.05 was considered as significant. The variables for which the unadjusted \(p\) value was < 0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. \(p\) value < 0.05 was considered as significant and confidence interval (CI) was 95%. All statistical analyses were performed with the SPSS version 15 (SPSS, Inc., Chicago, Illinois).

**RESULTS**

Clinical characteristics of both groups are shown in Table 1. There was no significant difference between two groups in demographics of age, blood pressure, and body mass index \((p>0.05)\). On physical examination, no clinically significant disorder was detected in any of the study subjects. Echocardiographic examination revealed no significant cardiac disorder. All study subjects had sinus rhythm. The 24 hour baseline heart rate tended to be significantly higher in smokers than in non-smokers \((76.25 \pm 6.67 \text{ vs. } 71.87 \pm 7.44 \text{ beats/min, } p<0.001)\). Between the Holter parameters, group 1 patients had a significantly higher mean TO value than group 2 \((\text{group 1: } 0.89 \pm 0.5, \text{ group 2: } 0.08 \pm 0.06; p<0.001)\), whereas mean TS values was smaller in group 1 than group 2, but not significantly \((\text{group 1: } 2.41 \pm 3.06, \text{ group 2: } 3.14 \pm 2.33; p=0.212)\). In heart rate turbulence analyses, turbulence onset values was > 0% in 48 patient in Group 1, and six patient in Group 2 \((p<0.05)\), turbulence slope values was < 2.5 ms/R-R 20 patient in Group 1, and four patient in Group 2 \((p<0.05)\). When HRT parameters were compared to the risk stratification categories, there were significant differences between smokers and non-smokers for all categories \((p<0.05)\). (Figure 1). The mean value of m-FNDT score in smoking group was found to be 4.61 ± 2.28, while the mean value of smoking duration was 3.81 ± 2.08 years. In the risk stratification categories analyses, m-FNDT score was 2.14 ± 1.08 in category 0, 4.31 ± 1.51 in category 1 and 7.06 ± 1.70 in category 0. A significant relationship
A strong positive correlation was also found between the value of NDI and the value of TO (r = 0.845, p < 0.001).

**DISCUSSION**

The principal findings of our study are:

I. Smoking group had a significantly higher mean TO value when compared to non-smokers;

II. When HRT parameters were compared to the risk stratification categories, there were significant differences between smokers and non-smokers;

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Table 1. The comparison of general features, echocardiographic and Holter parameters between group 1 (smoking) and group 2 (non-smoking) patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Smokers (n= 64)</th>
<th>Non-smokers (n= 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>29.9 ± 6.6</td>
<td>29.0 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male) %*</td>
<td>54.7%</td>
<td>53.3%</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>23.54 ± 3.17</td>
<td>23.86 ± 3.22</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)*</td>
<td>110.17 ± 14.14</td>
<td>105.50 ± 11.32</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)*</td>
<td>65.70 ± 9.18</td>
<td>65.33 ± 6.68</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)*</td>
<td>76.25 ± 6.67</td>
<td>71.87 ± 7.44</td>
<td>p = 0.008</td>
</tr>
<tr>
<td>LVEF (%)*</td>
<td>61.32 ± 5.23</td>
<td>61.92 ± 5.68</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (cm)*</td>
<td>4.32 ± 0.31</td>
<td>4.28 ± 0.33</td>
<td>NS</td>
</tr>
<tr>
<td>TO (%)*</td>
<td>0.89 ± 0.5</td>
<td>0.08 ± 0.06</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>TS (ms/beat)*</td>
<td>2.41 ± 3.06</td>
<td>3.14 ± 2.33</td>
<td>NS (p = 0.212)</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>16.22 ± 8.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of smoking</td>
<td>3.81 ± 2.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values are mean ± SD.

LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; BMI: Body mass Index; NS: Non-significant; TO: Turbulence onset; TS: Turbulence slope.

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Figure 1. Heart rate turbulence groups values of the two study groups.

was observed at the value of the m-FNDT score and the risk stratification categories (r = 0.768, p < 0.05, Figure 2).

A strong positive correlation was also found between the value of NDI and the value of TO (r = 0.845, p < 0.001).
III. A significant relationship was observed at the value of the m-FNDT score and the smoking group risk stratification categories;

IV. The NDI of the cigarette smoking group is positively correlated with the value of TO;

V. For an abnormal TO value (≥ 0), the number of patients in smoking group were statistically higher than non-smoking group;

VI. For an abnormal TS value (< 2.5 ms/R-R), the number of patients in smoking group were statistically higher than non-smoking group;

VII. The 24 hour baseline heart rate tended to be significantly higher in smokers than in non-smokers.

Cigarette smoking is a major and an independent risk factor for cardiovascular morbidity and mortality. Previous reports suggested that chronic smokers have a higher pulse rate and blood pressure compared with non-smokers\(^{(3,14,15)}\). Smoking has some adverse effects on the neurocardiovascular regulation. These effects have been attributed to the nicotine, the main constituent of cigarette\(^{(16)}\). In addition to nicotine, tobacco smokers inhale over four thousand chemicals that have possible pharmacological and toxicological effects. Some investigators showed the mechanism of increasing blood pressure and heart rate by nicotine; activation of the sympathetic nervous system with a release of norepinephrine and epinephrine, vasopressin release or by direct effects on endothelial function\(^{(17,19)}\). Nicotine has a wide spectrum of cardiovascular morbidity and mortality. Previous studies clearly showed the effect of the nicotine on the heart rate\(^{(15,17,22)}\). Impaired HRT is associated with an increased risk of mortality and susceptibility to life threatening arrhythmias\(^{(8-10)}\). In our study we found a strong correlation between smoking and impaired HRT. The common point of the underlying reason is mostly cardiac autonomic system dysfunction. Our findings suggested that as the smoking dependence gets worse, the cardiac rhythm disorders get more. Several previous studies have focused on the effect of cigarette smoking on cardiac autonomic system. Several investigators have reported that reduced heart rate variability (HRV) in smoking subjects, is a strong indicator for autonomic disturbances that may be involved in the mechanism promoting arrhythmias and sudden death in smoking subjects\(^{(23-26)}\). Previous studies showed that there is a strong correlation between HRT and HRV\(^{(27,28)}\). Yap et al., found that TS and TO has significant correlation with almost all heart rate variability time domain parameters\(^{(28)}\). Our study support that there is a close relation between our results and previous HRV studies for smoking. Interestingly Rosamond et al., found that smoking-associated CVD risk appears to be the greatest among younger smokers\(^{(29)}\). Together with the previous results, our findings suggest that impairment of cardiovascular autonomic system in healthy long-term adult smokers may be a possible component of deleterious effect of smoking.

Studies in normal populations suggested that the 24 hours baseline heart rate measured by ambulatory monitoring, might be a predictor of total, cardiovascular and non-cardiovascular mortality\(^{(30-35)}\). In our results, the 24 hour baseline heart rate tended to be significantly higher in healthy young smokers than in non-smokers. Previous studies clearly showed the effect of the nicotine on the heart rate\(^{(15,17,22)}\).

The main limitation of our study seems to be the small sample size. Because the small sample size results in low statistical power for equivalency testing, negative results may be simply due to chance. However, it should be taken into account that establishing a smoking group without co-morbidities (e.g. diabetes mellitus, hypertension, cardiovascular and renal disorders) is difficult. Secondly, we did not make subgroup analysis in our study according to the smoking grade because the classification of patients according to NDI would decrease the sample size in subgroups. In this situation, the statistical power of these subgroups would decrease, too. Also we did not check the impact of circadian variation. Diurnal fluctuations in autonomic tone suggest one value for HRT in 24 hours. This may also influence the results.

Our study demonstrated that the autonomic modulation of the heart is reduced in smokers and it becomes apparent particularly during parasympathetic manoeuvre and that the impaired autonomic cardiac control may in part explain the mechanism promoting arrhythmias and sudden death in smoking subjects. To achieve a meaningful reduction in the societal burden of coronary heart disease, cigarette smoking in young adults must be targeted for reduction.

REFERENCES


