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Effect of habitual cigarette smoking on the index of cardiac electrophysiological balance in apparently healthy individuals☆

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ABSTRACT

Background and aim: Chronic cigarette smoking has been suggested to portend risk for cardiac arrhythmia generation. Index of cardiac electrophysiological balance (iCEB) is a relatively new ECG parameter indicating balance between ventricular depolarization and repolarization, thereby providing more insight concerning ventricular arrhythmogenesis (VA) than other classical ECG parameters such as QT and corrected QT (QTc) intervals. The present study aimed to assess the status of iCEB in healthy habitual smokers.

Methods: This retrospective study included a total of 80 apparently healthy subjects (45% female, mean age 39.4 ± 8.1 years) with smoking habit and 82 healthy non-smoking subjects (40% female, mean age 37.0 ± 8.6 years) were included between January–September 2019. Demographic, clinical and ECG characteristics were obtained from medical records. iCEB and corrected iCEB values were calculated by dividing respective QT and QTc intervals by QRS duration.

Results: Mean PR, QRS and QT intervals were similar between the groups, whereas mean heart rate and QTc interval were greater in the smoker group compared with the non-smokers [(82.0 ± 8.9 bpm vs 77.8 ± 12.4 bpm, respectively, $p = 0.016$) and (427.05 ± 22.6 msec vs 399.9 ± 12.8 msec, respectively, $p < 0.001$)]. Subject with smoking habit had greater iCEBc than the controls (5.10 ± 0.49 vs 4.68 ± 0.39, respectively, $p < 0.001$). However, there was no significant difference in regard of iCEB between the groups (4.37 ± 0.46 vs 4.32 ± 0.42, respectively, $p = 0.456$).

Conclusion: iCEBc increases significantly in healthy smokers compared with non-smokers. This may suggest an increased predisposition to Torsades de Pointes-mediated VA in healthy smokers, or in chronic smokers with inherent QT-prolonging genetic variations or those on QT-prolonging drug therapy.

Introduction

Cigarette smoking has still been occupying a very top position in the development of a number of cardiovascular (CV) disorders [1]. More specifically, exposure to cigarette smoke implicates various hemodynamic and cardiac electrophysiological deteriorations through complex mechanisms both in the short and long runs [2–4]. Nicotine, a major constituent of cigarette smoke, was reported to delay ventricular repolarization, release catecolamines into circulation, activates sympathetic nervous system, and to prolong membrane repolarization via direct blockage of inward K^+ channels in ventricular myocardium [5]. Furthermore, nicotine, together with carbon monoxide and other oxidative agents, was suggested to be casually related to the development of myocardial fibrosis in different cardiac compartments [2]. All these intermingled mechanisms were proposed to hold responsibility in the increased susceptibility to cardiac arrhythmias, and hence emergence of severe ventricular arrhythmias and even sudden death, in cigarette smokers.

Previous studies have already stated clearly that surface electrocardiography (ECG) could provide valuable data concerning increased cardiac arrhytmogenesis, such as increased QT and corrected QT (QTc) intervals, PR interval, Tpeak to Tend interval (Tp-Te), dispersion of QT interval, and dispersion of P wave [6–12]. On the other hand, index of cardiac electrophysiological balance (iCEB), namely the ratio of QT to QRS (QT/QRS) calculated from surface ECG, is a novel and simple ECG marker that may predict ventricular arrhythmogenesis [13,14]. It is suggested that the iCEB is a surrogate marker of the cardiac wavelength λ (λ = effective refractory period [ERP] x conduction velocity [CV]), and an ultimate representation of the balance between cardiac repolarization and depolarization [13]. For this reason, either of increased or decreased iCEB values relates to certain ventricular arrhythmic events.

☆ Take-Home Tweet: Cigarette smoking could relates more to Torsades de Pointes-mediated ventricular arrhythmias than non-Torsades-mediated arrhythmias.

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In the light of the afore-mentioned premises, we intended to assess the status of iCEB in otherwise healthy people with habitual cigarette smoking compared with healthy non-smoker subjects.

Materials and methods

Recruitment of the study subjects

This study was conducted in a retrospective manner in a single tertiary healthcare center. Hospital records of a total of 80 consecutive and apparently healthy people (36 female, 44 male, mean age 39.4 ± 8.1 years) with cigarette smoking habit who had been admitted to our institution's cardiology outpatient clinics with non-specific symptoms between January 2019 and September 2019 were retrospectively scanned and these subjects were enrolled to the smoker group. In addition, 82 healthy subjects without smoking habit who had presented to the cardiology outpatients clinics within the same time period were retrospectively included to constitute the non-smoking control group. Demographic and clinical characteristics and ECG recordings were retrieved from medical records. The study participants had no previous history of major clinical problem. Smoking habit was defined as at least 3 cigarette smoking per day for at least 1 year. All of the participants were subjected to a comprehensive physical examination, and echocardiographic and ECG evaluation to inquire probable cardiac disorders. The exclusion criteria were set as follow: history of cardiovascular disease, diabetes mellitus, hypertension, cerebrovascular disease, chronic kidney failure and chronic inflammatory disease, endocrine disorders, acute infections, and chronic medication usage. The body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Our institutional ethics committee approved the protocol of the study, and this study complies with the standard set of rules by the Declaration of Helsinki.

Electrocardiography and echocardiography

12-lead ECGs had been obtained from all subjects in supine position using a standard ECG system (Nihon Kohden, Tokyo, Japan) at a paper speed of 25 mm/s. The ECG strips were scanned and transferred to the digital media and the digital records were analyzed under x300% magnification in personal computers. R-R, QT, PR and QRS intervals were measured manually from extremity lead 2 [12]. Then, QT interval was corrected (QTc) for heart rate using the Bazett's formula: $QTc = QT/\sqrt{(RR)}$ [15]. The definitions were as follows: R-R interval, the time period between two consecutive R waves; PR interval, the time period from the beginning of P wave to the beginning of QRS complex; QT interval, the time period from the beginning of Q or R wave to the end of T wave where it intersects with the isoelectric line; Tp-Te interval, the time interval from peak of the T-wave to the point where tangent of descending arm of the T-wave merge with the isoelectric line; and, iCEB, the ratio of QT to QRS (QT/QRS); and, iCEBc, the ratio of QTc to QRS (QTc/QRS). Three consecutive beats were averaged to obtain the ultimate measurement for each parameter. These intervals were measured by an experienced cardiologist blinded to the study data in order to prevent inter-observer variability.

All the transthoracic echocardiographic assessment of the study participants were performed using Vivid S5 (GE Vingmed Ultrasound AS, Horten, Norway).

Statistical analysis

The statistical analysis was implemented by using SPSS (Version 21.0 for Windows, SPSS Inc., Chicago, USA). Categorical variables of the subjects were given in numbers and percentages, whereas continuous variables were expressed as mean ± SD and median (25–75 interquartile range). Quantitative data were assessed for normality by using Kolmogorov-Smirnov test. While normally-distributed variables were compared using independent sample *t*-test, the variables which show non-normal distribution were compared by the help of Mann-Whitney *U* test. p value was considered statistically significant, if it is <0.05.

Results

There was no clinically crucial disorder detected during history taking and physical examination. Echocardiographic and ECG assessments revealed no clinically important pathology. Normal sinus rhythm was observed in the ECG strip of each study subjects. Baseline demographic and clinical features of the study subjects were presented in Table 1. Age and gender distribution between the groups were homogeneous in general. Specifically, of a total of 80 subjects included in the smoker group, 36 (45%) were female. On the other hand, 32 (40%) out of total 82 subjects were female in the non-smoker control group ($p>0.05$). Mean age of the smoker and the non-smoker groups was 39.4 ± 8.1 and 37.0 ± 8.6 years, respectively ($p = 0.073$). In addition, no significant difference concerning mean BMI, systolic/diastolic office blood pressure readings and LVEF was evident between the groups.

Table 2 depicts the ECG findings of the whole study population. Respective median PR, mean QRS and mean QT intervals were similar and seemed within the normal ranges between the groups [16]. Of note, however, mean heart rate and QTc intervals were greater in the smoker group compared with those in the non-smokers [(82.0 ± 8.9 bpm vs 77.8 ± 12.4 bpm, respectively, $p = 0.016$) and (427.05 ± 22.6 msec vs 399.9 ± 12.8 msec, respectively, $p < 0.001$)]; while mean RR interval was shorter in the smoker group compared with the non-smokers [731.7 ± 63.7 msec vs 771.2 ± 110.2 msec, respectively, $p = 0.021$]. Furthermore, mean Tp-Te duration was revealed to be significantly prolonged in the smokers compared with that of non-smokers [78.05 ± 6.4 msec vs 72.1 ± 5.1 msec, respectively, $p = 0.032$].

When it comes to the iCEB and iCEBc, the subject with smoking habit tended to have greater iCEBc values compared with the non-smoking controls (5.10 ± 0.49 vs 4.68 ± 0.39, respectively, $p<0.001$). However, there was no significant difference in regard of iCEB between the two groups (4.37 ± 0.46 vs 4.32 ± 0.42, respectively, $p = 0.456$).

Table 3 represents the gender comparison of the ECG parameters in the group with smoking habit. Mean heart rate, and PR, QT, QTc and Tp-Te intervals were similar between the gender groups. However, QRS duration was more prolonged in male smokers than that of female smokers. Of note, both iCEB and iCEBc were greater in female smokers compared with male smokers due particularly more prolonged QRS duration in male smokers.

Comparison of the smoking and non-smoking subjects within each gender subgroup were depicted in Table 4. Similar to the comparison between the smokers and non-smokers in whole study population, mean heart rate, and Tp-Te and QTc intervals were significantly greater in the smokers in each respective gender subgroup as compared with their same-gender counterparts ($p<0.05$). In addition, despite comparable iCEB values, mean iCEBc was also found to be greater in the female- and male-smokers compared with their respective non-smoking counterparts ([5.25 ± 0.51 vs 4.83 ± 0.36 between respective female smokers vs female non-smokers; $p = 0.002$], and [4.91 ± 0.42 vs

Table 1
Baseline demographic findings of the study groups.

Variable	Smoker group (n = 80)	Non-smoker group (n = 82)	p value
Age, years	39.4 ± 8.1	37.0 ± 8.6	0.073
Gender, female, n (%)	36 (45)	32 (40)	0.221
Body-mass index, kg/m^2	25.02 ± 1.9	24.79 ± 2.3	0.246
Systolic BP, mmHg	119.1 ± 8.2	121.3 ± 7.1	0.311
Diastolic BP, mmHg	68.4 ± 7.1	71.2 ± 8.2	0.202
LVEF, %	60.8 ± 3.6	59.9 ± 3.5	0.396

LVEF, left ventricular ejection fraction. BP, blood pressure.

Table 2
Electrocardiographic findings of the study subjects.

Variable	Smoker group (n = 80)	Non-smoker group (n = 82)	p value
Heart rate, beats/min	82.0 ± 8.9	77.8 ± 12.4	**0.016**
R-R interval, msec	731.7 ± 63.7	771.2 ± 110.2	**0.021**
PR interval, msec	147.8 (132.2–158.1)	147.9 (131.4–160.3)	0.897
QRS duration, msec	84.3 ± 7.6	85.8 ± 6.5	0.168
QT interval, msec	365.9 ± 22.3	369.0 ± 24.6	0.399
QTc interval, msec	427.05 ± 22.6	399.9 ± 12.8	**<0.001**
Tp-Te, msec	78.05 ± 6.4	72.1 ± 5.1	**0.032**
iCEB	4.37 ± 0.46	4.32 ± 0.42	0.456
iCEBc	5.10 ± 0.49	4.68 ± 0.39	**<0.001**

iCEB: index of cardiac electrophysiological balance. iCEBc: index of cardiac electrophysiological balance with heart rate correction.
P values in bold indicate the comparison is of statistical significance.

4.44 ± 0.33 between respective male smokers vs male non-smokers; p = 0.001]).

Discussion

Main findings of the present study was that although iCEB seemed not to be affected by smoking habit, iCEBc was found to be greater in otherwise healthy people with habitual smoking compared with the non-smokers. Secondly, mean resting heart rate was greater and baseline QTc interval was prolonged in smokers when compared with those of non-smokers. In this respect, this is the first study in adults which provides evidence that chronic smoking habit relates to a significant shift in the balance between ventricular depolarization and repolarization which may in turn translate into increased susceptibility to certain modes of ventricular arrhythmias.

Chronic smoking has been a robust risk factor for future cardiovascular events. Moreover, habitual smoking brings about a chronic inclination to decreased vagal tone, blunted baroreflexes, and increased sympathetic autonomic tone [17]. This unopposed escalation in sympathetic autonomic tone is implicated to a certain extent in all cardiovascular and hemodynamic complications of smoking, and even sudden cardiac death [17,18]. A specific reflection of this unopposed chronic sympathetic activation could simply be exemplified by the increase in basal heart rate in chronic cigarette smokers compared with that of non-smokers. Venkatesh et al. [19] revealed in their study a faster basal heart rate in chronic smokers than that of non-smokers. Sharma et. Al [20] evaluated ECG changes in 150 chronic smoker and also reported a significant increase in resting heart rate in the smokers compared with non-smokers. In another recent and large-scale study encompassing a total of 141.317 subjects, Linneberg et al. [21] found a significant relationship between chronic cigarette smoking and greater resting heart rate. On the contrary, they could not reveal any causal relationship between chronic smoking and higher blood pressure or development of a new hypertension. In this regard, our study findings seem consistent with the previous reports.

Table 3
Gender comparison of ECG parameters in the smoker group.

Variable	Female smokers (n = 36)	Male smokers (n = 44)	p value
Heart rate, beats/min	83.9 ± 8.8	79.7 ± 8.8	0.144
PR interval, msec	142.8 ± 15.5	153.5 ± 20.5	0.072
QRS duration, msec	81.3 ± 7.7	87.8 ± 6.2	**0.006**
QT interval, msec	364.5 ± 22.4	367.6 ± 23.0	0.663
QTc interval, msec	424.6 ± 26.7	430.0 ± 17.5	0.469
Tp-Te, msec	76.12 ± 7.2	79.07 ± 6.9	0.264
iCEB	4.51 ± 0.44	4.20 ± 0.45	**0.041**
iCEBc	5.25 ± 0.51	4.91 ± 0.42	**0.033**

iCEB: index of cardiac electrophysiological balance. iCEBc: index of cardiac electrophysiological balance with heart rate correction.
P values in bold indicate the comparison is of statistical significance.

QT and QTc intervals encompass the complete period of ventricular depolarization and repolarization and their prolongation portents risk for Torsades de Pointes- (TdP-) mediated ventricular arrhythmia occurrence and sudden cardiac death [7]. Current data is conflicting with regard to the ultimate change in QT interval in chronic smokers, where some studies suggested an increase [22], some others reported no change [20,23,24] or even decrease in mean QT interval [20,25] in healthy smokers. Contrary to QT interval, studies investigating the effects of cigarette smoking on QTc interval revealed more consistent results in favor of a significant increase in mean QTc in smokers as compared to non-smokers [18,20,23,25]. In our study, mean QT interval did not change significantly between the smokers and non-smokers. In contrast, we revealed a significant prolongation in baseline QTc interval in the smoker group compared with the non-smoking controls, which we thought was compatible with the previous reports.

iCEP is a relatively new non-invasive ECG parameter may prove useful in predicting TdP and non-TdP mediated ventricular arrhythmic events, far beyond sole QT and Tp-Te intervals [13,14]. In their animal study conducted 2013, Lu et al. [13] introduced this simple parameter and suggested that a marked increase in iCEB could potentially exert a TdP mediated arrhythmogenic effect, while a marked decrease could give rise to non-TdP mediated ventricular arrhythmias. Thereafter, Robyns et al. [14] showed in their clinical study a close and significant relationship between invasive cardiac electrophysiology study-derived (EPS-derived) ventricular ERP and ECG-derived QT interval, thus introducing a new ECG-derived surrogate marker of cardiac wavelength. They further reported that such respective drugs and clinical conditions conducive to TdP-mediated ventricular arrhythmias as sotalol and possessing mutations of congenital long QT syndrome increased both of iCEB and iCEBc, whereas some other conditions such as Brugada syndrome and use of flecainide which were conducive to non-TdP-mediated ventricular arrhythmias decreased the same parameters [14]. In our study, although iCEB was similar between the smoker and non-smoker groups, iCEBc was revealed to be significantly greater in habitual cigarette smokers. In addition, this increase in iCEBc is mainly derived from increased QTc interval in the smoker group, as mean QRS duration was similar between the study groups. Main strength of our study is the fact that we reported for the first time a significant increase in iCEBc in healthy subjects with chronic smoking habit. On the basis of our study findings, we may speculate that chronic cigarette smoking may pose an additive risk of TdP-mediated ventricular arrhythmias to those habitual smokers who had already been on QT-prolonging medications and/or inherently been carrying long QT syndrome mutations.

This study should be evaluated in the light of a number of limitations. First of all, our study population is relatively small and reflects only single-center experiences. Future larger-scale studies encompassing various health care centers may actually yield different results. Secondly, there is no widely-accepted reference range for normal iCEB(c) values, although Robyns et al. [14] proposed a preliminary reference range between 3.14 and 5.35 based on their study data. However, this reference may not apply correctly to our study population due to lack of confirmation with future studies with larger number of participants. Thirdly, we are not aware of the exact effect of acute cigarette smoking, since a certain portion of our study population might have smoked a cigarette shortly before ECG recordings. Moreover, the amount of the nicotine and tar that each participant consumed during cigarette smoking was not recorded, as different cigarette brands may have quite variable ingredients in differing amounts. This may have affected our study results to some extent. In addition, the participants were not stratified according to their total years of tobacco use to make a further comparison in regard of its effect on the relevant ECG parameters. Therefore, we tried to build our methodology on whether or not our smoker population was composed of the habitual smokers or not. By this way, we consider that our study population reflects a much more resemblance to ordinary smoker population samples in terms of randomization.

Table 4
Comparison of the ECG parameters between the smokers and non-smokers within each gender subgroup.

Variable	Female smokers (n = 36)	Female non-smokers (n = 32)	P* value	Male smokers (n = 44)	Male non-smokers (n = 50)	P** value
Heart rate, beats/min	83.9 ± 8.8	78.1 ± 9.6	**0.012**	79.7 ± 8.8	76.1 ± 10.1	**0.040**
PR interval, msec	142.8 ± 15.5	145.4 ± 16.6	0.591	153.5 ± 20.5	151.7 ± 9.8	0.742
QRS duration, msec	81.3 ± 7.7	83.7 ± 6.0	0.240	87.8 ± 6.2	89.1 ± 6.1	0.567
QT interval, msec	364.5 ± 22.4	371.4 ± 19.3	0.258	367.6 ± 23.0	365.2 ± 31.8	0.663
QTc interval, msec	424.6 ± 26.7	403.2 ± 11.5	**0.002**	430.0 ± 17.5	394.6 ± 13.7	<**0.001**
Tp-Te, msec	76.12 ± 7.2	71.23 ± 8.8	**0.017**	79.07 ± 6.9	74.81 ± 7.6	**0.028**
iCEB	4.51 ± 0.44	4.58 ± 0.40	0.665	4.20 ± 0.45	4.11 ± 0.39	0.517
iCEBc	5.25 ± 0.51	4.83 ± 0.36	**0.002**	4.91 ± 0.42	4.44 ± 0.33	**0.001**

P*, Female smokers vs Female non-smokers.
P**, Male smokers vs Male non-smokers.
iCEB: index of cardiac electrophysiological balance. iCEBc: index of cardiac electrophysiological balance with heart rate correction.
P values in bold indicate the comparison is of statistical significance.

Conclusion

In conclusion, iCEBc increases significantly in otherwise healthy subjects with habitual cigarette smoking, compared with the healthy non-smokers. In addition, this effect is mainly derived from increased QTc duration rather than shortened QRS duration. Our findings may suggest an increased predisposition to TdP-mediated ventricular tachycardia and fibrillation even in healthy habitual smokers, or may call attention to a possible increase in the susceptibility to TdP-mediated arrhythmias in chronic smokers with inherent QT-prolonging genetic variations or those on QT-prolonging drug therapy.

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CRediT authorship contribution statement

Levent Özdemir: Conceptualization, Methodology, Software, Visualization, Investigation, Supervision. **Erdoğan Sökmen:** Data curation, Writing - original draft, Writing - review & editing.

Declaration of competing interest

We declared this study possess no conflict of interests.

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