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Acute effect of cigarette smoking on frontal planar QRS-T angle in apparently healthy subjects with habitual smoking

Sigara içen sağlıklı bireylerde anlık sigara içiminin frontal planar QRS-T açısı üzerine etkileri

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Abstract

Aim: It has been well recognized that smoking exerts various detrimental cardiovascular effects. Although the effect of chronic smoking on cardiac electrophysiology is well known, little is known about the effect of acute smoking on surface ECG. Previous reports suggested that frontal planar QRS-T angle (fpQRS-Ta), measured by surface ECG, may be associated with ventricular arrhythmias and cardiac death. Hence, we primarily aimed to assess the effect of acute smoking on fpQRS-Ta.

Methods: A total of 92 apparently healthy subjects [44 female, 48 male, mean age 38.7(8.02) years] with smoking habit were enrolled in this prospective cohort study between May-July 2019. Demographic and clinical characteristics were recorded, and fpQRS-Ta together with some ECG parameters were noted before and 10 minutes after smoking for comparison. Spearman's analysis was implemented to seek the probable correlation of the difference between pre- and post-smoking ECG parameters.

Results: Ten minutes after smoking, median heart rate, QRS duration and fpQRS-Ta increased significantly (72.6 beats/min vs 81.5 beats/min, $P<0.001$; 84 ms vs 86 ms, $P=0.012$; 14.5° vs 25°, $P<0.001$; respectively), while PR and QTc duration did not significantly change (150.0 ms vs 150.0 ms, $P=0.774$; and, 423.5 ms vs 429.5 ms, $P=0.372$). In Spearman's correlation analysis, the difference between pre- and post-smoking fpQRS-Ta significantly and negatively correlated with C-reactive protein (CRP) levels (r: -0.272, $P=0.027$).

Conclusion: Acute smoking may widen fpQRS-Ta in healthy habitual smokers, and serum CRP negatively correlates with the degree of fpQRS-Ta widening. Our observation may further enlighten the pathophysiological mechanism of smoking in cardiac arrhythmias and sudden death.

Keywords: Cigarette smoking, Frontal planar QRS-T angle, Electrocardiography, Nicotine

Öz

Amaç: Sigara içiminin çeşitli kardiyovasküler etkilere sahip olduğu iyi bilinmektedir. Kronik sigara içiminin kardiyak elektrofizyoloji üzerine etkileri daha net tanımlanmış olduğu halde, akut sigara içiminin yüzey EKG'si üzerindeki etkileri hakkında çok az bilgi mevcuttur. Daha önceki çalışmalarda yüzeysel EKG ile hesaplanan frontal planar QRS-T açısının (fpQRS-Ta) ventriküler aritmiler ve kardiyak ölüm ile ilişkili olabileceği ifade edilmiştir. Bu nedenle bu çalışmada temel olarak akut sigara içiminin fpQRS-Ta üzerindeki etkilerini incelemeyi amaçladık.

Yöntemler: Bu çalışma prospektif kohort çalışmasıdır. Mayıs ve Temmuz 2019 tarihleri arasında sigara içme alışkanlığı olan sağlıklı 92 birey [44 kadın, 48 erkek, ortalama yaş 38(8.02) yıl] çalışmaya prospektif olarak dâhil edilmiştir. Demografik ve klinik özelliklerin kaydedildi; yanı sıra sigara içiminden önceki ve akut sigara içiminden 10 dakika sonraki bazı EKG parametreleri ile birlikte fpQRS-Ta not edilerek karşılaştırma yapıldı. Sigara içimi öncesi ve sonrası EKG parametrelerinin arasındaki olası ilişkilerin incelenmesi amacıyla Spearman korelasyon analizi yapıldı

Bulgular: Medyan kalp atım hızı, QRS süresi ve fpQRS-Ta sigara içiminden 10 dakika sonra anlamlı şekilde arttı (sırasıyla 72,6 atım/dak vs 81,5 atım/dak, $P<0,001$; 84 ms vs 86 ms, $P=0,012$; 14,5° vs 25°, $P<0,001$). PR ve QTc sürelerinde sigara içimi sonrasında anlamlı değişim izlenmedi (sırasıyla 150,0 ms vs 150,0 ms, $P=0,774$; 423,5 ms vs 429,5 ms, $P=0,372$). Spearman korelasyon analizinde ise sigara içimi öncesi ve sonrası fpQRS-Ta değişiminin C-reaktif protein (CRP) ile anlamlı ve negatif bir korelasyona sahip olduğu belirlendi (r: -0,272, $P=0,027$).

Sonuç: Sigara alışkanlığı olan bireylerde akut sigara içimi fpQRS-Ta'de genişlemeye neden olabilir ve bu genişlemenin derecesi CRP ile negatif korelasyon göstermektedir. Çalışmamızda elde ettiğimiz sonuçlar, sigara içiminin kardiyak aritmi gelişimi ve ani ölüm üzerindeki patofizyolojik etki mekanizmasının açıklanmasına ışık tutabilir.

Anahtar kelimeler: Sigara içiciliği, Frontal planar QRS-T açısı, Elektrokardiyografi, Nikotin

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Introduction

It has long been recognized that chronic cigarette smoking associates with various cardiovascular disorders, such as coronary artery disease, acute coronary syndrome, stroke, arrhythmias and sudden death [1-4]. Apart from its chronic detrimental effects, acute exposure to cigarette smoke also appears to cause hemodynamic and cardiac electrophysiologic modifications through complex mechanisms [5,6].

Nicotine was reported to delay ventricular repolarization, thereby increasing susceptibility to cardiac arrhythmias by catecholamine release, boost sympathetic nervous system activation and delay membrane repolarization via directly blocking inward K+ channels in ventricular myocardial cells [4,7]. Carbon monoxide, another important constituent of cigarette smoke, is likely to induce cardiac arrhythmias by hindering oxygen transportation to cardiac tissues. Research on animal models as well as human studies reported an increased likelihood of complex ventricular arrhythmias in the setting of coronary ischemia [8,9]. Among other known acute hemodynamic effects of smoking are an increase in blood pressure, heart rate, vascular resistance and hence cardiac workload, possibly due to acute escalation in sympathetic tone and transient hypoxia [10].

Frontal planar QRS-T (fpQRS-T) angle is a surface electrocardiographic (ECG) parameter indicating the angle between QRS and T-wave axes [11]. Moreover, it provides an electrophysiological insight regarding the crude orientation of ventricular depolarization and repolarization vectors. Recently, fpQRS-T angle has appealed much to the researchers and become a topic of interest due to accumulating evidence that suggests fpQRS-T might be of utility in prognostic as well as diagnostic scopes [12-16]. Previous studies suggested that increased fpQRS-T angle would translate into increased cardiovascular and all-cause deaths in diabetes mellitus, acute myocardial infarction, ischemic heart diseases and heart, and even in general population [14-18].

Predicated on these premises, we hypothesize that acute exposure to cigarette smoke would widen fpQRS-T angle in otherwise healthy subjects with a smoking habit.

Materials and methods

A total of 92 apparently healthy subjects [hospital staff, 44 females, 48 males, mean age 38.7(8.02) years] with smoking habit were enrolled in this prospective cohort study between May 2019 and July 2019. The participants had no previous history of any major clinical problems. Smoking habit was defined as at least 3 cigarette smoking per day for at least 1 year. All participants were subjected to a comprehensive physical examination, and echocardiographic and ECG evaluation to inquire probable cardiac disorders. The exclusion criteria were set as following: History of cardiovascular disease, diabetes mellitus, hypertension, endocrine disorder, cerebrovascular disease, chronic renal failure and chronic inflammatory disease, acute infections, and being on chronic medication. The body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI >30 kg/m2.

Written informed consent was obtained from every participant and the institutional ethics committee approved the protocol of the study (Kirsehir Ahi Evran University Ethics Committee, No: 2019-08/95, Date: 04/30/2019). This study complies with the standards of the Declaration of Helsinki.

Smoking, laboratory analysis and electrocardiographic evaluation

All participants were asked to refrain from cigarette smoking, alcohol, caffeinated beverages, and food intake at least 8 hours prior to study. On the day of the study, a standard 12-lead ECG (MAC 2000, GE Medical Systems, Milwaukee, WI, USA) with 50 mm/sec paper speed and 10 mm/mV amplitude was recorded as baseline strip while the patient was resting in supine position and quietly respirating for at least 10 minutes between 7:30-09:00 AM in the morning. Afterward, they were asked to smoke a single cigarette as in their daily routine. Ten minutes later, another ECG strip was recorded again with the patient in supine position to compare with the prior ECG strip.

R-R, QT, PR and QRS intervals were measured manually from Lead 2 [19]. Then, QT interval was corrected (QTc) for heart rate using Bazett's formula [20]. The definitions were as follows: R-R interval: The time between two consecutive R waves. PR interval: The time from the beginning of P wave to the beginning of QRS complex. QT interval: The time from the beginning of Q or R wave to the end of T wave where it intersects with the isoelectric line. The mean of the three consecutive beats was calculated to end up with the ultimate values. These intervals were measured by an experienced cardiologist blinded to the study data to prevent interobserver variability.

As for the QRS and T-wave axes, they were obtained from the intrinsic reports provided by the ECG device [13,14,21]. To compute the fpQRS-T angle, the absolute difference between the QRS and T-wave axes were measured to obtain values between 0 and 180°. The value was subtracted from 360° if it exceeded 180°.

Venous blood samples were drawn through venipuncture between 7:30-9:00 am before the baseline ECG recording. Routine serum biochemical parameters were measured using standard laboratory methods via Roch Cobas 8000 Autoanalyser, and hematological parameters were defined by using Sysmex XN-1000 automated blood cell counter (Sysmex Corporation, Kobe, Japan).

Statistical analysis

The statistical analysis was implemented using SPSS (Version 21.0 for Windows, SPSS Inc, Chicago, USA). Quantitative data were assessed for normality with the Kolmogorov- Smirnov test. Categorical variables of the subjects were presented in numbers and percentages, whereas continuous variables were expressed as mean (SD) and median (25-75 interquartile range). Since ECG parameters intended to be compared showed non-normal distribution, comparison of these parameters before and after smoking were performed using Wilcoxon signed-rank test. Spearman's correlation analysis was done to determine the linear correlation between the changes in fpQRS-T angles and demographic and laboratory parameters of the patients. *P*-value was regarded as statistically significant when <0.05.

Results

Our study population's demographic and clinical characteristics were presented in Table 1. Among 92 subjects enrolled, 44 (47.8%) were female and 48 (52.2%) were male. Mean BMI was 26.69 (4.16) kg/m^2. There was no clinically crucial disorder detected during history taking and physical examination. Moreover, echocardiography and ECG revealed no important cardiac problems. Normal sinus rhythm was evident in ECG strips of all subjects.

Table 2 represents the ECG parameters before and after 10 minutes of cigarette smoking in a comparative manner. No statistically significant difference was observed before and after smoking in respective median QTc (423.5 ms vs 429.5 ms, *P*=0.372) and PR durations (150.0 ms vs 150.0 ms, *P*=0.774). However, median heart rate and QRS duration were significantly increased 10 minutes after smoking compared with baseline (72.6 beats/min vs 81.5 beats/min, *P*<0.001: and 84 ms vs 86 ms, *P*=0.012). Moreover, the median fpQRS-T angle which was 14.5 (IQR:8-21) degree at baseline widened significantly to 25 (IQR:18-39) degree 10 minutes after smoking (*P*<0.001).

Spearman's correlation analysis depicted a significant and positive correlation between fpQRS-T angles before and after smoking (r=0.576, *P*<0.001) (Figure 1). Furthermore, upon interrogating probable correlations of fpQRS-T angle differences before and after smoking with the other ECG parameters and the subjects' baseline demographics, only C-reactive protein (CRP) level was revealed to correlate significantly but negatively with the difference between pre- and post-smoking fpQRS-T angles (r:-0.272, *P*=0.027) (Figure 2, Table 3).

Table 1: Demographic and clinical characteristics of the study participants (n=92).

Variable	Value
Age, years	38.7(8.0)
Gender, female, n (%)	44 (47.8%)
Body-mass index, kg/m^2	26.69(4.16)
LVEF, %	62.1(3.12)
Total cholesterol, mg/dL	170.1(32.4)
LDL cholesterol, mg/dL	97.1(29.3)
Triglyceride, mg/dL	141.2(107.7)
HDL cholesterol, mg/dL	44.0(10.3)
CRP, mg/dL	0.27(0.44)
WBC, 10^3/uL	8.46(2.68)
Hb, g/dL	14.02(3.0)
MCV, fL	86.5(5.3)
RDW, %	13.0(1.15)
Platelets, 10^3/uL	258.5(53.7)
Neutrophil, 10^3/uL	4.95(2.57)

LVEF: left ventricular ejection fraction, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein, WBC: white blood cell count, Hb: hemoglobin, MCV: mean corpuscle volume, RDW: red cell distribution width. Values were given in mean(SD)

Table 2: Electrocardiographic parameters of the study subjects before and 10-min after acute smoking

Variable	Before smoking	After smoking	*P*-value
Heart rate, beats/min	72.6 (69-79)	81.5 (78-86)	<0.001
fpQRS-T angle, degree	14.5 (8-21)	25 (18-39)	<0.001
PR interval, ms	150 (131.5-160)	150 (135.5-160.5)	0.774
QRS duration, ms	84 (78-94)	86 (80-94)	0.012
QTc interval, ms	423.5 (404-438)	429.5 (407-443)	0.372

fpQRS-T: frontal planar QRS-T. Values were given as median (25-75 interquartile range)

Table 3: Correlation of the deference between pre- and post-smoking frontal planar QRS-T angle with demographic and clinical characteristics.

Variable	r	*P*-value
Age	0.056	0.599
Body-mass index	0.048	0.699
Total Cholesterol	0.165	0.178
Triglyceride	-0.054	0.664
HDL cholesterol	-0.125	0.318
LDL cholesterol	0.205	0.099
CRP	-0.272	0.027*
WBC	-0.011	0.917
Hb	0.062	0.563
Platelets	0.159	0.134
RDW	-0.149	0.160

***** Correlation is significant at the 0.05 level, HDL: high density lipoprotein, LDL: low density lipoprotein, CRP: C-reactive protein, WBC: white blood cell count, RDW: red cell distribution width, r: Rho

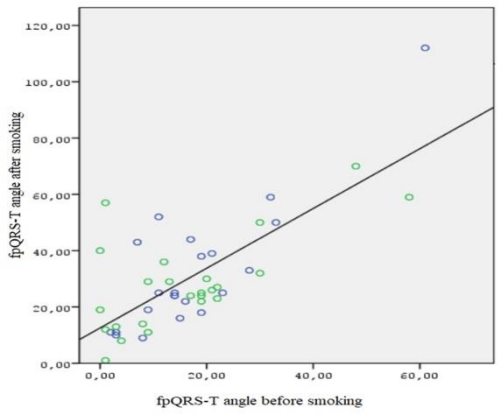

Figure 1: Correlation between pre- and post-smoking fpQRS-T angles (r=0.576, *P*<0.001; correlation is significant at 0.01 level)

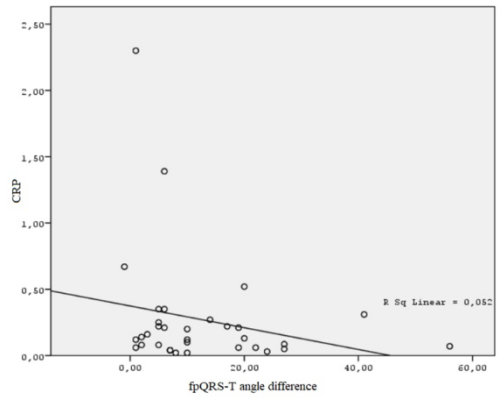

Figure 2: Correlation of the difference between pre- and post-smoking fpQRS-T angle and C-reactive protein (r= -0.272, *P*=0.027, correlation is significant at 0.05 level).

Discussion

Chronic smoking has been a robust risk factor for chronic and acute cardiovascular events. Moreover, habitual smoking brings about a chronic inclination to decreased vagal tone, blunted baroreflexes, and increased sympathetic autonomic tone. This unopposed escalation in sympathetic autonomic tone is implicated to a certain extent in all cardiovascular and hemodynamic complications of smoking in addition to its detrimental effects on vascular endothelium and its induction of systemic inflammation [22].

Other than its chronic effects, acute exposure to cigarette smoking causes a rapid catecholamine discharge from nerve endings and also stimulation of sympathetic nervous system through neural nicotinic acetylcholine receptors, which in turn is responsible for the acute increase in heart rate and blood pressure especially within 10 minutes of smoke exposure [23].

In their study, Akbarzadeh et al. [5] showed a significant increase in the heart rates of healthy non-smoker subjects as well as otherwise healthy professional-smokers 10 minutes after smoking compared with the baseline ECG. Karakaya et al. [6] reported a significant decrease in mean RR interval within 10 minutes after cigarette smoking compared with the same interval at baseline in a cohort of non-smokers. However, this statistically significant decrease vanished after 10 minutes in their study. In another study conducted on chronic heavy smokers by Karakaya et al. [24], heart rate significantly increased 15 minutes after smoking compared to baseline. In agreement with the previous studies, we also documented a heart rate increase 10 minutes after smoking in a cohort of otherwise healthy habitual smokers.

Although there are relatively more studies reporting significant increase in various parameters of ventricular repolarization such as QT interval, QTc interval, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios, QT-dispersion (QTd) and corrected QT-dispersion (QTcd) between long-term smokers and non-smokers [25-27], studies on acute effect of cigarette smoking on different ECG parameters are very scanty and focus only on such parameters of ventricular repolarization as QT-dispersion (QTd) and corrected QT-dispersion (QTcd) with conflicting results. Akbarzadeh et al. [5] and Khosropanah et al. [28] reported an escalation in QTd and QTcd following acute exposure to cigarette smoke, whereas another study by Karakaya et al. [24] did not reveal a significant difference either in QTd and QTcd or in QT interval. İlgenli et al. [26] also did not find a significant difference in PR, QT and QTc intervals between baseline and following acute cigarette smoking. In agreement with the findings of Karakaya et al. [24] and İlgenli et al. [26], we also did not find a significant change in QTc and PR intervals after acute smoking. The discrepancy between the results of these different studies may have stemmed from the male-only inclusion methodology of the former two studies, as it may be speculated that autonomic nervous system discharge and opposing baroreflexes would have influenced the pooled data of these studies by modulating the cardiac electrophysiology to varying degrees. On the other hand, the latter two studies and ours enrolled female subjects as well.

fpQRS-T angle is a relatively novel ECG index utilized in the risk assessment of cardiac and overall deaths. It proves much more useful in risk stratification either QRS axis or T-wave axis alone [16]; however, there is no certain reference range for a normal fpQRS-T angle owing to its variability by age and gender. On the other hand, the spatial QRS-T angle is actually more revealing with regard to risk of ventricular arrhythmias, sudden arrhythmic death, cardiovascular death and overall death compared with fpQRS-T angle [29]. However, since most of the physicians are not acquainted with the spatial QRS-T angle due to its lack of wide availability, fpQRS-T angle appeals more to them owing to the fact that it is readily available from a surface ECG and has a significantly well correlation with the spatial QRS-T angle [12].

In healthy persons possessing normal cardiac structure, fpQRS-T angle is expected to be narrow. On the other hand, wider fpQRS-T angles point out to a more heterogeneity and distortion in the delicate balance between ventricular depolarization and repolarization, which translates into the presence of such cardiac fabric that is relatively more susceptible to ventricular arrhythmias and hence cardiovascular and all-cause deaths [30-32].

The main strength of our study is that contrary to the previous reports we mainly sought to assess the status of fpQRS-T angle after acute cigarette smoking, together with its probable correlations with demographic and clinical characteristics in healthy habitual smokers. We found that fpQRS-T angle dramatically widened 10 minutes after acute smoking. To our knowledge, this is the first study that compares this novel electrocardiographic parameter in the setting of acute smoking.

Of note, serum CRP level interestingly showed a significantly negative correlation with the degree of difference between pre- and post-smoking fpQRS-T angles in our study. This may seem paradoxical at first glance. Previous reports suggested that chronic exposure to cigarette smoke led to an elevation in serum levels of inflammatory markers such as interleukin-6, tumor necrosis factor-alpha and CRP in smokers [2,33-35]. Furthermore, chronic tobacco use may lead to gradually more nicotine tolerance, desensitization of autonomic nervous system, and blunting in baroreflexes compared with non-smokers and those smoking cigarette for a relatively shorter periods [22,36]. In this respect, it would be prudent to conjecture that lower serum CRP level may reflect relatively shorter periods of total tobacco exposure and hence a relatively more dramatic sympathetic nervous system response, catecholamine release and more direct effect membrane K+ channels on cardiac myocytes compared with those smokers with longer periods of total tobacco exposure, which in turn translate into a more dramatic widening in fpQRS-T angle soon after acute smoking.

Although there is no certain reference range for a normal fpQRS-T angle, some studies opt to regard a fpQRS-T angle <45 degrees as normal, between 45-90 degrees as borderline and >90 degrees as abnormal [11,16,37]. In their study, Chua et al. [16] pointed out to a cut-off value >90 degrees for a fpQRS-T angle to predict sudden cardiac death independently of the left ventricular ejection fraction in a large cohort of patients possessing cardiovascular disease risk factors. One may be eager to speculate that both pre- and post-smoking values of fpQRS-T angles seem within the expected range for healthy subjects. However, since we detected a significant and positive correlation between fpQRS-T angles before and 10 minutes after acute smoking in Spearman's analysis, this finding is very likely to be used as a future perspective in other studies such that a wider fpQRS-T angle at baseline expected in patients with heart failure, prior myocardial infarction and high blood pressure could be subject to a much greater widening compared with a narrower fpQRS-T angle healthy subjects.

Limitations

This study should be evaluated together with some limitations. Firstly, our study is a single-center study and includes a relatively small number of subjects. Secondly, the amount of the nicotine and tar that each participant consumed during a single cigarette smoking was not recorded, as different cigarette brands may have quite variable ingredients and amounts. This may have affected our study results. Thirdly, the participants were not stratified according to their total years of tobacco use to make a further comparison based on such stratification. In addition, we did not follow up the subjects for potential future cardiovascular endpoints.

Conclusion

Our study shows that even single smoking may widen fpQRS-T angle, a novel parameter with cardiac prognostic significance, 10 minutes after cigarette smoking in healthy subjects with habitual smoking. In addition, serum CRP level correlates negatively and significantly with the degree of fpQRS-T angle widening. Our observation may shed further light on the pathophysiological mechanism of smoking in cardiac arrhythmias and cardiac death. However, future studies, especially on patients with cardiovascular risk factors, are warranted to confirm and further enhance our findings.

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