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The Effects of Cigarette Smoking on the Tp-e Interval, Tp-e/QT Ratio and Tp-e/QTc Ratio

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Background. Cigarette smoking increases the risk of sudden cardiac death. Smoking may predispose individuals to ventricular fibrillation and sudden cardiac death by altering ventricular repolarization and stimulating sympathetic nervous system activity.

Objectives. The aim of the study was to investigate the instantaneous effects of smoking on ventricular repolarization.

Material and Methods. The study included 47 healthy subjects; 24 long-term heavy smokers (10 women, mean age: 40 ± 5 years) constituted the study group, and 23 non-smokers (10 women, mean age: 42 ± 10 years) constituted the control group. ECGs were performed on all the subjects. The Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were measured and compared between the groups.

Results. There were no significant differences between smokers and nonsmokers in the basic clinical and echocardiographic variables ($p > 0.05$). The QT interval and QTc interval were similar in both groups. The Tp-e interval ($p = 0.02$) and Tpe/QT ratio ($p = 0.001$) were higher in the heavy smokers than in the non-smokers. The Tpe/QTc ratio ($p = 0.001$) was also higher in the smokers. Other ECG parameters were similar between the smokers and nonsmokers.

Conclusions. The results show that chronic cigarette smoking is associated with a prolonged Tp-e interval, increased Tp-e/QT ratio and Tp-e/QTc ratio. These observations may indicate that there may be a relationship between smoking and altered ventricular repolarization. Abnormal ventricular repolarization values on an ECG may explain the increased cardiovascular event risk in long-term heavy cigarette smokers (*Adv Clin Exp Med* 2015, 24, 6, 973–978).

Key words: smoking, Tp-e/QT ratio, Tp-e/QTc ratio, Tp-e interval.

Cigarette smoking is a major risk factor for cardiovascular morbidity and mortality. The relation between smoking and cardiovascular events is dose dependent [1]. Studies suggest that chronic cigarette smoking is associated with sympathetic hyperactivity [2, 3]. Plasma catecholamine levels increase with smoking and may be arrhythmogenic [4]. Smoking and its effect on the cardiovascular system represent a complex interaction between the autonomic nerve system and the heart. Impaired autonomic function has been found to be

related to arrhythmogenesis and may explain the relationship between smoking and the increased risk of cardiac mortality [5].

As Kors et al. noted, “Myocardial repolarization can be evaluated with QT interval (QT), corrected QT interval (QTc), QT dispersion (QTd), and transmural dispersion of repolarization (TDR). [The] Tp-e interval, which is the interval between the peak and the end of the T-wave on an electrocardiogram (ECG), is accepted as an index” of TDR [6]. The Tp-e/QT ratio and Tp-e/QTc

ratio are also used as an electrocardiographic index of ventricular arrhythmogenesis [7].

This case-control study was conducted to demonstrate the effects of smoking on ventricular repolarization by assessing the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio.

Material and Methods

Study Population

The study population consisted of 23 non-smokers (Group 1: 13 males and 10 females, mean age 42 ± 10 years) and 24 long-term heavy smokers (Group 2: 14 males and 10 females, mean age 40 ± 5 years). Long-term heavy cigarette smoking was defined as more than 20 cigarettes smoked per day for at least five years. The study population was enrolled between January 2012 and May 2012 at Gölcük Military Hospital (Kocaeli, Turkey). Individuals with a history of coronary artery disease, diabetes mellitus, valvular heart disease, prior pacemaker implantation, a history of atrial fibrillation, cardiomyopathy, an abnormal thyroid function test, abnormal electrolyte values or antiarrhythmic drug treatment were excluded. The study protocol was approved by Gölcük Military Hospital's ethics committee and informed consent was obtained from each participant.

Physical and echocardiographic examinations were performed on all the participants. All the subjects were taken to the examination room after an overnight fasting period and a light breakfast. All the participants were asked to refrain from alcoholic and caffeinated beverages and from strenuous exercise for 24 h before the study. The smokers were also asked not to smoke cigarettes for eight hours before the study. Baseline ECG was obtained for all the participants. After taking the baseline ECG recordings, the Group 2 participants were asked to smoke a cigarette. Another ECG recording was performed after each had finished smoking.

Electrocardiography

For the analysis of the electrocardiographic parameters, lead II was recorded at a sampling frequency of 512 Hz. A 10-second strip was used. The P-wave duration, RR interval, PR interval, QRS duration, QT interval and Tp-e interval were measured manually. The Tp-e/QT ratio and Tp-e/QTc ratio were calculated from these measurements. The onset of the P-wave was defined as the first visible upward departure from the baseline and the end of the P wave was defined as a return to the baseline. The QT interval was defined

as the time from the onset of the QRS to the point at which the T-wave returned to the baseline. The QTc interval was calculated using Bazett's formula. The Tp-e/QT ratio and Tp-e/QTc ratio were calculated. The Tp-e interval was measured from the peak of T-wave to the end of T-wave. The end of the T-wave was defined as the intersection of the isoelectric line with the tangent drawn through the down slope of T-wave. All the measurements were performed by two investigators. The intraobserver and interobserver coefficients of variation (the SD of differences between two observations divided by the mean value and expressed as a percentage) were found to be 1.2% and 2.3% respectively.

Statistical Analysis

The required sample size was calculated to be 40 with a 95% confidence interval and 80% study power. Continuous variables are expressed as mean \pm standard deviation. Categorical variables were expressed as percentages. The independent-samples *t*-test and the χ^2 test were used for comparisons of continuous and categorical variables. Spearman's rank correlation test was used to examine correlations between variables. A p-value of < 0.05 was considered significant. The statistical analysis was performed using a commercially available statistical package (SPSS for Windows 10.0).

Results

The baseline clinical characteristics of both groups are shown in Table 1. There were no significant differences between the groups in terms of age, blood pressure and body mass index. The physical examinations revealed no clinically significant disorders in any of the study subjects. The echocardiographic examinations were normal. All the subjects were in sinus rhythm. Heart rate values were higher in the smokers than in the non-smokers, but the difference was not statistically significant.

The baseline PR, QT and QTc values were not significantly different in the two groups. Although the QT and QTc intervals were similar, the baseline Tp-e interval was significantly prolonged in the smokers' group compared to the control group (85.3 ± 10.7 msn and 78.9 ± 7.3 msn respectively; $p = 0.02$). The baseline Tp-e/QT ratio was also significantly higher in the smokers' group compared to the control group (0.25 ± 0.03 and 0.21 ± 0.02 respectively; $p = 0.001$). The baseline Tp-e/QTc ratio was also higher in the smokers' group compared to the nonsmokers (0.23 ± 0.03 and 0.20 ± 0.02 respectively; $p = 0.001$) (Table 2).

Table 1. Baseline characteristics of the study population

	Group 1 nonsmokers	Group 2 smokers	p
Male/female	13/10	14/10	ns.
Age (years)	42 ± 10	40 ± 5	0.328
Body mass index (kg/m ²)	27 ± 4	27 ± 3	0.681
Systolic blood pressure (mm Hg)	111.3 ± 13.7	108.8 ± 15.7	0.554
Diastolic blood pressure (mm Hg)	72.6 ± 11.0	66.8 ± 9.5	0.062
Mean blood pressure (mm Hg)	85.5 ± 11.5	80.1 ± 11.7	0.119
Heart rate (beats/min)	70 ± 8	75 ± 10	0.111
Creatinine (mg/dL)	0.91 ± 0.11	0.84 ± 0.17	0.830
Sodium (mEq/dL)	141.0 ± 5.1	139.7 ± 2.8	0.275
Potassium (mEq/dL)	4.1 ± 0.4	4.1 ± 0.2	0.417
Hemoglobin (mg/dL)	14.7 ± 0.9	14.4 ± 0.8	0.213
Platelet (mg/dL)	282.6 ± 58.2	250 ± 55.5	0.580
LVEF (%)	61.9 ± 1.9	62.3 ± 2.1	0.470

LVEF – left ventricular ejection fraction, values are presented as mean ± SD.

In Group 2, the Tp-e interval was found to be significantly prolonged after smoking a cigarette compared with the baseline (90.8 ± 13.1 and 85.3 ± 10.7 respectively; $p < 0.001$). The Tp-e/QT ratio and Tp-e/QTc ratio were also significantly higher after smoking a cigarette compared with the baseline. Other ECG parameters were similar after smoking a cigarette compared with baseline (Table 3).

Discussion

The main finding of the present study is that the mean Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio are prolonged in long-term heavy smokers. The study also investigated the immediate effect of smoking a cigarette, and found that the

Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio are also prolonged after smoking a cigarette. The study provides evidence that smoking is associated with ventricular repolarization alteration. The finding that the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio are increased in smokers is very important. This study is the first to report on the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in smokers. The results may contribute to explaining the pathophysiological mechanisms of the increased prevalence of ventricular arrhythmias among smokers by revealing increased ventricular repolarization heterogeneity in smokers.

Many studies have reported that increased dispersion of repolarization might predispose individuals to ventricular arrhythmias [8, 9]. Antzelevich et al. [10] reported an association between

Table 2. Electrocardiographic measurements of the groups

	Group 1 nonsmokers	Group 2 smokers	p
PR (ms)	157.8 ± 21.1	148.8 ± 19.9	0.136
QT (ms)	381.6 ± 24.1	341.3 ± 22.5	0.554
QTc (ms)	389.8 ± 22.3	379.8 ± 35.2	0.535
Tpe (ms)	78.9 ± 7.3	85.3 ± 10.7	0.020
TPe/QT	0.21 ± 0.02	0.25 ± 0.03	0.001
TPe/QTc	0.20 ± 0.02	0.23 ± 0.03	0.001

Values are presented as mean ± SD.

Table 3. Clinical and electrocardiographic variables of Group 2 participants before and after smoking

	Before smoking	After smoking	p
Systolic blood pressure (mm Hg)	108.8 ± 15.7	114.8 ± 15.5	0.001
Diastolic blood pressure (mm Hg)	66.8 ± 9.5	67.9 ± 12.0	0.218
Heart rate (beat/min)	75 ± 10	76 ± 11	0.100
PR (ms)	148.8 ± 19.9	149.2 ± 19.3	0.802
QT (ms)	341.3 ± 22.5	346.3 ± 25.7	0.287
QTc (ms)	379.8 ± 35.2	387.9 ± 25.5	0.101
Tpe (ms)	85.3 ± 10.7	90.8 ± 13.1	< 0.001
TPe/QT	0.25 ± 0.03	0.26 ± 0.03	0.006
TPe/QTc	0.23 ± 0.03	0.23 ± 0.03	0.028

Values are presented as mean ± SD.

ventricular arrhythmogenesis and Tp-e interval prolongation. The duration of action potential is longer in midmyocardial M-cells than in other myocardial cells. The earliest completion of repolarization occurs in the epicardial cells. The peak of the T-wave represents the end of the epicardial action potential, and the end of the T wave represents the end of the midmyocardial action potential. Therefore, the Tp-e interval is a reflection of transmural dispersion of repolarization [11]. Previous studies have reported on prolongation of the Tp-e interval in Brugada syndrome, in long QT syndrome, in hypertrophic cardiomyopathy, in patients undergoing primary percutaneous coronary intervention for myocardial infarction and in patients with obstructive sleep apnea [8–12]. However, to the best of the current authors' knowledge, the Tp-e interval has not previously been evaluated in smokers. It has been reported that prolongation of the Tp-e interval is associated with sudden cardiac death (SCD) [13]. Thus, the results of the present study may explain this increased SCD risk by showing that dispersion of ventricular repolarization is increased in smokers.

Cigarette smoking is a strong and independent risk factor for SCD. Cigarette smoking is associated with increased sympathetic tone and reduced vagal modulation [14, 15]. Acute exposure to cigarette smoking has a sympathetic excitatory effect on smokers [16]. An acute increase in heart rate shortly after smoking is well documented. The effects of smoking on cardiovascular modulation are ascribed to nicotine, the main constituent of cigarette smoke. Nicotine transiently raises blood pressure by 10 to 20 mm Hg, and in habitual smokers elevates the average daytime blood pressure [17]. It has been shown that smoking increases plasma

catecholamine levels and effects heart rate variability [4]. Smoking also has various effects on ECGs, increasing conduction velocities and decreasing refractory periods [18]. Ramakrishnan et al. showed that heart rate and ectopic beats increase acutely following smoking, although spectral analysis of heart rate variability remain in normal ranges [19]. Dilaveris et al. evaluated the effects of smoking on ventricular repolarization and found that QT parameters were significantly lower in smokers but rate-corrected QT maximum and QT median differences were not significant [20]. Singh investigated chronic smokers and showed that the R-R interval, QTc and QT dispersion were increased in smokers [21]. The present study findings showed no difference between groups in terms of QT or QTc. The acute effect of smoking on autonomic modulation, characterized by sympathetic overactivity and parasympathetic withdrawal, is well defined [22]. But there are also some conflicting results about the effect of smoking on autonomic modulation. The SDNN, RMSDD and HF indices of heart rate variability (HRV) have been shown to be decreased shortly after smoking [23], although some investigators failed to find any relation between smoking and HRV indices [24, 25]. Kupari et al. found that HRV was lower among individuals who smoke more than ten cigarettes per day [26]. The present study population included participants who smoke more than twenty cigarettes per day.

In the present study, the QT and QTc intervals were not different in the smoking and non-smoking groups. However, it was found that the other indices of ventricular repolarization (namely the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio) are increased in long-term heavy smokers.

Limitations

The present study has some limitations. Associations between ventricular arrhythmias and the Tp-e interval were not evaluated. Therefore, the prognostic importance of Tp-e interval prolongation and increased Tp-e/QT ratio in the participants remains uncertain. However, the Tp-e interval and Tp-e/QT ratio are accepted as important prognostic markers in many different patient groups. The number of participants in this study

was relatively small. A larger study population would provide more precise results.

The results of this study show that chronic cigarette smoking is associated with a prolonged Tp-e interval, increased Tp-e/QT ratio and Tp-e/QTc ratio. These observations may indicate that there may be a relationship between smoking and altered ventricular repolarization. Abnormal ventricular repolarization values on ECG may explain the increased cardiovascular event risk in long-term heavy cigarette smokers.

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Conflict of interest: None declared

Received: 22.03.2014

Revised: 23.04.2014

Accepted: 10.07.2014