Journal of the American Heart Association

ORIGINAL RESEARCH

Ventricular Repolarization in Healthy Young Adults Who Use Combusted Cannabis: A Cross-Sectional Parallel Group Comparison Study

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BACKGROUND: Inhaled combusted cannabis and co-use of combusted cannabis and nicotine electronic cigarettes (ECIGs) are emerging trends among young adults, yet the potential cardiovascular disease risks associated with these substances remain unclear. This study examined whether cannabis use increases cardiovascular disease risk, specifically, arrhythmia risk, as estimated by ventricular repolarization, and whether ECIG co-use further amplifies this risk.

METHODS: A cross-sectional parallel group comparison study was conducted with 3 groups: healthy adults (21–30 years) who (1) chronically use combusted cannabis but no tobacco, (2) chronically co-use both nicotine ECIGs and combusted cannabis, and (3) are nonusers (controls). The primary outcomes, Tpeak-Tend (Tp-e) interval, Tp-e/QT, and Tp-e/QTc, were assessed using 5-minute ECG recordings during supine rest and abrupt standing. Secondary outcomes included resting hemodynamic parameters and heart rate variability.

RESULTS: The study enrolled 134 participants (cannabis use=59, cannabis/ECIG co-use=26, control=49). The demographics among the groups did not differ. At supine rest, the Tp-e interval was not different between the combusted cannabis users (88±18 milliseconds) and controls (91±20 milliseconds; P=0.68). In contrast, the Tp-e was significantly shorter in the cannabis/ECIG co-use group (77±15 milliseconds) compared with the cannabis (P=0.017) and control (P=0.003) groups. These findings were confirmed upon abrupt standing. Hemodynamic and heart rate variability parameters did not differ among groups.

CONCLUSIONS: In healthy young adults, chronic co-use of inhaled combusted cannabis and nicotine ECIGs, but not exclusive cannabis use, is associated with alterations in ventricular repolarization as estimated by Tp-e. The implications of short ventricular repolarization in people who co-use nicotine ECIGs and inhaled combusted cannabis warrant further investigation.

Key Words: cannabis ■ co-use ■ electronic cigarette ■ heart rate variability ■ ventricular repolarization

Thirty-eight states and the District of Columbia have now legalized cannabis for medical or nonmedical use, contributing to both its widespread use and the widely held belief that cannabis is safe.[1] Although many forms of cannabis are available, including vaporized and edible, combusted cannabis remains the most popular form.[2] In contrast, combusted tobacco use has never been lower, especially among young people.[3] Nicotine electronic cigarettes (ECIGs) have become the tobacco product of choice among young people; in fact, their popularity caused the Food and Drug Administration Commissioner, Scott Gottlieb, to

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This article was sent to William W. Aitken, MD, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 11.

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CLINICAL PERSPECTIVE

What Is New?

- In young people, combusted cannabis use and co-use of combusted cannabis and nicotine electronic cigarettes are highly prevalent, but the cardiovascular risks, specifically the arrhythmia risks, associated with chronic use of these substances, are not known.
- People who (1) chronically use combusted cannabis but not nicotine products, (2) chronically use combusted cannabis and nicotine electronic cigarettes, or (3) are nonusing controls, who met eligibility criteria, were invited to enroll in our cross-sectional study comparing ventricular repolarization and heart rate variability as measured on the ECG, at baseline (in the absence of acute exposure).
- In our small study, in cannabis users, ventricular repolarization was not different from that in controls, but after a provocative maneuver, abrupt standing, some measures became significantly shorter compared with controls. In the co-use group, ventricular repolarization was significantly shorter at baseline compared with the cannabis group and controls, and following abrupt standing, additional measures of ventricular repolarization became significantly shorter compared with the control and cannabis groups.

What Are the Clinical Implications?

- Although traditionally it is prolongation of ventricular repolarization that has been associated with increased cardiovascular risk, emerging research has found that short ventricular repolarization may also be associated with increased risk for lethal ventricular arrhythmias. Because rates of co-use of cannabis/ECIG are very high, further studies into this novel and potentially concerning finding are warranted.

Nonstandard Abbreviations and Acronyms

CUDIT-R	Cannabis Use Disorder Identification Test-Revised
ECIGs	electronic cigarettes
HF	high-frequency
HRV	heart rate variability
LF	low-frequency
TCIGs	traditional cigarettes
Tp-e	Tpeak-Tend

declare "an epidemic of e-cigarette use" among young people in 2018.[4] The candy flavorings and novel dispensing devices that typify ECIGs have contributed to their popularity and to the widespread belief that they are safe.[5] Unfortunately, the long-term health effects of these popular products, combusted cannabis and nicotine ECIGs, are not known. Further, the health risks of co-use, defined as regular use of both products within the past year, remain unknown.

We have reported that exclusive nicotine electronic cigarette use increases key instigators of cardiovascular disease (CVD), including altered sympathetic nerve activity,[6,7] inflammation,[8,9] and oxidative stress,[9–12] factors that contribute to atherogenesis as well as arrhythmogenesis, the focus of the present research. It has been suggested,[13] but remains uncertain, whether combusted cannabis use also has an adverse impact on these key instigators. It is possible that the adverse cardiac effects of ECIG and combusted cannabis co-use may be additive—or even synergistic—leading to harm amplification.

Arrhythmia risk can be estimated through ECG measures of ventricular repolarization and heart rate variability (HRV). Prolongation of the QT interval, a clinically useful measure of ventricular repolarization, has long been associated with ventricular arrhythmias and cardiovascular mortality[14]; however the QT interval includes both ventricular depolarization as well as repolarization.[14] T-wave related indices, such as the time from the peak of the T wave to the end of the T wave, the Tpeak-Tend (Tp-e) interval, have been promoted as a more precise measure of ventricular *repolarization*, the period most vulnerable to reentry and arrhythmogenesis. Prolongation of the Tp-e has been associated with increased risk of arrhythmia and sudden cardiac death in several populations and may be superior to QT in some settings.[15,16] We have reported that acute and chronic ECIG use may associated with alterations in the Tp-e, Tp-e/QT, and Tp-e/QTc.[17,18] However, little is known about the impact of chronic combusted cannabis use, either alone or with co-use of nicotine ECIGs, on measures of ventricular repolarization.

A shift in the cardiac sympathovagal balance towards decreased vagal tone, measurable through HRV, is another indicator of increased arrhythmia risk. Decreased HRV is associated with increased cardiac mortality in several populations with cardiac conditions[19–21]—and even in those without known cardiac disease.[22] Chronic ECIG use has been associated with decreased HRV[10]; conversely, chronic cannabis use has been associated with increased HRV in young men,[23] consistent with increased vagal tone. The effects of chronic cannabis use in women, and the combined effects of chronic co-use of nicotine ECIGs and cannabis on HRV remain unknown.

The purpose of the present study was to determine the association of chronic combusted cannabis use, and the co-use of combusted cannabis and nicotine ECIG, on ECG measures of ventricular repolarization and HRV, markers of arrhythmia risk. We hypothesized that compared with nonusing controls (1) exclusive combusted cannabis use would be associated with an adverse, proarrhythmic profile in ventricular repolarization but not HRV; and (2) co-use of both substances would also be associated with abnormalities in ventricular repolarization, as well as an adverse proarrhythmic pattern of HRV.

METHODS

The data that support the findings of this study are available upon reasonable request from the corresponding author, who has full access to the data and takes responsibility for data integrity and analysis.

Study Population

This parallel group comparison study evaluated healthy male and female subjects between the ages of 21 and 30 years who do not smoke traditional cigarettes (TCIGs). Participants were eligible for enrollment in the study if they met the following criteria: (1) nonobese (≤30 kg/m^2 body mass index); (2) no known health problems (including asthma, diabetes, heart disease, hypertension, or hyperlipidemia); (3) not a competitive athlete; (4) alcohol intake ≤2 drinks per day; (5) no illicit drug use other than cannabis, determined through screening questionnaire and urine toxicology testing; and (6) no TCIG use in the prior 1 year. Participants were categorized into 3 cohorts based on their patterns of inhaled cannabis and nicotine ECIG use: chronic (≥1 year, ≥1 time per week) use of (1) inhaled combusted cannabis, (2) inhaled combusted cannabis and nicotine ECIGs, or (3) nonusing controls. A fourth group of people who exclusively use ECIGs was initially included in the recruitment procedures; however, despite broad recruitment strategies, we were able to enroll only 4 healthy young adults who exclusively used ECIGs and did not also co-use TCIGs, cannabis, or other substances. As a result, the exclusive ECIG group was excluded from final analysis. Participants who used noncombusted forms of cannabis were eligible for the inhaled combusted cannabis group if they also regularly (≥1 time per week) used combusted cannabis. Former TCIG smoking was allowed if it had been at least 1 year since quitting. Participants were excluded from the study if they met the following exclusion criteria during the study visit: (1) nonsinus cardiac rhythm on ECG (eg, atrial fibrillation), (2) positive urine pregnancy test, (3) positive urine toxicology test for any substance other than cannabis, or (4) end tidal carbon monoxide measurement >10 ppm consistent with recent (within 8 hours) combusted cannabis use. The experimental protocol was approved by the Institutional Review Board at the University of California, Los Angeles (Los Angeles, CA) and written informed consent was obtained from each participant. All procedures were followed in accordance with institutional guidelines.

Phlebotomy

Blood samples were drawn by a trained medical assistant and sent to the University of California, Los Angeles Clinical Laboratory for measurement of plasma cotinine levels (half-life 36 hours), which was performed by the commercial laboratory, ARUP Laboratories, using the method of quantitative liquid chromatography—tandem mass spectrometry.

Urine Toxicology Screen

As previously reported,[24] at the beginning of each experimental session, participants provided a urine sample for immediate urine toxicology point-of-care testing for up to 12 drugs including delta-9-tetrahydrocannabinol as well as amphetamines, benzodiazepines, cocaine, methamphetamines, opiates, and oxycodone (Alere iCup Dx Pro 2, Avatar).

Questionnaire

Cannabis Use Disorder Identification Test-Revised (CUDIT-R)[25] was administered. This is a validated screening tool for cannabis use disorder that assesses patterns of cannabis consumption; impact on social, psychological, and physical functioning; and symptoms of dependence.

Ventricular Repolarization

Twelve-lead ECG recordings were analyzed using commercially available software (LabChart Pro 8 with ECG module, AdInstruments) as previously described.[26] For each of the 12 leads, all beats were averaged via block averaging resulting in 1 PQRST complex per lead for analysis. The ECG Analysis Module software automatically identified the onset of the QRS complex, the peak of the T wave, and the end of the T wave; cursors were placed on each autoidentified point and placement was confirmed by at least 2 investigators (J.S., R.F.). The software designated the Tp-e interval as the difference between the peak of the T-wave and the end of the T-wave. The software automatically identified the end of the T-wave as the intersection of the tangent to the T-wave's downslope and the isoelectric line.[16] For inverted T-waves, the Tp-e was measured as the interval from the nadir of the T-wave to the end of the T-wave.[27] Leads in which T waves were low amplitude (<1.5 mm) or flattened were not included in the analysis.[28] U-waves were not included in the Tp-e interval.[16] QTc was calculated using Bazett's formula.[28] QT dispersion was calculated as the difference between the maximum QT and minimal QT intervals among the 12 ECG leads. To establish interobserver validity, 2 independent investigators assessed and analyzed all ECGs for Tp-e and QT (J.S., R.F.). Any discrepancies >30% between the 2 investigators were flagged, independently reassessed, and reviewed by both investigators to reach an agreed upon measurement. The final reported mean Tp-e and QT values reflect an average of the mean Tp-e and QT values determined by the 2 independent investigators. Ratios were then calculated from these means including Tp-e/QT and Tp-e/QTc. The 5-minute ECG recordings recorded during supine rest and the 30-second recordings recorded during abrupt standing were analyzed separately.

Provocative Maneuver: Abrupt Standing

Provocative maneuvers, which acutely increase cardiac sympathetic tone, have been used to unmask occult differences in ventricular repolarization not evident during supine rest.[29–31] Accordingly, at the end of the 5-minute supine ECG recording, each participant was asked to stand abruptly, and a 30-second ECG recording was recorded.

Heart Rate Variability

HRV parameters were measured by an independent investigator (K.H.) from 1 lead of a 5-minute supine ECG using commercially available software (LabChart 8, ADInstruments) for HRV in the frequency domain and the time domain as previously described.[32] Briefly, in the time domain, the SD of RR intervals and the root mean square differences of successive RR intervals, both of which decrease with a decrease in relative parasympathetic dominance[32] were recorded. In the frequency domain, the high-frequency (HF) range (0.15–0.4 Hz), which indicates vagal activity; the low-frequency (LF) range (0.04–0.15 Hz), representing a blend of vagal and sympathetic influences; and the LF-to-HF ratio (LF:HF), which reflects the cardiac sympathovagal balance,[32] were recorded.

Study Session

Studies were conducted between 8 AM and 2 PM to avoid the potential influence of circadian rhythm on autonomic tone. Participants fasted and abstained from ECIGs, cannabis, caffeine, and exercise for 8 hours before the study. Participants provided a urine sample at the beginning of the study and completed questionnaires describing their cannabis use patterns.[25] Then, as previously described,[33] participants were placed in a supine position in a reclining chair with a footrest, in a quiet, temperature-controlled (21 °C) room in the Cannabis and Cannabinoid Research Laboratory in the University of California, Los Angeles Center for Cannabis and Cannabinoids. Skin was cleaned with alcohol wipes and 10 electrodes (3M Red Dot) were placed on the chest according to standard ECG protocol. Recording electrodes were foam silver-silver chloride conductors, 3.0 cm in diameter, with adhesive hydrogel. After a 10-minute rest period, blood pressure (BP) and HR were measured. Participants were not allowed to use their cell phones or talk during data acquisition. An ECG was then recorded for 5 minutes for later analysis for ventricular repolarization and HRV. The ECG was recorded with digital recording software (LabChart Pro 8 with ECG module, ADInstruments, 1000 Hz sampling frequency). Recordings were optimized to minimize noise and artifacts. At the end of the 5-minute recording period, the footrest was abruptly lowered, and the participant stood up quickly and then remained still. The ECG recording was continued for 30 seconds with standing, capturing peak HR and its subsequent return toward baseline. Blood was drawn, and the study was concluded. Investigators were not blinded to participant group during the experimental session but were blinded to group during the analysis of ventricular repolarization and HRV, which was performed later.

Statistical Analysis

The primary outcome measures were supine and standing Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. Secondary outcome measures included supine and standing QTc and QT dispersion, supine HRV parameters (SD of RR intervals, root mean square differences of successive RR intervals, HF, LF, and LF:HF ratio), and hemodynamic parameters (HR, systolic and diastolic BP, and mean arterial pressure). We performed all analyses using R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). The nonparametric Fisher least significant difference criterion was used to assess statistical significance differences in sex, race, or ethnicity among each group, and the unpaired nonparametric 1-way Kruskal–Wallis procedure was used to compute *P* values when comparing primary and secondary outcome measures among each group. The nonparametric Kruskal–Wallis was used because most outcomes did not follow a normal distribution, particularly in the tail area, although means are reported. All *P* values reported in text or figures are based on the absolute differences between primary outcomes. To convey the magnitude of differences in primary outcomes, mean percent differences and 95% CIs were calculated for the exclusive cannabis and cannabis/ECIG co-use groups relative to the control group. A multivariable regression analysis was performed to examine the associations between primary outcomes of ventricular repolarization (Tpe, Tpe/QT, and Tpe/QTc) and potential predictors, including age, blood cotinine level, total CUDIT-R score, urine positivity for tetrahydrocannabinol, and sex. All subjects were used in the analysis as there were no missing data. The regression coefficients are reported in standardized (partial correlation) units. Participant group (ie, control, exclusive cannabis, cannabis/ECIG co-use) was not included as a potential predictor in the model because groups were defined by the combination of urine tetrahydrocannabinol positivity, blood cotinine level, and CUDIT-R score. For a given outcome, when comparing means among groups, the Fisher least significant difference criterion based on the overall F test was used to control for overall type I error. Estimates of variability are presented as SDs unless otherwise stated. Differences were considered statistically significant at $P \leq 0.05$. In-text references to significance refer to statistical significance unless otherwise stated.

RESULTS

Participant Baseline Characteristics

A total of 134 participants were enrolled in 3 groups including (1) the control group (n=49), (2) cannabis group (n=59), and (3) cannabis/ECIG co-use group (n=26). Groups did not differ significantly by sex, age, race, or ethnicity (Table 1).

Cannabis Use Characteristics

Among the subgroup of participants who use cannabis with or without ECIGs (n=85), the primary method of cannabis use was smoking (n=53; 62.4%) followed by vaping (n=12; 14.1%), although all participants in this subgroup regularly used combusted cannabis. The majority used cannabis 4 or more times per week (n=42; 49.4%) followed by 2 to 3 times per week (n=26; 30.6%). Cannabis use patterns or risk for problematic cannabis use did not differ between the exclusive cannabis and cannabis/ECIG co-use groups as estimated by their mean CUDIT-R score (12.7±5.6 versus 13.1±6.3, P=0.939) or urine positivity for Δ9-tetrahydrocannabinol (61.5% versus. 49.2%, P=0.337), indicative of similar cannabis use burdens. The median blood cotinine level in both the control group and the exclusive cannabis group was 0 ng/mL (interquartile range, 0–0 ng/mL). The median blood cotinine level in the cannabis/ECIG co-use group was 65.5 ng/mL (interquartile range, 10.3–140.0 ng/mL), indicative of regular ECIG use.

Hemodynamic Parameters

Measures of hemodynamic parameters including HR, systolic BP, diastolic BP, and mean arterial pressure did not differ significantly among the 3 groups while supine or after abrupt standing (Table 2).

Ventricular Repolarization: Supine

During supine rest, in the exclusive cannabis use group compared with the control group, primary outcome measures of ventricular repolarization, including the Tp-e, Tp-e/QT, or Tp-e/QTc, did not differ (Figure 1A through 1C). In contrast, during supine rest in the cannabis/ECIG co-use group compared with exclusive cannabis and control groups, the primary outcome measures of ventricular repolarization were significantly shorter (Figure 1A through 1C). While participants were supine, the mean Tp-e interval was significantly shorter in the cannabis/ECIG co-use group (77±15 milliseconds) compared with both the cannabis (88±18 milliseconds; P=0.017) and control group (91±20 milliseconds; P=0.0030; mean percentage of difference versus control, −15.3% [95% CI, −24.1% to −6.5%]). Additionally, the ratio of Tp-e/QT while supine

Table 1. Participant Characteristics

Demographic variables	Control (n=49)	Cannabis (n=59)	Cannabis/ECIG co-use (n=26)	Total (N=134)	*P* value (overall)
Age, y	24.6±3.0	24.1±3.1	23.3±2.3	24.1±2.9	0.20
Sex, n (% female)	26 (53.1)	33 (55.9)	14 (53.8)	73 (54.5)	0.97
Race or ethnicity, n (%)					0.05
American Indian or Alaska Native	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.8)	
Asian	20 (40.8)	15 (25.4)	11 (42.3)	46 (34.3)	
Black	3 (6.1)	2 (3.4)	2 (7.7)	7 (5.2)	
Hispanic	8 (16.3)	24 (40.7)	3 (11.5)	36 (26.2)	
White	10 (20.4)	14 (23.7)	7 (26.9)	31 (23.1)	
>1	7 (14.3)	2 (3.4)	1 (3.8)	10 (7.5)	
Unknown or not reported	1 (2.0)	1 (1.7)	2 (7.7)	4 (3.0)	

Values for age are mean±SD. ECIG indicates electronic cigarettes.

Table 2. Secondary Outcome Measures of Hemodynamic Parameters and Heart Rate Variability

Variable	Control (n=49)	Cannabis (n=59)	Cannabis/ECIG co-use (n=26)	*P* value
Hemodynamic parameters, supine				
Heart rate, bpm	61.9±9.26	64.1±8.56	63.4±7.69	0.31
Systolic blood pressure, mm Hg	115.2±12.2	112.1±10.2	114.6±11.6	0.35
Diastolic blood pressure, mm Hg	73.6±6.85	72.1±5.95	73.1±6.22	0.46
Mean arterial pressure, mm Hg	87.5±8.11	85.4±6.95	87.0±7.46	0.34
Hemodynamic parameters, standing				
Heart rate, bpm	88.2±13.6	93.8±14.8	89.3±13.0	0.19
Systolic blood pressure, mm Hg	116.1±12.3	111.8±10.5	115.0±11.2	0.17
Diastolic blood pressure, mm Hg	73.9±7.1	71.9±6.1	73.6±6.1	0.30
Mean arterial pressure, mm Hg	88.0±8.3	85.2±7.2	87.4±7.3	0.18
Heart rate variability, supine				
Root mean square differences of successive RR intervals, msec	69.6±35.1	70.8±39.7	79.8±47.1	0.70
SD of RR intervals, msec	72.1±27.4	73.0±34.9	74.7±30.2	0.85
LF power (normal units)	42.1±21.5	40.3±19.2	38.0±20.7	0.81
HF power (normal units)	56.5±20.2	58.2±18.9	61.0±20.0	0.73
LF:HF ratio	1.2±1.7	1.0±1.3	0.8±0.7	0.78

Values are mean±SD. ECIG indicates electronic cigarettes; HF, high frequency; and LF, low frequency.

was significantly shorter in the cannabis/ECIG co-use group compared with the cannabis group (0.205±0.036 versus 0.229±0.043, respectively; *P*=0.037). Lastly, the Tp-e/QTc ratio was significantly shorter in the cannabis/ECIG co-use group compared with the control group (0.201±0.034 versus 0.228±0.043; *P*=0.018; mean percentage of difference versus control, −12.2% [95% CI, −20.1% to −4.4%]). Secondary outcome measures including mean QT, QTc, and QT dispersion were not significantly different among the 3 groups (Figure 1D through 1F).

Ventricular Repolarization: Standing

At the end of the 5-minute supine recordings, participants abruptly stood, a provocative maneuver that acutely increases cardiac sympathetic nerve activity, and the ECG was recorded for an additional 30 seconds. The effect on ventricular repolarization was measured. Due to artifact introduced by the standing maneuver, data were analyzable in 52 participants in the exclusive cannabis use group, 24 cannabis/ECIG co-use group, and 42 in the control group. After abrupt standing, there were no significant differences in Tp-e, Tp-e/QT, or Tp-e/QTc between the cannabis group and the control group (Figure 2A through 2C). In contrast, after abrupt standing, the mean Tp-e, Tp-e/QT, or Tp-e/QTc intervals were all significantly shorter in the cannabis/ECIG co-use group compared with the control group (Figure 2A through 2C). Specifically, compared with the control group, the cannabis/ECIG co-use group had a shorter Tpe interval by −25.42% (95% CI, −40.00% to −10.84%), a shorter Tpe/QT ratio by −17.99% (95% CI, −30.25% to −5.74%), and a shorter Tpe/QTc ratio by −20.90% (95% CI, −32.66% to −9.13%).

Additionally, after abrupt standing, the mean QT but not the QTc or QT dispersion was significantly shorter in the exclusive cannabis use group (413±41 milliseconds) compared with the control group (438±53; *P*=0.041; mean percentage of difference versus control, −5.69% [95% CI, −10.15% to −1.22%]; Figure 2D through 2F). The cannabis/ECIG co-use group exhibited both a significantly shorter QT (402±27 milliseconds) compared with the control group (*P*=0.0078; mean percent difference versus control, −8.26% [95% CI, −12.74% to −3.79%]; Figure 2D through 2F) and a significantly shorter QTc compared with the control group (473±50 versus 509±51 milliseconds; *P*=0.013; mean percentage of difference versus control, −7.06% [95% CI, −11.28% to −2.83%]). No differences were observed in QT dispersion between groups (Figure 2F).

Ventricular Repolarization: Associations With Potential Predictors

In the supine condition, an adjusted multivariable logistic regression model revealed that male sex was significantly associated with a higher Tp-e/QT and Tp-e/QTc (Table 3). Additionally, blood cotinine level showed a weak association with a lower Tp-e/QT (r=−0.184, *P*=0.036). In the standing condition, the adjusted model revealed that age was positively associated with all 3 primary outcomes (Table 3). Additionally, higher CUDIT-R scores showed a weak association with lower Tp-e/QTc (r=−0.220, *P*=0.019), and showed a trend toward a weak association with lower Tp-e (r=−0.183, *P*=0.052)

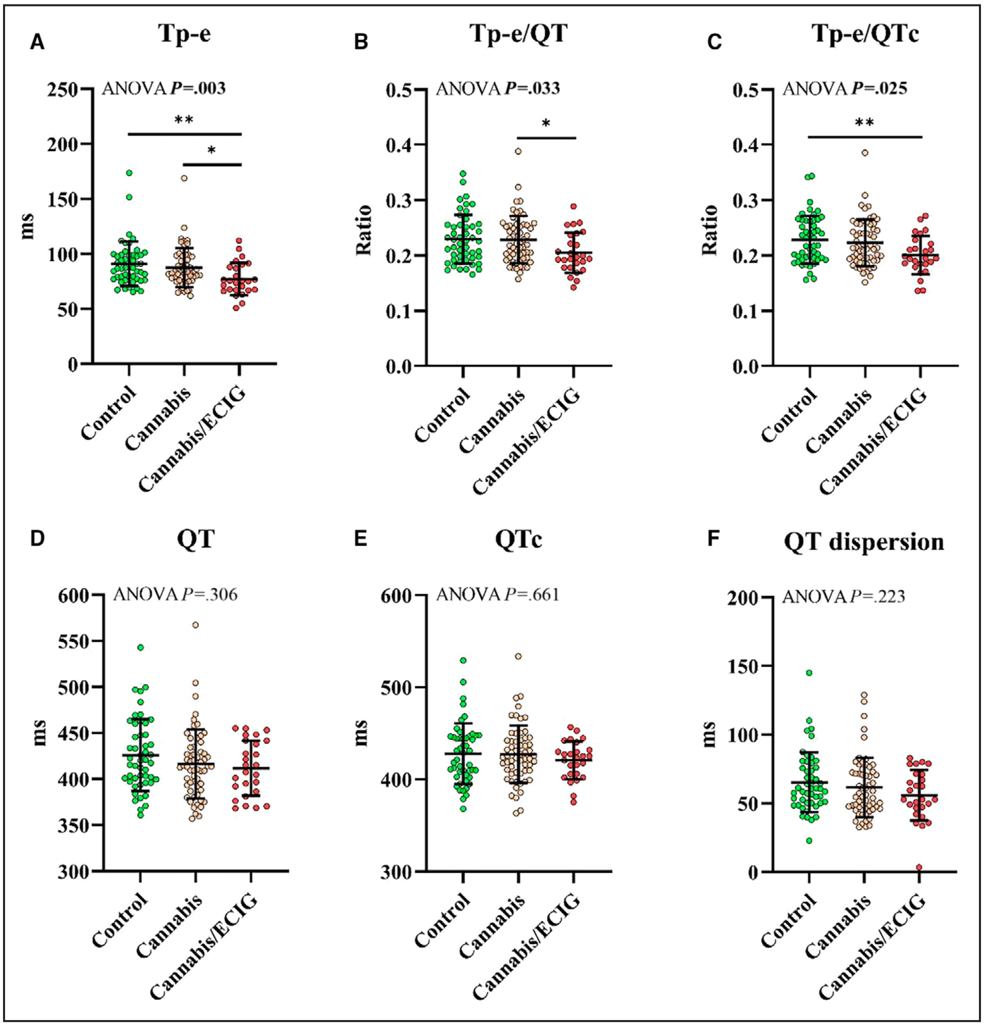

Figure 1. Primary outcome measures of ventricular repolarization while supine.
The mean±SD of ventricular repolarization measures while supine is presented for chronic ECIG and cannabis co-use, chronic exclusive cannabis use, and nonusing controls. Data were analyzed using a 1-way ANOVA with post hoc Tukey's test. **P*<0.05, ***P*<0.01 indicate statistically significant differences between groups. **A**, The Tp-e interval was significantly shorter in the cannabis/ECIG co-use group (77±15 milliseconds) compared with both the cannabis (88±18 milliseconds; *P*=0.0172) and control group (91±20 milliseconds; *P*=0.0030). **B**, The ratio of Tp-e/QT while supine was significantly shorter in the cannabis/ECIG co-use group compared with the cannabis group (0.205±0.036 vs 0.229±0.043, respectively; *P*=0.0365). **C**, The Tp-e/QTc ratio was significantly shorter in the cannabis/ECIG co-use group while supine compared with the control group (0.201±0.034 vs 0.228±0.043; *P*=0.0184). **D** through **F**, Secondary outcome measures including QT, QTc, and QT dispersion were not significantly different among the 3 groups (all *P*>0.2). ECIG indicates electronic cigarettes; and Tp-e, Tpeak-Tend.

and Tp-e/QT (r=−0.174, *P*=0.064). These findings suggest that while participants are supine, greater ECIG use as measured by blood cotinine level is weakly associated with shorter Tp-e/QT, whereas after standing, greater cannabis use as measured by total CUDIT-R is weakly associated with shorter Tp-e/QTc.

Heart Rate Variability

Measures of HRV in the time domain, including SD of RR intervals and root mean square differences of successive RR intervals, showed no significant differences between groups (Table 2). Further, measures of HRV in the frequency domain including LF, HF, and LF:HF ratio were not significantly different among the groups (Table 2).

DISCUSSION

For decades TCIG use has been the most prevalent, modifiable risk factor for CVD in the United States, but among current young adults, the prevalence of TCIG smoking has never been lower.[3] At the same

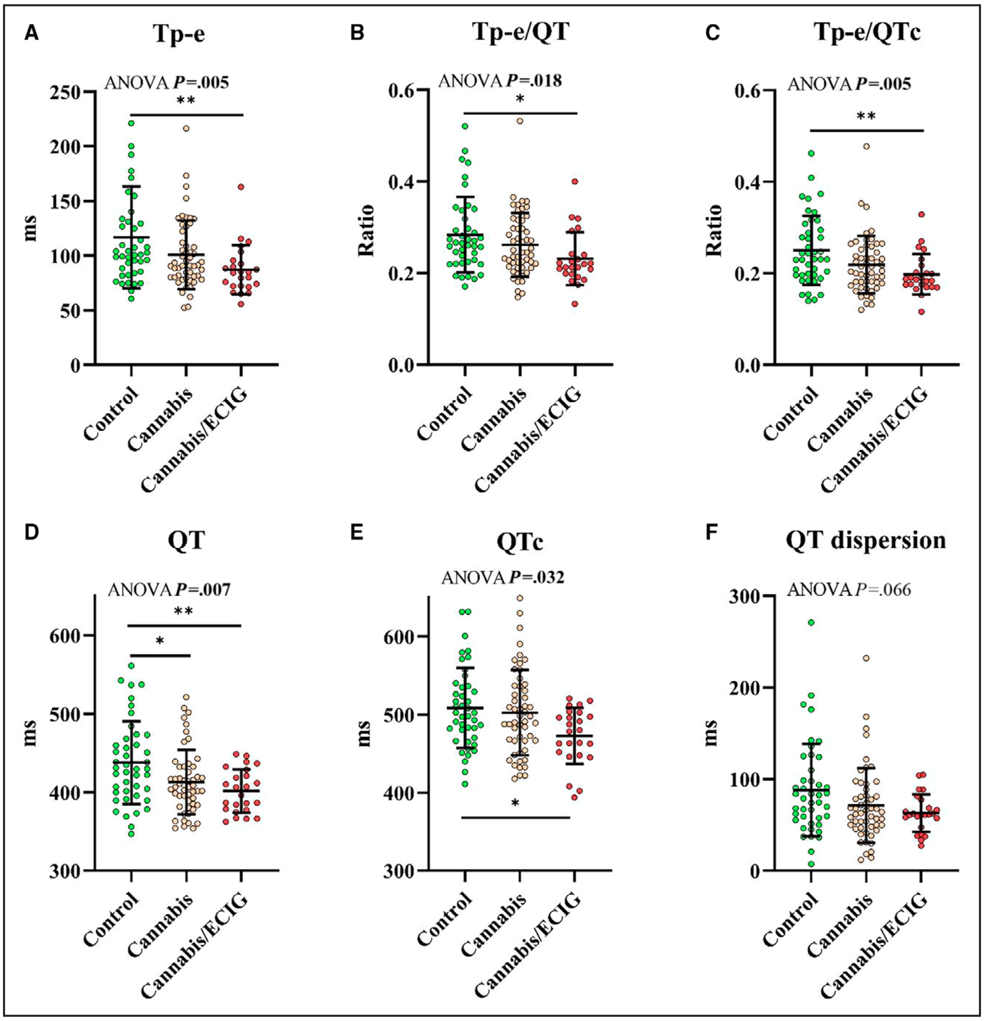

Figure 2. Primary outcome measures of ventricular repolarization after abrupt standing.
The mean±SD of ventricular repolarization measures after abrupt standing is presented for chronic ECIG and cannabis co-use, chronic exclusive cannabis use, and nonusing controls. Data were analyzed using the 1-way Kruskal–Wallis method with post hoc Tukey's test. *P<0.05, **P<0.01 indicate statistically significant differences between groups. **A**, The Tp-e interval was significantly shorter in the cannabis/ECIG co-use group compared with the control group (87±22 vs 116±47 milliseconds; P=0.0027). **B**, The Tp-e/QT was significantly shorter in the cannabis/ECIG co-use group compared with the control group (0.231±0.058 vs 0.282±0.082; P=0.013). **C**, The Tp-e/QTc ratio was shorter in the cannabis/ECIG co-use group compared with the control group (0.198±0.044 vs 0.250±0.076; P=0.0028). **D**, QT was significantly shorter in the cannabis/ECIG co-use group (402±27 milliseconds) compared with control (438±53 milliseconds; P=0.0078) and in the exclusive cannabis use group (413±41 milliseconds) compared with control (P=0.041). **E**, The QTc was significantly shorter in the cannabis/ECIG co-use group compared with control (473±50 vs 509±51 milliseconds; P=0.013). ECIG indicates electronic cigarettes; and Tp-e, Tpeak-Tend.

time, cannabis use has reached epidemic proportions among young adults, with 47% of young adults ages 21 to 22 years reporting past year (2020) inhaled cannabis use.[3] Long term follow up in middle-aged adults who chronically use cannabis has uncovered increased myocardial infarction risk,[34] but these results are confounded by the high prevalence of co-use of TCIGs in this group.[35,36] Whether exclusive long-term cannabis use is associated with increased CVD risk remains uncertain. At present, although the majority of young adults who use inhaled cannabis do not smoke TCIGs, many do use nicotine ECIGs.[3] According to the Monitoring the Future National survey, an alarming 30% of young adults ages 19 to 22 years report nicotine ECIG use in the past year (2023), far more than would ever have smoked TCIGs.[37] Although increasing evidence supports the notion that CVD risk from chronic ECIG use is likely lower than that of lethal TCIGs, it is not zero.[38] Further, the potency of cannabis has increased significantly over the past decade;

Table 3. Multivariable Regression Analysis of Primary Outcomes of Ventricular Repolarization in Supine and Standing Conditions

Supine	Tp-e		Tp-e/QT		Tp-e/QTc	
Continuous predictor	Adj. correlation	Sig.	Adj. correlation	Sig.	Adj. correlation	Sig.
Age	0.017	0.849	0.002	0.982	0.024	0.784
Blood cotinine level	−0.139	0.114	−0.184	0.036	−0.136	0.122
CUDIT-R score	−0.078	0.375	−0.061	0.492	−0.076	0.390
Bivariate predictor	Adj. mean difference	Sig.	Adj. mean difference	Sig.	Adj. mean difference	Sig.
Sex (M)	0.203 (3.65)	0.956	17.75 (7.89)	0.026	18.40 (7.86)	0.020
Urine tetrahydrocannabinol (positive)	0.292 (4.50)	0.949	4.62 (9.72)	0.635	1.67 (9.68)	0.863
Overall model R^2	0.085		0.182		0.159	
Standing	Tp-e		Tp-e/QT		Tp-e/QTc	
Continuous predictor	Adj. correlation	Sig.	Adj. correlation	Sig.	Adj. correlation	Sig.
Age	0.223	0.017	0.193	0.040	0.228	0.015
Blood cotinine level	0.010	0.913	0.041	0.665	0.062	0.516
CUDIT-R score	−0.183	0.052	−0.174	0.064	−0.220	0.019
Bivariate Predictor	Adj. mean difference	Sig.	Adj. mean difference	Sig.	Adj. mean difference	Sig.
Sex (male)	−6.57 (6.44)	0.853	2.78 (13.73)	0.840	−3.35 (12.21)	0.784
Urine tetrahydrocannabinol (positive)	0.56 (7.82)	0.967	9.65 (16.68)	0.564	0.92 (14.83)	0.951
Overall model R^2	0.251		0.221		0.248	

Values are model adjusted (partial) correlation for continuous predictors and model adjusted mean difference with standard error in parenthesis for binary predictors. Adj. indicates adjusted; CUDIT-R, Cannabis Use Disorder Identification Test—Revised; and Tp-e, Tpeak-Tend.

the average concentrations of tetrahydrocannabinol, the plant cannabinoid that underlies the cannabinoid-1 receptor-mediated adverse cardiovascular effects, has more than quadrupled since 1995.[39,40] It has been predicted that a large proportion of the young adults who currently use inhaled combusted cannabis, with its increased potency, will become lifelong users[41]; accordingly, studies such as the present one, which examine biomarkers that portend increased CVD risk associated with chronic cannabis use, and cannabis and ECIG co-use, assume increased urgency and importance.

The major new findings in this study of 134 healthy adults, which included 59 participants who chronically used inhaled combusted cannabis, 26 participants who chronically co-used nicotine ECIGs and inhaled combusted cannabis, and 49 healthy nonusing controls are that (1) in participants who exclusively use cannabis, ventricular repolarization as estimated by Tp-e, Tp-e/QT, and Tp-e/QTc is not different from nonusing controls; (2) in contrast, in participants who co-use cannabis/ECIG compared with those who exclusively use cannabis or who are nonusing controls, ventricular repolarization as estimated by Tp-e, Tp-e/QT, and Tp-e/QTc is shorter compared with those who exclusively use cannabis or who are nonusing controls; (3) after abrupt standing, despite similar increases in HR, these same primary measures of ventricular repolarization as well as QT and QTc were significantly shorter among people who co-use cannabis/ECIG compared with nonusing controls; (4) in contrast, in people who exclusively use cannabis compared with controls, despite similar increases in HR, abrupt standing did not unmask differences in ventricular repolarization as measured by Tp-e, Tp-e/QT, and Tp-e/QTc. However, upon standing, a significantly shorter QT interval was observed in this cannabis group compared with controls; and (5) resting hemodynamics and measures of HRV were similar among the 3 groups. Importantly, the mean percentage of differences in primary outcomes of Tp-e, Tp-e/QT, and Tp-e/QTc observed in cannabis/ECIG co-users compared with nonusing controls is similar in magnitude to those detected in other cohorts associated with increased risk of sudden death.[15–17] These differences in ventricular repolarization between the exclusive cannabis and cannabis/ECIG co-use groups are not explained by differences in cannabis use burdens, as estimated by the CUDIT-R score and prevalence of positivity on urine toxicology screening at the time of the experimental session. These findings in healthy young adults demonstrate that chronic co-use of nicotine ECIG and combusted cannabis, and to a lesser extent, exclusive combusted cannabis use, are associated with alterations in ventricular repolarization implicate nicotine ECIG emissions and potentially their interactions with combusted cannabis emissions as contributing factors, although our study design does not afford this attribution. It remains to be uncovered which constituents in these emissions may contribute to this pathology. We acknowledge that the culprit(s) will be challenging to identify, especially with the rapid evolution of ECIG devices and flavorings.[42]

These findings contribute to the growing body of literature describing the impact of nicotine ECIG use on baseline (ie, in the absence of acute exposure) markers of ventricular repolarization. In a retrospective study from our group evaluating ECIG effects on the ECG, we found no significant differences at baseline in measures of ventricular repolarization among people who chronically used either nicotine ECIGs or TCIGs, and healthy controls,[17] but after acute ECIG use, the prolongation of Tp-e was significantly greater than after puffing on an empty (control) ECIG.[17] Notably, in a follow-up, prospective study, we reported a trend toward shorter Tp-e and Tp-e/QT in people who chronically use ECIGs compared with healthy controls while supine (P=0.07); after abrupt standing, the Tp-e, Tp-e/QT, and Tp-e/QTc became significantly shorter in the ECIG group.[18] In the current study, the people who co-use cannabis and ECIGs, but not cannabis alone, also had significantly shorter primary markers of ventricular repolarization both at rest and after abrupt standing. Overall, these results support the notion that chronic nicotine ECIG use contributes to shortened baseline markers of ventricular repolarization, particularly following maneuvers that acutely increase sympathetic tone (abrupt standing). It has been proposed that chronic exposure to tobacco products may lead to electrophysiological remodeling of cardiac myocytes,[42–44] perhaps explaining the chronically shortened ventricular repolarization observed now in several distinct cohorts[17,18] and the present study. A recent study of adults who use TCIGs showed an inverse relationship between serum cotinine level and QTc, further underscoring the potential role of nicotine in alteration of ventricular repolarization.[45] However, in the current study, serum cotinine was only weakly inversely associated with Tpe/QT while supine, suggesting that nicotine exposure alone does not explain the shorter measures of ventricular repolarization observed in healthy young adults who co-use cannabis and ECIGs. Although data are limited, and in fact confined to the present study, chronic combusted cannabis use does not seem to be associated with this alteration at rest, although the observation that a shortened QT is unmasked with standing is intriguing, and further studies are needed to confirm these early observations.

Interestingly, the alteration, specifically the shortening, in ventricular repolarization in the co-use cannabis/ECIG group is not in the direction typically associated with increased arrhythmia risk. Typically, prolongation of ventricular repolarization, such as in the congenital or acquired long QT syndromes, is associated with ventricular arrhythmias that lead to sudden cardiac death. However, within the past 25 years, several reports have identified short QT syndrome as another example of an alteration in ventricular repolarization that is also associated with increased incidence of lethal ventricular arrhythmias.[46–49] Initially, short QT syndrome was thought to be an inherited condition and several genetic variants mostly associated with diverse channelopathies have been described,[47–50] but more recently acquired forms of short QT have also been reported.[51,52] Attempts to describe the electrocardiographic features in patients with short QT syndrome have been made, and include, somewhat vaguely, tall and peaked T waves and abnormal changes in the QT interval with changes in HR.[50,53] General consensus supports the notion that there is a "healthy window" for ventricular repolarization and that neither too long nor too short is desirable.[47] Certainly, much work still needs to be done to understand this relatively new entity, and the role, if any, of specific exposures, including nicotine ECIG emissions alone or in combination with combusted cannabis, in its acquired form.

In the present study, we also found that chronic combusted cannabis use or co-use with nicotine ECIGs does not affect baseline hemodynamic parameters, such as HR and BP, in healthy young adults when compared with nonusing controls. This observation aligns with previous studies, including our own research on chronic ECIG use, which found no significant differences in baseline hemodynamic measures between ECIG users and non-users.[10,17,18]

Lastly, in this study, indices of HRV, which reflect sympathetic and vagal tone, were similar across the 3 groups, those who exclusively use combusted cannabis, those who co-use ECIGs and cannabis, and nonusing controls. This contrasts with previous research into the effects of chronic cannabis use on HRV (which was limited to men), in which increased HRV indicative of increased vagal tone was reported.[23] It also differs from studies in people who chronically use nicotine ECIGs, in whom an increase in sympathetic tone, as reflected by a higher LF:HF ratio compared with control nonusers was reported; however, this may be due to differences in participant demographics and session timing.[10] These findings suggest that the combined, opposing effects of chronic cannabis and nicotine ECIG use in people who co-use both products may produce neutral or mixed outcomes on HRV and cardiac sympathetic and vagal tone. Given limited research and contrasting findings, further investigation into indices of HRV in chronic cannabis and ECIG users, especially women, is warranted.

Limitations

We acknowledge several limitations in this study. The study population consisted of healthy young adults, which limits the generalizability of our findings to older populations or individuals with underlying health conditions. However, young adults are the population with the greatest exposure to these substances, and with the fewest known confounders, and thus are the ideal population to enroll in such a study. Using well-accepted biomarkers of disease risk is another strength of this study, providing the possibility of early detection, so that meaningful interventions, including on the public health level, may be developed to prevent a resurgence of CVD as this group ages. Despite robust recruiting efforts, very few people who exclusively use nicotine ECIGs were enrolled. Recent surveys have reported a decline in the prevalence of exclusive ECIG use in high school students,and that those who do use ECIGs tend to engage in other risky behaviors including use of other recreational substances such as inhaled cannabis.[54,55] Accordingly, our recruitment likely reflects the changing demographic. Lastly, this study does not assess changes in outcomes in response to acute exposure to ECIGs or cannabis, which may differ in the context of current use, underscoring the need for further research into the acute effects of cannabis/ECIG co-use on arrhythmia risk.

CONCLUSIONS

In summary, in this study of 134 healthy participants, ECG indices of ventricular repolarization including Tp-e, Tp-e/QT, and Tp-e/QTc were not different in chronic cannabis users compared with controls but were shorter in people who chronically co-use cannabis/ECIG compared with exclusive cannabis and nonusing controls at baseline (ie, in the absence of acute exposure) both during supine rest and after abrupt standing. To our knowledge, this is the first study to report the effects of chronic combusted cannabis use on measures of ventricular repolarization in healthy young adults. These findings build on prior research from our group showing that exclusive ECIG use is associated with shorter measures of ventricular repolarization only after abrupt standing. This study also found that exclusive cannabis use is associated with shorter QT after standing compared with nonusing controls, which has not been previously reported. Although traditionally it is prolongation of ventricular repolarization that has been associated with increased cardiovascular risk, emerging research has found that short ventricular repolarization may also be associated with increased risk for lethal ventricular arrhythmias. Because co-use of cannabis/ECIG is very high, further studies into this novel and potentially concerning finding are warranted.

ARTICLE INFORMATION

Received January 27, 2025; accepted June 23, 2025.

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Sources of Funding

This work was supported by Tobacco Related Research Program (T32IP4659), the Sandler Foundation, and the Semel Charitable Foundation.

Disclosures

Outside of this work, Ziva D. Cooper reports receiving study drug from Canopy Growth Corp and True Terpenes, and study-related materials from Storz & Bickel. Ziva D. Cooper's research is funded by grants from the National Institute on Drug Abuse, National Center for Complementary and Integrative Health, California Department of Cannabis Control, Center for Medicinal Cannabis Research, and the California Highway Patrol. The other authors have no disclosures to report.

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