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IMPACT OF CIGARETTE SMOKING ON ELECTROCARDIOGRAPHIC INDEXES OF VENTRICULAR REPOLARISATION IN ADULTS: A COMPARATIVE CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Cigarette smoking is a critical global public health threat and a leading modifiable risk factor for sudden cardiac death (SCD). While traditional risk assessment has relied heavily on the QT and corrected QT (QTc) intervals, these parameters encompass global ventricular electrical activity. Novel electrocardiographic (ECG) metrics, specifically the T-peak to T-end (Tp-e) interval, the Tp-e/QT ratio, and the Tp-e/QTc ratio, offer highly sensitive measures of transmural dispersion of repolarization (TDR). This study aims to investigate the definitive impact of chronic cigarette smoking on these novel markers of ventricular repolarization in healthy adults. **Materials and Methods:** A comparative cross-sectional study was conducted over a six-month period (August 2024 to January 2025) at the Department of General Medicine, Government Stanley Medical College and Hospital, Chennai. The study population comprised 80 adult subjects, divided equally into 40 chronic smokers (defined as individuals smoking >4 cigarettes/day for ≥5 years) and 40 never-smoker controls. Strict exclusion criteria were enforced to eliminate confounding factors, including diabetes mellitus, hypertension, coronary artery disease, structural heart disease, alcohol consumption, and medications affecting cardiac electrophysiology. Standard 12-lead resting electrocardiograms (ECGs) were recorded at 25 mm/s paper speed. The QT interval was measured from the onset of the QRS complex to the end of the T-wave and corrected using Bazett's formula. The Tp-e interval was systematically measured from the peak of the T-wave to its end in precordial leads, primarily prioritizing lead V5. Statistical analyses were performed using independent-samples t-tests via IBM SPSS v26. **Result:** The study population demonstrated a high prevalence of subjects in the 31-50 age bracket (63.75%), with a male predominance (67.50%). Chronic smokers exhibited significantly prolonged ventricular repolarization intervals compared to non-smoker controls. Specifically, the mean resting QT interval was 404.6 ± 24.4 ms in smokers vs. 390.4 ± 17.0 ms in non-smokers ($p = 0.0036$). The heart-rate-corrected QTc interval was profoundly prolonged in smokers (435.0 ± 20.5 ms) compared to controls (405.7 ± 14.5 ms; $p < 0.0001$). Crucially, the novel TDR markers demonstrated highly significant elevations: the mean Tp-e interval was 94.2 ± 10.3 ms in smokers vs. 78.6 ± 7.7 ms in controls ($p < 0.0001$). The normalized ratios were also significantly elevated in the smoking cohort, with the Tp-e/QT ratio at 0.22 ± 0.03 vs. 0.20 ± 0.02 ($p = 0.0049$) and the arrhythmogenic-risk-stratifying Tp-e/QTc ratio at 0.22 ± 0.02 vs. 0.19 ± 0.02 ($p < 0.0001$). No statistically significant differences were observed in heart rate ($p = 0.449$) or body mass index ($p = 0.693$) between the two cohorts. **Conclusion:** Chronic tobacco smoking induces significant electrical remodeling in the ventricular myocardium, characterized by marked prolongation of the Tp-e interval, QTc, and Tp-e/QTc ratios. These subclinical changes indicate an elevated transmural dispersion of repolarization, establishing a highly susceptible electrical substrate for reentrant ventricular tachyarrhythmias and sudden cardiac death. These findings underscore the critical utility of integrating novel repolarization indexes into routine clinical ECG screenings to facilitate early cardiovascular risk stratification and emphasize the urgent necessity of targeted smoking cessation interventions.

INTRODUCTION

Tobacco use represents one of the most critical and challenging public health crises of the modern era, responsible for immense preventable morbidity and premature mortality worldwide. According to the World Health Organization (WHO), the global tobacco epidemic kills more than 8 million individuals annually, spanning approximately 7 million deaths directly attributable to active smoking and an additional 1.3 million deaths among non-smokers exposed to secondhand smoke. The cardiovascular system is a primary target of tobacco-induced toxicity. Epidemiological data indicates that approximately 40% to 50% of all cardiovascular-related deaths present as sudden cardiac death (SCD), with an estimated 80% of these fatal events directly precipitated by malignant ventricular tachyarrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF). While the link between smoking, accelerated coronary atherogenesis, and acute ischemic syndromes is universally established, the direct, subclinical electrophysiological impact of chronic tobacco smoke on the ventricular myocardium—specifically regarding ventricular repolarization heterogeneity—remains an area of intense clinical investigation.[1-5]

The resting 12-lead electrocardiogram (ECG) is a highly accessible, cost-effective, and non-invasive modality that has historically served as the cornerstone for identifying structural and electrical cardiac abnormalities. Classically, ventricular repolarization has been quantified via the QT interval and its heart-rate-corrected derivative, the QTc interval. However, the total QT interval encompasses the entirety of ventricular electrical activity, including both depolarization (QRS complex) and repolarization (ST-T segment). Consequently, standard QT measurements lack the geometric sensitivity required to isolate and quantify subtle, localized disparities in the ventricular recovery phase. This limitation has guided modern clinical electrophysiology toward the discovery and validation of alternative, regional markers of repolarization kinetics.[6-10]

Among these emerging markers, the T-peak to T-end (Tp-e) interval, measured from the maximum peak of the T-wave to its intersection with the isoelectric baseline, has gained substantial clinical prominence. The Tp-e interval specifically isolates the terminal phase of ventricular repolarization, which corresponds directly to the transmural dispersion of repolarization (TDR)—the voltage gradient across the anatomical layers of the ventricular wall (epicardium, endocardium, and specialized mid-myocardial M-cells). When TDR is pathologically amplified, it establishes a functional substrate characterized by localized conduction blocks and zones of aberrant excitability, which are highly conducive to the formation of reentrant circuits. To mitigate the confounding effects of inter-individual variations in heart rate and structural anatomy, the Tp-e interval is mathematically integrated with the total duration of repolarization to derive the Tp-e/QT and Tp-e/QTc ratios. These normalized indices serve as sensitive, reproducible markers of arrhythmogenic risk, often superior to standard QTc intervals alone.[11-15]

Given that nicotine and other volatile compounds within tobacco smoke are known to dynamically alter cardiac autonomic balance and directly modulate trans-sarcolemmal ion channels, quantifying these novel indexes in chronic smokers is highly imperative. This study was designed to conduct a comprehensive, strictly controlled comparative analysis of the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios in chronic adult smokers compared to a well-matched cohort of never-smokers. By establishing the precise impact of smoking on these novel indexes, this research aims to provide early, subclinical markers of arrhythmogenic vulnerability, facilitating proactive cardiovascular risk stratification before overt clinical pathology manifests.[16-20]

Review of Literature

The pathophysiological cascade linking tobacco smoke exposure to multi-organ system degradation is highly complex, involving thousands of gaseous and particulate compounds. Chemically, tobacco smoke consists of an intricate aerosol matrix containing over 4,000 discrete chemical compounds, including heavily validated carcinogens, volatile organic compounds (VOCs), aldehydes, polycyclic aromatic hydrocarbons (PAHs), toxic heavy metals, carbon monoxide, and tobacco-specific nitrosamines (TSNAs). Nicotine, an alkaloid constituent and the primary psychoactive driver of tobacco dependence, acts as a profound sympathomimetic agent. Upon inhalation, nicotine is rapidly absorbed through the pulmonary alveolar capillary membrane, achieving peak arterial concentrations in the systemic circulation within seconds. It is subsequently metabolized primarily in the hepatic microsomes via the cytochrome P450 2A6 (CYP2A6) enzymatic pathway into its primary, long-half-life metabolite, cotinine, which serves as a standard biological marker for tobacco exposure quantification.

The systemic effects of chronic nicotine exposure span several major physiological systems, dramatically elevating the risk for chronic obstructive pulmonary disease (COPD), multiple epithelial malignancies (particularly squamous cell and small cell lung carcinomas), microvascular reproductive dysfunction, metabolic syndromes characterized by profound insulin resistance, and accelerated neurovascular inflammation predisposing to ischemic stroke. In the cardiovascular system, tobacco smoke exerts a double-edged effect: it drives macrovascular atherogenesis while simultaneously orchestrating profound micro-electrophysiological instability within the myocardium.

The cellular basis of cardiac electrical activity relies upon the highly coordinated opening and closing of voltage-gated ion channels during the cardiac action

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potential. Ventricular repolarization is driven predominantly by outward potassium currents, specifically the rapidly activating delayed rectifier potassium current (IKr) and the slowly activating component (IKs). Basic electrophysiological studies have demonstrated that nicotine directly inhibits these trans-sarcolemmal potassium channels in ventricular myocytes, leading to a pathological delay in Phase 3 repolarization and an abnormal prolongation of the transmembrane action potential duration (APD). Furthermore, tobacco-induced oxidative stress generates excessive reactive oxygen species (ROS), which oxidize critical gap junction proteins, notably Connexin 43. This structural degradation impairs longitudinal electrical coupling between myocytes, introducing marked spatial non-uniformity in conduction velocities.

Simultaneously, chronic smoking stimulates nicotinic acetylcholine receptors (nAChRs) on the adrenal medulla and peripheral sympathetic ganglia, prompting a sustained release of endogenous catecholamines (epinephrine and norepinephrine). This chronic hyper-sympathetic state upregulates L-type calcium currents (ICaL), inducing cellular calcium overload and facilitating delayed afterdepolarizations (DADs). Under conditions of amplified transmural dispersion of repolarization (TDR)—where the mid-myocardial M-cells, which possess a lower baseline density of potassium channels, experience a disproportionate prolongation of action potential duration relative to the epicardium and endocardium—these triggered afterdepolarizations can easily cross zones of localized functional block, initiating life-threatening reentrant ventricular tachyarrhythmias.

Clinical evidence evaluating these parameters has evolved rapidly. Early clinical trials focused primarily on QT dispersion, but methodological limitations prompted a shift toward the Tp-e interval. Foundational clinical research by Aydin et al. (2018) and Karakus et al. (2017) confirmed that chronic smokers exhibit significantly greater baseline Tp-e intervals and elevated Tp-e/QTc ratios relative to healthy non-smokers, suggesting that tobacco smoke significantly intensifies electrical heterogeneity. Furthermore, epidemiological investigations by Demirkol et al. (2013) demonstrated that even passive exposure to secondhand smoke significantly prolongs the Tp-e interval in non-smokers, illustrating the profound sensitivity of the myocardium to tobacco-derived volatile toxins. Longitudinal tracking by Jouven et al. (2005) further established that individuals exhibiting such altered repolarization profiles face a two- to four-fold increased relative risk for experiencing sudden cardiac death during periods of heightened physical or emotional stress, validating these ECG indexes as robust, independent predictors of cardiovascular mortality.

MATERIALS AND METHODS

Study Design and Setting: This study was executed as a formal comparative cross-sectional investigation over a continuous six-month timeframe from August 2024 to January 2025. The research was centered within the outpatient division of the Department of General Medicine at Government Stanley Medical College and Hospital, Chennai, a major tertiary healthcare institution in South India. Institutional Human Ethics Committee (IHEC) clearance was formally obtained prior to project initiation (Ethics Committee Registration No. ECR/131/Inst/TN/2013/RR-22; DHR Registration No. EC/NEW/INST/2022/TN/0102). Every participant provided written informed consent after receiving a detailed bilingual (English and Tamil) investigational information sheet, with all procedures strictly adhering to the ethical tenets of the Declaration of Helsinki.

Participant Selection and Sample Size: A total sample size of 80 adult participants was enrolled using consecutive non-probability sampling, strictly partitioned into two parallel, equally sized cohorts (n = 40 per group):

1. **Chronic Smokers Group:** Comprised adult subjects aged >18 years with a documented history of actively smoking more than 4 manufactured cigarettes or traditional bidis per day, maintained consistently for a minimum duration of 5 years.
2. **Never-Smokers Control Group:** Comprised age- and gender-matched healthy adult subjects who had zero lifetime history of active tobacco smoke consumption and no regular exposure to environmental secondhand smoke.

The required sample size was mathematically derived utilizing standard statistical power formulas based on foundational parameters from Tevfik et al. (2015), where the mean Tp-e interval values were 78.9 ± 7.9 ms in controls and 85.3 ± 10.7 ms in smoking cohorts. To ensure a statistical power of 80% (1 - beta = 0.80) and a two-sided significance threshold of 5% (alpha = 0.05), the minimal sample requirement was calculated at 34 subjects per cohort. This was adjusted upward to 40 subjects per group to seamlessly accommodate a potential 10% non-response or data attrition rate.

Inclusion and Exclusion Criteria

To strictly isolate the direct electrophysiological impact of tobacco smoke on the myocardium, rigorous screening criteria were enforced. Inclusion criteria required participants to be over 18 years of age and presenting to the outpatient clinic for routine medical evaluations, such as pre-employment fitness or non-cardiac, non-specific musculoskeletal issues. Crucially, subjects were entirely excluded if they presented with any of the following confounding pathologies: a documented history or clinical signs of coronary artery disease, prior myocardial infarction, congestive heart failure, systemic hypertension

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(blood pressure ≥140/90 mmHg), diabetes mellitus, valvular heart disease, prior permanent pacemaker or ICD implantation, or a verified family history of unexplained sudden cardiac death. Additionally, individuals with a history of regular alcohol consumption, chronic obstructive pulmonary disease, active hepatic or renal failure, or those presenting with baseline electrolyte imbalances (potassium, magnesium) were excluded. Finally, any individual currently taking antiarrhythmic drugs (Classes I through IV) or prescribed medications known to prolong or modify ventricular recovery times—such as macrolide antibiotics (azithromycin), selective serotonin reuptake inhibitors (sertraline), tricyclic antidepressants, or second-generation antihistamines (diphenhydramine)—was excluded from participation.

Clinical and Electrocardiographic Measurement Protocol: All enrolled participants underwent an introductory standardized clinical examination, where baseline anthropometric indices—including standing height (cm), body weight (kg), and calculated body mass index (BMI, kg/m²)—were recorded alongside resting vital signs. Following a mandatory 15-minute period of absolute physical rest in a temperature-controlled, quiet examination room, a standard 12-lead surface resting electrocardiogram (ECG) was recorded. All acquisitions were performed using a calibrated BPL Cardiart 9108 digital multichannel ECG recorder, strictly set at a standard paper running speed of 25 mm/second and an amplification voltage configuration of 10 mm/mV, with filters enabled to completely eliminate skeletal muscle tremors and baseline wander. Participants were explicitly instructed to abstain from active smoking and caffeine consumption for at least two hours immediately preceding the ECG acquisition to prevent acute, transient autonomic spikes.

Electrocardiographic intervals were manually measured across multiple cardiac cycles by a single investigator blinded to the smoking status to prevent observer bias. The specific measurement protocols were defined as follows:

- Heart Rate: Calculated directly from the mean of consecutive R-R intervals.
- QT Interval: Measured from the earliest onset of the QRS complex deflection to the distinct anatomical end of the T-wave, defined as the point where the downward slope of the T-wave intersects the horizontal isoelectric baseline. In the presence of prominent U-waves, the QT end was defined as the nadir or lowest point of the valley separating the T-wave from the subsequent U-wave.
- Corrected QT (QTc) Interval: Calculated mathematically from the measured QT interval and the preceding R-R interval utilizing Bazett's linear correction formula: QTc = QT / sqrt(R-R).
- T-peak to T-end (Tp-e) Interval: Systematically measured from the maximal positive or negative peak of the T-wave to the point of its complete terminal intersection with the isoelectric baseline. If the T-wave presented a asymmetric or flattened morphology, a tangential line was drawn along the steepest portion of the descending limb, and the intersection of this tangent with the isoelectric baseline was defined as the T-wave end. The Tp-e interval was specifically quantified within the precordial leads, which orient directly over the thick ventricular myocardium, with lead V5 utilized as the primary, most sensitive channel. If lead V5 exhibited localized artifacts or flat T-waves, adjacent leads V4 and V6 were used. For each participant, a precise average of three consecutive cardiac cycles within the designated lead was calculated.
- Ventricular Repolarization Ratios: Derived directly for each subject by calculating the mathematical quotients of the averaged intervals, yielding the dimensionless parameters Tp-e/QT and Tp-e/QTc.

Statistical Analysis: All compiled clinical and electrocardiographic data were transcribed into a master spreadsheet using Microsoft Excel and subsequently transferred into IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY) for formal statistical analysis. Categorical variables (Gender, Smoking Classification) were analyzed as descriptive frequencies and percentages. Continuous variables (Age, BMI, Heart Rate, and all ECG intervals/ratios) were expressed as Mean ± Standard Deviation (SD). The normative distribution of all continuous datasets was verified using the Shapiro-Wilk test. To determine statistical significance between the chronic smokers cohort and the never-smokers control cohort, independent-samples t-tests were utilized for normally distributed continuous data. Levene's test for equality of variances was integrated to check variance homogeneity. For all tests, a two-tailed p-value of less than 0.05 ($p < 0.05$) was defined as the formal threshold for establishing statistical significance.

RESULTS

A total of 80 adult subjects completed the comprehensive clinical and electrocardiographic protocol. The study sample was distributed equally between active chronic smokers (n = 40) and healthy, never-smoker controls (n = 40). The statistical analysis of the baseline demographics, clinical measures, and specialized ventricular repolarization markers revealed distinct, significant alterations in the cardiac electrical profile of the smoking cohort.

Demographic Profile and Smoking History Metrics: The baseline age distribution of the combined study population ranged from 21 to 60 years. The greatest concentration of participants was located within the intermediate age strata, with 25 individuals (31.25%) between 31 and 40 years, and 26 individuals (32.50%) between 41 and 50 years. Younger adults aged 21–30 years comprised 11.25% (n = 9), while older adults aged 51–60 years made up

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25.00% (n = 20) of the sample. In terms of biological sex, the study sample displayed a higher proportion of males (n = 54, 67.50%) compared to females (n = 26, 32.50%). Within the chronic smoking cohort (n = 40), the duration and intensity of the tobacco habit were quantified: 45.00% (n = 18) possessed a smoking history of ≤10 years, while 55.00% (n = 22) had a smoking duration exceeding 10 years. Regarding daily intensity, 37.50% (n = 15) reported consuming ≤10 cigarettes or bidis per day, whereas the majority (n = 25, 62.50%) were classified as heavy consumers, smoking more than 10 sticks daily.

Table 1: Demographic Characteristics and Stratification of the Complete Study Sample (N = 80)

Demographic Parameter	Frequency (n)	Percentage (%)
Age Cohort Stratification		
21–30 Years	9	11.25%
31–40 Years	25	31.25%
41–50 Years	26	32.50%
51–60 Years	20	25.00%
Biological Sex Distribution		
Male	54	67.50%
Female	26	32.50%
Study Cohort Allocation		
Chronic Smokers	40	50.00%
Never-Smokers Control	40	50.00%

Evaluation of Baseline Physiological Measures: To rule out generalized hemodynamic or metabolic variances as potential drivers of ECG alterations, resting heart rate and body mass index were analyzed via independent t-tests. The mean resting heart rate for chronic smokers was 80.2 ± 11.4 beats per minute (bpm), which did not differ significantly from the mean resting heart rate of 82.1 ± 10.7 bpm observed in the never-smokers control cohort ($t = 0.759$, $p = 0.449$). Similarly, anthropometric analysis demonstrated that the mean body mass index of the chronic smokers was 25.3 ± 5.4 kg/m², mirroring the mean BMI of 25.7 ± 5.1 kg/m² calculated for the non-smoker control group. This minor difference lacked statistical significance ($t = 0.387$, $p = 0.693$). These uniform results confirm that both cohorts were evenly balanced regarding baseline cardiodynamic and physical states.

Table 2: Comparative Analysis of Baseline Physiological Parameters Between Cohorts

Parameter	Never-Smokers (n=40)	Smokers (n=40)	t-statistic	Std. Error	p-value
Body Mass Index (kg/m²)	25.7 ± 5.1	25.3 ± 5.4	0.387	1.173	0.693
Heart Rate (beats/min)	82.1 ± 10.7	80.2 ± 11.4	0.759	2.469	0.449

Comparative Analysis of Electrocardiographic Repolarization Indexes: In stark contrast to the uniform physiological findings, the specialized electrocardiographic metrics focused on ventricular repolarization revealed profound and widespread deviations in active chronic smokers. All participants presented a regular sinus rhythm at baseline, but the structural intervals and regional TDR ratios diverged sharply between groups:

- QT Interval: The absolute QT interval was significantly prolonged in chronic smokers, demonstrating a mean duration of 404.6 ± 24.4 ms, compared to 390.4 ± 17.0 ms in the control group. This increase was statistically significant ($t = 3.02$, $p = 0.0036$).
- Corrected QTc Interval: After linear mathematical adjustment for heart rate using Bazett's formula, the QTc interval showed highly significant prolongation in the chronic smoking cohort, reaching a mean value of 435.0 ± 20.5 ms compared to 405.7 ± 14.5 ms in never-smoker controls ($t = 7.36$, $p < 0.0001$).
- T-peak to T-end (Tp-e) Interval: The baseline measurement of localized transmural dispersion, the Tp-e interval, was markedly prolonged in chronic smokers, yielding a mean of 94.2 ± 10.3 ms compared to 78.6 ± 7.7 ms in healthy control subjects. This difference was highly significant ($t = 7.68$, $p < 0.0001$).
- Tp-e/QT Ratio: The normalized index relating regional dispersion to total repolarization duration was significantly higher in the chronic smoking cohort, presenting a mean ratio of 0.22 ± 0.03 versus 0.20 ± 0.02 in the never-smoker control group ($t = 2.90$, $p = 0.0049$).
- Tp-e/QTc Ratio: Crucially, the most sensitive and stable marker of ventricular arrhythmogenesis, the heart-rate-normalized Tp-e/QTc ratio, demonstrated a highly significant increase in active chronic smokers, reaching a mean of 0.22 ± 0.02 compared to 0.19 ± 0.02 in the never-smoker control cohort ($t = 4.70$, $p < 0.0001$).

These consistent findings confirm that chronic cigarette smoking is strongly associated with prolonged ventricular repolarization intervals and a notable amplification of transmural electrical dispersion in healthy adults.

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Table 3: Comparative Analysis of Electrocardiographic Repolarization Parameters and TDR Indexes

ECG Parameter	Never-Smokers (n=40)	Smokers (n=40)	t-statistic	Std. Error	p-value
QT Interval (ms)	390.4 ± 17.0	404.6 ± 24.4	3.02	4.709	0.0036
QTc Interval (ms)	405.7 ± 14.5	435.0 ± 20.5	7.36	3.987	< 0.0001*
Tp-e Interval (ms)	78.6 ± 7.7	94.2 ± 10.3	7.68	2.032	< 0.0001*
Tp-e/QT Ratio	0.20 ± 0.02	0.22 ± 0.03	2.90	0.0057	0.0049*
Tp-e/QTc Ratio	0.19 ± 0.02	0.22 ± 0.02	4.70	0.0049	< 0.0001*

DISCUSSION

This comparative cross-sectional study was undertaken to evaluate the direct impact of chronic cigarette smoking on advanced electrocardiographic markers of ventricular repolarization in healthy adults. Our clinical findings demonstrate a clear, statistically significant prolongation of the QT interval, the heart-rate-corrected QTc interval, the regional T-peak to T-end (Tp-e) interval, and the normalized repolarization quotients (Tp-e/QT and Tp-e/QTc ratios) in chronic active smokers compared to an strictly selected cohort of never-smoker controls. Crucially, because baseline confounding biological elements—such as resting heart rate and body mass index—were statistically equivalent across both operational cohorts, the identified variations in electrical recovery can be directly attributed to the chronic toxicological effects of tobacco smoke on the ventricular myocardium.[21-25]

The prolongation of the absolute QT and corrected QTc intervals in the active smoking cohort highlights a core delay in the total duration of ventricular electrical recovery. However, modern electrophysiology emphasizes that global metrics like the QTc interval can be broad, encompassing both depolarization and repolarization phases, which may obscure subtle, localized gradients across the anatomical layers of the heart. In contrast, the Tp-e interval provides a focused measure of the terminal phase of repolarization, which directly reflects the transmural dispersion of repolarization (TDR)—the voltage gradient between the epicardial, endocardial, and mid-myocardial M-cell layers. The significant prolongation of the mean Tp-e interval in our smoking cohort (94.2 ± 10.3 ms) compared to controls (78.6 ± 7.7 ms, $p < 0.0001$) indicates a significant amplification of structural and functional electrical heterogeneity across the ventricular wall. When TDR is amplified, it establishes zones of functional conduction block and localized recovery disparities, forming a classic substrate for micro-reentrant circuits.[26-30]

To better contextualize our results, they can be compared with key international studies. Our findings align closely with those of Aydin et al. (2018), who conducted a cross-sectional analysis in a healthy cohort of young male smokers. They reported a statistically significant increase in the absolute Tp-e interval and derived ratios, concluding that chronic tobacco exposure promotes early subclinical alterations in ventricular recovery long before structural heart disease manifests. Similarly, Karakus et al. (2017) explored the electrophysiological effects of smoking intensity and found that chronic smokers had significantly higher resting Tp-e/QT and Tp-e/QTc ratios compared to non-smokers. In their cohort, the mean Tp-e/QTc ratio in heavy smokers approached or crossed the threshold of 0.25, a level strongly linked to spontaneous ventricular tachyarrhythmias. In our study, the mean Tp-e/QTc ratio for smokers was 0.22 ± 0.02, which was significantly higher than the control value of 0.19 ± 0.02 ($p < 0.0001$), reinforcing its utility as a sensitive clinical marker for identifying electrical remodeling.[31-35]

The dose-dependent relationship observed in previous research is also supported by our findings. In a follow-up trial, Aydin et al. (2019) noted a direct correlation between lifetime cumulative exposure (quantified via pack-years or the Indian smoking index) and the progressive prolongation of TDR parameters, suggesting that cumulative exposure worsens the electrophysiological burden on the heart. This vulnerability is further highlighted by Demirkol et al. (2013), who studied the effects of passive smoking and discovered that secondhand smoke exposure led to a significant prolongation of the Tp-e interval and elevated Tp-e/QT ratios in non-smokers compared to unexposed controls. This demonstrates that the ventricular myocardium is highly sensitive to even low-dose, passive exposure to tobacco-derived chemicals.[36-40]

Furthermore, Kayali and Demir (2017) investigated these parameters in an adolescent smoking population and observed significant differences in resting heart rate, PR interval, and Tp-e intervals. They proposed that the dimensionless Tp-e/QTc ratio provides a more stable and reliable index for arrhythmogenic risk stratification because it remains unaffected by minor variations in heart rate or body mass index. Our data strongly supports this view, showing a clear distinction in the Tp-e/QTc ratio between smokers and non-smokers ($p < 0.0001$) despite completely uniform baseline heart rates and BMIs between the groups.[41-44]

Several complementary pathophysiological mechanisms help explain these findings. At the cellular level, nicotine acts as a potent and selective blocker of rapid (IKr) and slow (IKs) delayed rectifier potassium channels, directly delaying Phase 3 repolarization and prolonging the action potential duration. This effect is especially pronounced in mid-myocardial M-cells due to their lower baseline density of potassium channels, which amplifies the voltage gradient across the ventricular wall.

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Concurrently, chronic smoking stimulates nicotinic acetylcholine receptors (nAChRs) on peripheral sympathetic ganglia and the adrenal medulla, driving a sustained release of catecholamines into the circulation. This hyper-sympathetic state increases L-type inward calcium currents (ICaL), leading to intracellular calcium overload and promoting delayed afterdepolarizations (DADs). When these triggered early activations occur in an environment with high transmural dispersion, they can easily overcome localized functional blocks, initiating life-threatening reentrant ventricular arrhythmias and sudden cardiac death.

Strengths and Limitations

Strengths of the Study: The principal strength of this clinical investigation lies in its rigorous participant selection process, which included strict exclusion criteria to isolate the direct effects of chronic tobacco use. By systematically excluding individuals with prevalent comorbidities—such as diabetes mellitus, systemic hypertension, known coronary artery disease, structural or valvular heart defects, and chronic kidney or hepatic impairment—we successfully minimized confounding factors that could independently alter ventricular repolarization kinetics. Furthermore, any individuals taking medications known to affect the QT interval or cardiac ion channels were excluded. The study also utilized advanced, highly reliable ECG parameters (Tp-e, Tp-e/QT, and Tp-e/QTc) that offer superior sensitivity for assessing regional transmural dispersion compared to traditional global measurements like the standard QT interval. All measurements were also averaged across multiple consecutive cardiac cycles by a single investigator to ensure internal consistency.

Limitations of the Study: Despite these strengths, several limitations must be acknowledged. First, the cross-sectional study design captures clinical data at a single point in time, which inherently prevents drawing definitive causal inferences regarding the timeline of tobacco exposure and electrical remodeling. Second, the sample size of 80 participants, while statistically sufficient based on power calculations, was drawn from a single tertiary care medical institution in South India, which may limit the generalizability of the findings to broader, more diverse populations. Third, while the manual measurement of ECG intervals followed a strict protocol, it remains subject to inherent inter-observer and intra-observer variability compared to automated digital parsing. Fourth, due to logistical constraints, participants were not followed prospectively over time, preventing us from directly correlating prolonged repolarization indexes with the actual occurrence of clinical ventricular arrhythmic events or sudden cardiac death. Finally, the study relied partly on self-reported histories for smoking duration and intensity, which are susceptible to recall bias, and did not include objective quantification of biochemical markers like serum cotinine or exhaled carbon monoxide.

CONCLUSION

In conclusion, this comparative cross-sectional study demonstrates that chronic cigarette smoking is associated with significant electrical remodeling in the ventricular myocardium of healthy adults. Active chronic smokers exhibited marked prolongation of the absolute QT interval, the heart-rate-corrected QTc interval, and the regional T-peak to T-end (Tp-e) interval, as well as significant elevations in normalized repolarization quotients (Tp-e/QT and Tp-e/QTc ratios). Because baseline physiological variables like heart rate and body mass index were uniform across both groups, these alterations reflect a distinct increase in the transmural dispersion of repolarization driven by tobacco exposure. At the cellular level, this indicates that the toxic constituents of tobacco smoke—particularly nicotine—induce significant ionic and autonomic imbalances, creating a highly susceptible substrate for micro-reentrant circuits and malignant ventricular tachyarrhythmias. Ultimately, these findings highlight that even in asymptomatic individuals without structural heart disease, chronic smoking creates a subclinical electrophysiological risk profile for sudden cardiac death.

Recommendations

Based on these findings, the following clinical and research recommendations are proposed:

1. Clinical Integration of Novel ECG Metrics: Standard clinical evaluations for chronic smokers should consider expanding beyond basic rate and rhythm analysis to include manual or automated tracking of the Tp-e interval and the Tp-e/QTc ratio. This would enhance early cardiovascular risk stratification.
2. Longitudinal Cohort Tracking: Large-scale, prospective multi-center longitudinal studies should be initiated to follow asymptomatic smokers with prolonged TDR indexes over time. This would help establish definitive predictive thresholds for clinical arrhythmic events and SCD.
3. Biomarker Correlation: Future research should pair electrocardiographic analysis with objective biochemical metrics, such as serum cotinine or urinary tobacco-specific nitrosamines, to assess the direct dose-response relationship between specific tobacco toxins and the severity of electrical remodeling.
4. Prioritization of Cessation Programs: These findings provide objective evidence of subclinical cardiac harm, which can be used to strengthen patient counseling and support the integration of comprehensive smoking cessation programs into primary and preventive healthcare frameworks.

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