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Variation of Tpeak-end, corrected Tpeak-end, QT, and corrected QT intervals, Tpeak-end/QT, Tpeak-end/corrected QT ratios and heart rate variability according to decades in the healthy male subjects aged between 30 and 79 years

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Abstract

Background: Heart rate variability (HRV) is a predictor of cardiac autonomic functions. Ventricular repolarization markers can indicate ventricular arrhythmias. We aimed to evaluate variations of HRV and these repolarization markers in five healthy male groups between age 30 and 79 years according to decades.

Materials and Methods: The study group consisted of 500 healthy male subjects between October 2018 and May 2019. The male subjects were divided into five categories according to their ages. Then, electrocardiograms (ECG), transthoracic echocardiograms (TTE), and treadmill exercise test (TET) were performed. T-wave peak-end (Tp-e) interval was defined as the time between the peak point and end of T-wave. Tp-e, corrected Tp-e (cTp-e), QT, and corrected QT (QTc) were measured from the resting ECGs and HRV temporal parameters (SDNN, SDNN Index, SDANN Index, RMSSD, sNN50, and pNN50), and HRV frequency parameters (VLF, LF, HF, and LF/HF) were obtained from 24-hour Holter monitorization recordings. One-way ANOVA test was used for the differences between the groups. Pearson correlation test was used to determine the correlations between the values of all groups.

Results: Considering the repolarization parameters, there are significant differences in five groups in terms of Tp-e interval, but not Tp-e/QT and Tp-e/QTc ratios. Considering the HRV parameters, there were statistically significant differences between the five male healthy groups in terms of HRV temporal parameters and there are no significant differences in terms of HRV frequency parameters.

Conclusion: As the age increases, basal Tp-e interval increases and HRV temporal parameters decrease significantly in the male subjects aged between 30 and 79 years, but HRV frequency parameters do not change.

KEYWORDS

healthy male subjects, heart rate variability, Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, variation according to decades

1 | INTRODUCTION

The autonomic nervous system has a very important role in providing cardiovascular homeostasis. Many studies are showing that vagal tone decreases and sympathetic activity increases in both healthy women and men with age. Some of these studies have shown that in healthy men, vagal tone is higher than in women with age.[1]

Aging has proven to be a significant risk factor in itself and contributes to all cardiovascular morbidity and mortality. Consequently, cardiovascular diseases are associated with a decrease in vagal, an increase in sympathetic modulation, or a combination of both. It is well known that heart rate variability (HRV) decreases with aging; moreover, it is associated with increased cardiovascular morbidity and mortality in the elderly with low vagal modulated HRV levels.[2]

Aging of the heart is associated with a blunted response to sympathetic stimulation, reduced contractility, and an increased propensity for arrhythmias, with the risk of malign ventricular arrhythmia, which significantly increased in the elderly population. The altered cardiac structural and functional phenotype, as well as age-associated prevalent comorbidities, including hypertension and atherosclerosis, predispose the heart to atrial fibrillation, heart failure, and ventricular tachyarrhythmias.[3]

Low HRV has been shown as a marker of many pathophysiological conditions, including an increased risk of mortality. Limit values for increased mortality risk have also been proposed. Regarding age, it is known that HRV decreases with normal aging.[4]

Although there is a significant decrease in HRV values with age, this decrease is higher in women than in men.[5] Significant reductions in HRV have been an early detection and mortality indicator of cardiovascular diseases for many researchers.[6,7]

Electrophysiological studies have shown that different repolarization patterns occur in men and women.[8] In a study conducted on rabbits, J-T end and T peak-end (Tp-e) interval values were obtained showing different repolarization times in males and females.[9]

Increases in the duration of transmural myocardial repolarization can cause life-threatening malignant ventricular arrhythmias, such as torsades pointes or ventricular fibrillation, with or without underlying structural heart disease.[10] Increased ventricular repolarization times are associated with an increased risk of malignant ventricular arrhythmias in the general population, with or without structural heart disease.[11]

Several predictors for ventricular arrhythmias have been investigated. Some of these are reduced circadian HR, QT dispersion, QT prolongation, microvolt T-wave alternans, late atrial and ventricular potentials, V index, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios.[12-14]

While some researchers have suggested that the Tp-e interval can be used as a myocardial repolarization index,[15] some recently published articles state that the Tp-e interval does not fully show the ventricular repolarization dispersion and that the Tp-e interval cannot be used as a ventricular repolarization index.[16] Nevertheless, many studies have shown that significant increases in the Tp-e interval are closely related to malignant ventricular arrhythmias.[11]

It is emphasized that the Tp-e interval is prolonged in many diseases, and it is related to malignant ventricular arrhythmias and SCD.[17-19] However, Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios and the relation between Tp-e interval, QT interval, Tp-e/QT and Tp-e/QTc ratios and HRV values have not been evaluated in healthy male individuals in various decades. Our study aims to investigate the Tp-e and QT interval, Tp-e/QT and Tp-e/QTc ratios and correlations between Tp-e interval and HRV temporal and frequency parameters obtained from 24-hour Holter Monitorization in healthy male subjects between the age of 30 and 79 years, divided into five categories.

2 | METHODS

2.1 | Study design and study population

The study groups consisted of 500 healthy male subjects who applied to the cardiology outpatient clinics with the complaint of atypical chest pain and had a decision to be healthy according to history, physical examination, and routine blood tests between October 2018 and May 2019. The subjects were divided into five categories according to their ages, 100 male subjects were in each decade between the age of 30 and 79 years. The male subjects were included in the study with the strict exclusion of coronary artery disease with the resting electrocardiogram (ECG) and transthoracic echocardiogram (TTE) and treadmill exercise test (TET), and no history of any other illness. Informed consent was obtained from each subject.

2.2 | The exclusion criteria were as follows

- previous diagnosis of chronic obstructive pulmonary disease (COPD) and receiving bronchodilator therapy,
- having any systemic disease such as diabetes mellitus or hypertension,
- having impaired liver or kidney function test,
- having electrolyte imbalance in routine blood examination,
- having anemia or thyroid dysfunction,
- having a disease that may affect the heart,
- having coronary arterial disease,
- having a positive treadmill exercise test,
- having a diagnosis of cancer,
- taking any cardiac treatment,
- being a current or former smoker,
- using insulin, beta-blocker, calcium channel blocker, digitalis, or sympathomimetic agents,
- having a pacemaker or intra-cardiac defibrillator,
- having previous cardiac surgery, cardiovascular invasive procedure,
- having a history of myocardial infarction,

- having typical angina pectoris,
- having atrial fibrillation history or current atrial fibrillation on resting ECG,
- having artifacts above 5% on 24-hour Holter monitorization,
- having average HR above 100 beats per minute or under 60 beats per minute,
- having ejection fraction under 50% on TTE, and
- having a history of a central nervous system disease such as Parkinson.

2.3 | Electrocardiography (ECG)

The 12-lead electrocardiography (ECG) recordings were obtained at the supine position with paper at a speed of 25 mm/s and 10 mm/mV amplitude using a standard ECG system (CardiofaxV model 9320; Nihon Kohden). ECG length was 10 seconds, therefore depending on the HR, there were 4-6 beats per lead. ECGs were manually measured by the use of a magnifying Glass (TorQ 150 mm Digital Caliper LCD) by two blinded cardiologist having no information about the patients. The QT and Tp-e intervals of the ECG recordings were measured manually with an accuracy of 0.01 mm.

QT interval was accepted as the place where the T-wave returned to the isoelectric line from the onset of the QRS wave. This measurement was calculated at least nine leads and three consecutive QRS waves in one lead in 12-lead ECG. The data of ECG with papers at a speed of 25 mm/sc-amplitude of 10 mm/mV, measured values in millimeter with the digital caliper which was 1/100 mm in precision, were calculated as millisecond multiplied by 40. QTc was calculated using Bazett's formula.

Tp-e interval is defined as the value in milliseconds of the distance measured from the peak of the T-wave to the end of the T-wave. Tp-e interval was calculated by including the T-wave from the peak to baseline in the V_2-$_5$L leads (Left Precordial Leads). The Tp-e interval was calculated by multiplying the obtained value as the millisecond with 40. If the U-wave is present, the T-wave end was defined as the nadir between the T-wave and U-wave. The corrected Tp-e interval (cTp-e) was calculated using Bazett's formula. Arithmetic averages of measurements were used for analysis.

2.4 | Transthoracic echocardiography (TTE)

All subjects underwent two-dimensional echocardiography examination. We obtained standard parasternal long-axis, midventricular short-axis, long apical axis, apical two- and four-chamber images with the Phillips HD11XE, 2012 Netherland.

2.5 | Treadmill exercise test (TET)

Each group, after routine physical and blood examinations, TTE and resting ECG, were admitted to TET according to the Bruce

TABLE 1 Basal clinic findings of five groups

Variables	Group 1 (30-39 y)	Group 2 (40-49 y)	Group 3 (50-59 y)	Group 4 (60-69 y)	Group 5 (70-79 y)	*F*-value	*P*-value
SBP, mm Hg	117.36 ± 10.56	118.46 ± 12.72	118.56 ± 15.37	120.74 ± 15.84	121.52 ± 11.73	2.2	.08
DBP, mm Hg	71.56 ± 9.56	73.23 ± 9.83	75.35 ± 11.45	74.26 ± 11.65	76.48 ± 11.46	2.16	.084
BMI, kg/m^2	25.45 ± 2.47	25.73 ± 2.76	26.43 ± 2.24	26.73 ± 2.73	27.47 ± 1.95	2.1	.09
LV mass, g	175.25 ± 18.53	177.35 ± 19.52	176.37 ± 22.17	178.57 ± 18.37	178.92 ±	1.99	.11
Hemoglobin, g/dL	14.23 ± 1.36	14.14 ± 1.25	14.35 ± 1.63	13.98 ± 1.48	13.87 ± 1.13	1.56	.36
Basal sPAP, mm Hg	15.36 ± 2.67	15.37 ± 3.52	16.48 ± 3.84	16.27 ± 4.25	16.58 ± 3.72	1.84	.19
TC, mg/dL	174.56 ± 28.46	181.47 ± 31.63	191.46 ± 33.27	188.39 ± 28.48	193.68 ± 31.93	2.08	.088
LDL, mg/dL	141.63 ± 22.63	137.37 ± 25.74	139.21 ± 23.93	141.69 ± 22.63	143.84 ± 31.74	1.98	.11
Triglyceride, mg/dL	156.46 ± 26.35	161.36 ± 29.47	173.84 ± 21.73	166.27 ± 31.58	177.48 ± 39.51	1.88	.26
Calcium, mg/dL	9.46 ± 0.84	9.26 ± 0.73	9.09 ± 0.79	9.52 ± 0.65	9.85 ± 0.81	0.94	.73
Sodium, mEq/L	141.73 ± 1.64	139.64 ± 1.92	140.69 ± 2.63	141.83 ± 2.36	142.52 ± 2.53	1.23	.57
Potassium, mEq/L	3.95 ± 0.63	4.02 ± 0.73	4.23 ± 0.68	4.13 ± 0.72	4.07 ± 0.69	1.01	.69
Magnesium, mg/dL	1.95 ± 0.47	1.89 ± 0.37	1.83 ± 0.62	2.01 ± 0.73	2.13 ± 0.81	1.35	.42
TSH, mIU/L	3.52 ± 1.36	3.74 ± 2.14	2.74 ± 1.25	3.07 ± 1.69	2.99 ± 2.16	1.76	.35

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; LV, left ventricle; SBP, systolic blood pressure; TC, total cholesterol; TSH, thyroid stimulating hormone.

Protocol.[20] The patients, having a positive treadmill exercise test that was indicating important coronary heart disease, were excluded from the study.

2.6 | Twenty-four-hour 12-lead rhythm Holter monitorization

A 12-lead Holter (DMS-300, 12L, serial number: 8438; DM Software, 2011) monitor was connected to the patients at 02.00 pm and removed at 02.00 pm the next day. A 24-hour detailed evaluation was performed for assessing the 24-hour rhythm Holter. During the evaluation, patients having the right or left bundle branch block, patients detected with more than 10 000/day atrial or ventricular extra-systoles, those having irregular or persistent supraventricular or ventricular tachycardia, patients with ST-T-wave variations in ECG screening, and those with less than 22 hours of Holter recording were excluded from the study. ECG records, including minimum and maximum HRs of patients, were acquired, and calculations were made. Moreover, HRV values were recorded and compared for each group. SDNN (standard deviation of all NN intervals), SDANN Index (Standard deviation of the average NN intervals for each 5 minute segment of a 24 hour HRV recording), SDNN Index (mean of the standard deviations of all the NN intervals for each 5-minute segment of a 24 hour HRV recording), RMSSD (root mean square of successive RR interval differences), sNN50 (number of successive RR intervals that differ by more than 50 milliseconds), pNN50 (percentage of successive RR intervals that differ by more than 50 milliseconds), VLF (absolute power of the very-low-frequency band [0.0033-0.04 Hz]), LF (absolute power of the low-frequency band [0.04-0.15 Hz]), HF (absolute power of the high-frequency band [0.15-10.40 Hz]), and LF/HF (ratio of LF-to-HF power) values were recorded and compared between each group.

2.7 | Statistical analysis

Data on continuous variables are presented as mean ± SD. Categorical variables were expressed as percentages. To analyze various parameters in the study group, an unpaired *t* test or *t* test between independent variables was used. Also, one-way ANOVA

TABLE 2 Comparison of basal ECG and HRV findings of five groups

Variables	Group 1 (30-39 y)	Group 2 (40-49 y)	Group 3 (50-59 y)	Group 4 (60-69 y)	Group 5 (70-79 y)	*F*-value	*P*-value
Age, y	34.31 ± 2.79	45.1 ± 2.39	54.79 ± 2.66	65.24 ± 2.35	75.1 ± 2.45	1145.32	**<.0025**
Tp-e, ms	72.2 ± 4.15	76.44 ± 4.07	79.79 ± 4.26	84.82 ± 6.84	95.89 ± 6.9	81.44	**<.0025**
cTp-e, ms	88.13 ± 7.71	93.55 ± 6.74	96.93 ± 8.77	101.72 ± 7.93	111.17 ± 9.67	33.84	**<.0025**
QT, ms	322.48 ± 23.94	328.75 ± 22.28	341.55 ± 26.95	345.74 ± 15.48	432.79 ± 25.01	113.61	**<.0025**
QTc, ms	393.01 ± 33.50	401.41 ± 20.63	413.44 ± 26.9	413.48 ± 21.15	455.81 ± 35.75	21.92	**<.0025**
Tp-e/QT	0.225 ± 0.021	0.233 ± 0.02	0.234 ± 0.021	0.246 ± 0.021	0.261 ± 0.02	2.8	.042
Tp-e/QTc	0.183 ± 0.02	0.19 ± 0.01	0.193 ± 0.014	0.205 ± 0.02	0.22 ± 0.01	2.9	.04
Max RR, ms	702.24 ± 83.31	704.55 ± 63.46	718.58 ± 93.67	717.31 ± 65.74	754.72 ± 70.31	2.28	.063
Min RR, ms	669.96 ± 87.56	635.13 ± 70.06	659.48 ± 95.5	679.41 ± 65.01	743.27 ± 70.89	7.61	**<.0025**
Mean RR, ms	680.05 ± 87.13	672.67 ± 70.87	687.45 ± 95.52	698.12 ± 64.92	749.13 ± 70.88	4.32	**<.0025**
SDNN, ms	124.67 ± 22.56	115.75 ± 19.73	107.26 ± 18.81	96.37 ± 17.53	81.58 ± 15.73	5.56	**<.0025**
SDANN Index, ms	110.73 ± 22.16	99.64 ± 21.74	87.36 ± 22.64	79.33 ± 19.68	71.57 ± 17.47	4.78	**<.0025**
SDNN Index, ms	49.56 ± 13.63	43.65 ± 11.68	38.74 ± 12.74	33.74 ± 12.19	29.57 ± 11.63	12.19	**<.0025**
sNN50	556.35 ± 432.13	289.47 ± 199.63	224.64 ± 254.37	134.56 ± 104.74	99.62 ± 3671.47	6.64	**<.0025**
pNN50, %	13.56 ± 9.47	11.47 ± 7.31	7.14 ± 6.63	4.31 ± 3.27	2.93 ± 3.11	14.99	**<.0025**
RMS-SD, ms	33.68 ± 12.73	29.56 ± 9.57	24.68 ± 7.63	21.75 ± 7.29	18.54 ± 6.63	13.43	**<.0025**
LF, ms^2	5.67 ± 1.56	5.43 ± 1.43	5.21 ± 1.74	5.17 ± 1.46	4.91 ± 1.36	2.56	.074
HF, ms^2	4.78 ± 2.21	4.37 ± 2.17	4.01 ± 2.11	3.74 ± 1.95	3.11 ± 1.77	2.94	.035
LF/HF	1.23 ± 0.32	1.21 ± 0.31	1.29 ± 0.45	1.39 ± 0.51	1.58 ± 0.61	3.03	.027

Abbreviations: Tp-e, T peak-end interval; cTp-e, Corrected T peak-end interval; QTc, Corrected QT interval; Max, maximum; Min, minimum; NN, successive RR interval; SDNN, standard deviation of all NN intervals; SDANN Index, standard deviation of the average NN intervals for each 5 min segment of a 24 h heart rate variability recording; SDNN Index, Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording; RMSSD, Root mean square of successive RR interval differences; pNN50, Percentage of successive RR intervals that differ by more than 50 ms; sNN50, The number of successive RR intervals that differ by more than 50 ms; VLF, Absolute power of the very-low-frequency band (0.0033-0.04 Hz); LF, Absolute power of the low-frequency band (0.04-0.15 Hz); LF/HF, Ratio of LF-to-HF power; QT, QT interval; QTc, Corrected QT interval; HR, heart rate.

TABLE 3 Correlations between Tp-e values and HRV values/age

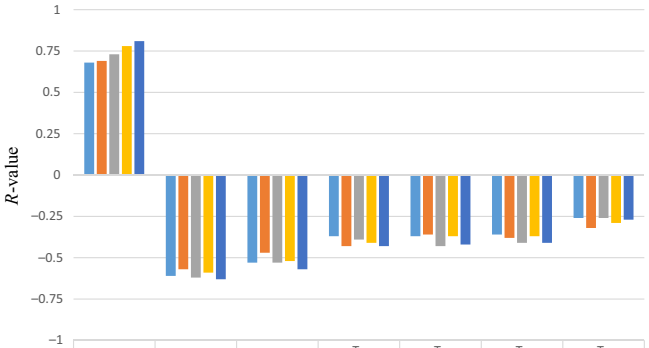
Variables	Group 1 (30-39 y)	Group 2 (40-49 y)	Group 3 (50-59 y)	Group 4 (60-69 y)	Group 5 (70-79 y)
Tp-e/age					
R-value	.76	.77	.79	.81	.82
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Strong positive	Strong positive	Strong positive	Strong positive	Strong positive
Tp-e/HR					
R-value	−.74	−.72	−.78	−.81	−.79
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Moderate negative	Moderate negative	Strong negative	Strong negative	Strong negative
Tp-e/SDNN 24-hour					
F-value	−.67	−.56	−.71	−.61	−.74
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Moderate negative	Moderate negative	Moderate negative	Moderate negative	Moderate negative
Tp-e/SDANN index					
F-value	−.46	−.51	−.53	−.48	−.52
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Weak negative	Moderate negative	Moderate negative	Weak negative	Moderate negative
Tp-e/RMSSD					
F-value	−.55	−.49	−.51	−.48	−.52
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Moderate negative	Weak negative	Moderate negative	Moderate negative	Moderate negative
Tp-e/sNN50					
F-value	−.43	−.42	−.47	−.42	−.55
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Weak negative	Weak negative	Weak negative	Weak negative	Moderate negative
Tp-e/pNN50					
F-value	−.39	−.41	−.36	−.38	−.39
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Weak negative	Weak negative	Weak negative	Weak negative	Weak negative

Abbreviations: Tp-e, T peak-end interval; NN, successive RR interval; SDNN 24-Hour, Standard Deviation of all NN intervals; SDANN Index, Standard deviation of the average NN intervals for each 5 min segment of a 24 h heart rate variability recording; SDNN Index, Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording; RMSSD, Root mean square of successive RR interval differences; pNN50, Percentage of successive RR intervals that differ by more than 50 ms; sNN50, The number of successive RR intervals that differ by more than 50 ms.

test was used to determine whether there was any statistical difference among various parameters in the study group. The Pearson correlation test was used to examine the correlation between variables. Since multiple hypotheses are tested, the likelihood of making Type I error (ie, incorrectly rejecting the null hypothesis) also increases. The usual approach to compensate this phenomenon is to use a stricter significance threshold for an individual hypothesis. There are a few methods for choosing the appropriate significance level: Bonferroni correction ($\alpha_{individual} = \alpha_{desired}/n$), Šidák correction ($\alpha_{individual} = 1-(1-\alpha_{desired})^{1/n}$), and Holm-Bonferroni method which progressively tries to balance the criterion against the strictest one. We chose to use Bonferroni correction since it is the most conservative one.[21] Thus, a significance level of 0.05/20 = 0.0025 was used throughout the study. Statistical analysis was performed using a commercially available statistical package SPSS version 20.0 (IBM Co.).

3 | RESULTS

There were no differences in basal clinic findings between five male groups (Table 1).



	cTp-e/Age	cTp-e/HR	cTp--e/SDNN	cTp-e/SDANN	cTp-e/RMSSD	cTp-e/sNN50	cTp-e/pNN50
Group 1	0.68	−0.61	−0.53	−0.37	−0.37	−0.36	−0.26
Group 2	0.69	−0.57	−0.47	−0.43	−0.36	−0.38	−0.32
Group 3	0.73	−0.62	−0.53	−0.39	−0.43	−0.41	−0.26
Group 4	0.78	−0.59	−0.52	−0.41	−0.37	−0.37	−0.29
Group 5	0.81	−0.63	−0.57	−0.43	−0.42	−0.41	−0.27

Group 1 Group 2 Group 3 Group 4 Group 5

FIGURE 1 The correlation graphic of Tpeak-end (Tp-e) interval and heart rate variability values. SDNN, standard deviation of all NN intervals; SDANN Index; standard deviation of the average NN intervals for each 5 min segment of a 24 h heart rate variability recording; SDNN Index, Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording; RMSSD, Root mean square of successive RR interval differences, pNN50; Percentage of successive RR intervals that differ by more than 50 ms, sNN50; The number of successive RR intervals that differ by more than 50 ms; VLF, Absolute power of the very-low-frequency band (0.0033–0.04 Hz); LF, Absolute power of the low-frequency band (0.04–0.15 Hz); HF, Absolute power of high-frequency band (0.15-0.40 Hz); LF/HF, Ratio of LF-to-HF power; Tp-e, T peak-end interval. *R*-value; 1/0.75: strong positive correlation; 0.75/0.50: moderate positive correlation; 0.50/0.00: weak positive correlation; −1/−0.75: strong negative correlation; −0.75/−0.50: moderate negative correlation; −0.50 to 0.00: weak negative correlation

There were statistically significant differences between the five groups in terms of age. Tp-e, cTp-e, QT, QTc intervals, and maximum RR, minimum RR, mean RR intervals were shown increasingly with age, and sNN50, and SDNN, SDNN Index, SDANN Index, RMSSD, and pNN50 values were shown decreasingly with age. There were no significant differences between the five groups in terms of Tp-e/QT and Tp-e/QTc ratios besides there were increases in these values, and also there were no significant differences in terms of HRV LF, HRV VLF, HRV HF, and LF/HF ratio, besides there were decreases in these values with age.

Considering the Tp-e interval, there were significant differences between group 1 and groups 2, 3, 4, and 5 ($P < .0025$). In addition, there were significant differences between group 2 and groups 3, 4, and 5 ($P < .0025$). Besides, there were significant differences between groups 3 and 4, and group 5 ($P < .0025$). And also, there was significant difference between groups 4 and 5 ($P < .0025$).

Considering cTp-e interval, there were significant differences between groups 1 and 2 groups 3, 4, and 5 ($P < .0025$). And also, there were significant differences between group 2 and groups 3, 4, and 5 ($P < .0025$). In addition, there were significant differences between groups 3 and 4 and group 5 ($P < .0025$). Besides, there was a significant difference between groups 4 and 5 ($P < .0025$; Table 2).

Considering Tp-e interval and aging, there were significant positive correlations for each group between Tp-e interval and age values. Furthermore, there were significant negative correlations for each group between Tp-e intervals and HR values. Besides, there were significant negative correlations between Tp-e interval and SDNN 24-Hour, SDANN index, RMSSD, sNN50, and pNN50 values for each group. Besides, there were no statistically significant positive or negative correlations between Tp-e interval and HRV LF, HF, VLF values, and LF/HF ratio for each group (Table 3, Figure 1).

Considering cTp-e interval and aging, there were significant positive correlations for each group between cTp-e interval values and age values. Furthermore, there were significant negative correlations for each group between cTp-e intervals and HR values. Also, there were significant negative correlations between cTp-e and SDNN 24-Hour, SDANN index, RMSSD, and sNN50 values for each group. Despite there was a significant negative correlation between cTp-e interval and pNN50 values in group 2, there were no significant correlations between cTp-e interval and pNN50 values in other groups (Table 4, Figure 2).

4 | DISCUSSION

In our present study, we found that Tp-e and cTp-e intervals increased significantly for five healthy male groups with age. Besides, there were no significant changes in terms of Tp-e/QT and Tp-e/QTc ratios. Furthermore, HRV temporal parameters decreased significantly in all groups, but there were no significant changes in terms of HRV frequency parameters. Besides, there were significant positive correlations between the Tp-e interval and age values of the five male groups. Furthermore, there were significant negative correlations between Tp-e interval and HRV temporal parameters. Besides, there were significant negative correlations between cTp-e interval values and HRV temporal parameters.

Heart disease remains the leading cause of death in the United States in part due to the aged population.[22] There is a significantly increased incidence of cardiovascular disease and arrhythmia in the elderly.[23,24]

Changes in HRV values are of great importance in patient groups. Statistically significant decreases in HRV values have a prognostic significance in the prediction of cardiovascular diseases.[7] Little attention is paid to the relationship between the age-related HRV data of the subjects and the mechanisms that regulate the organism's functions. Corino et al found that the correlation between HRV indices and the age of test subjects (20-85 years) showed that HRV indices could be used as a biological determinant of age.[25] We also found that HRV temporal parameters decreased with age significantly in healthy male subjects aged between 30 and 79 years. But there were no significant changes in HRV frequency parameters.

TABLE 4 Correlations between cTp-e values and HRV values

Variables	Group 1 (30-39 y)	Group 2 (40-49 y)	Group 3 (50-59 y)	Group 4 (60-69 y)	Group 5 (70-79 y)
cTp-e/age					
R-value	.68	.69	.73	.78	.81
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Moderate positive	Moderate positive	Moderate positive	Strong positive	Strong positive
cTp-e/HR					
R-value	−.61	−.57	−.62	−.59	−.63
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Moderate negative	Moderate negative	Moderate negative	Moderate negative	Moderate negative
cTp-e/SDNN 24-Hour					
R-value	−.53	−.47	−.53	−.52	−.57
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Moderate negative	Weak negative	Moderate negative	Moderate negative	Moderate negative
cTp-e/SDANN					
R-value	−.37	−.43	−.39	−.41	−.43
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Weak negative	Weak negative	Weak negative	Weak negative	Weak negative
cTp-e/RMSSD					
R-value	−.37	−.36	−.43	−.37	−.42
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Weak negative	Weak negative	Weak negative	Weak negative	Weak negative
cTp-e/sNN50					
R-value	−.36	−.38	−.41	−.37	−.41
P-value	<.0025	<.0025	<.0025	<.0025	<.0025
Correlation	Weak negative	Weak negative	Weak negative	Weak negative	Weak negative
cTp-e/pNN50					
R-value	−.28	−.32	−.26	−.29	−.27
P-value	.0047	<.0025	.0089	.0034	.0065
Correlation	Weak negative	Weak negative	Weak negative	Weak negative	Weak negative

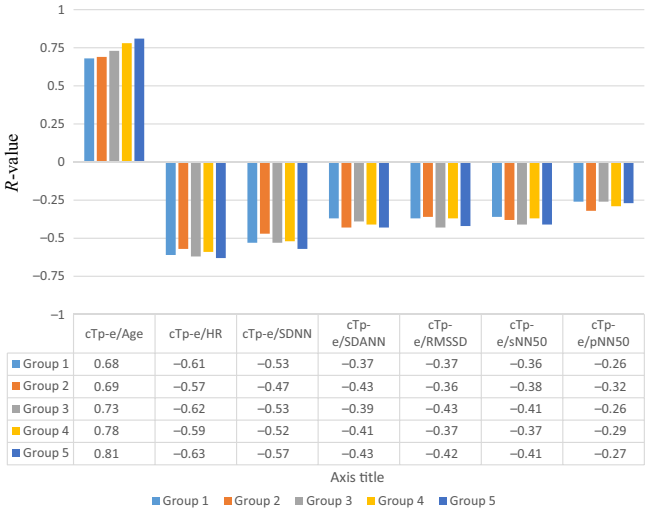
Abbreviations: Tp-e, T peak-end interval; NN, successive RR interval; SDNN 24-Hour, Standard Deviation of all NN intervals; SDANN Index, Standard deviation of the average NN intervals for each 5 min segment of a 24 h heart rate variability recording; SDNN Index, Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording; RMSSD, Root mean square of successive RR interval differences; pNN50, Percentage of successive RR intervals that differ by more than 50 ms; sNN50, The number of successive RR intervals that differ by more than 50 ms.

It was found that the HRV indexes varied according to the variability of age and level of physical activity among participants aged 45-56 years.[26] When evaluating HRV indices and determining reference values for healthy individuals (24-39 years), it was concluded that these indices were related to age, as well as the sex of test subjects. Arai et al also maintained the need to analyze HRV indices for men and women separately.[27] It is found to be significantly lower in elderly, women, diabetic, and obese.[5]

It was emphasized that increasing the difference between the action potentials of endocardial and epicardial cells led to an increase in myocardial repolarization time, leading to fatal ventricular arrhythmias.[28,29]

For the first time in the literature, Watanabe et al have prospectively demonstrated that increased myocardial repolarization dispersion was associated with spontaneous and inducible ventricular tachycardia and fibrillation in high-risk patients. As a result, it was suggested that long-term increases in transmural repolarization dispersion were associated with fatal ventricular arrhythmias and these parameters were indices that can be used to predict these arrhythmias. Tp-e interval times in patients with ventricular tachycardia induced by the electrophysiological study were found to be significantly higher than those in non-VT inducible patients and control group. In addition, Tp-e interval times in V_4 were significantly higher in patients with ejection fraction >35% and who had spontaneous ventricular tachycardia compared to the control group and the group without spontaneous ventricular tachycardia.[30]

Increased sympathetic activity and varying cardiac autonomic functions are closely associated with a heterogeneity of ventricular



	cTp-e/Age	cTp-e/HR	cTp-e/SDNN	cTp-e/SDANN	cTp-e/RMSSD	cTp-e/sNN50	cTp-e/pNN50
Group 1	0.68	−0.61	−0.53	−0.37	−0.37	−0.36	−0.26
Group 2	0.69	−0.57	−0.47	−0.43	−0.36	−0.38	−0.32
Group 3	0.73	−0.62	−0.53	−0.39	−0.43	−0.41	−0.26
Group 4	0.78	−0.59	−0.52	−0.41	−0.37	−0.37	−0.29
Group 5	0.81	−0.63	−0.57	−0.43	−0.42	−0.41	−0.27

FIGURE 2 The correlation graphic of corrected Tpeak-end (cTp-e) interval and heart rate variability values. SDNN, standard deviation of all NN intervals; SDANN Index, standard deviation of the average NN intervals for each 5 min segment of a 24 h heart rate variability recording; SDNN Index, Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording; RMSSD, Root mean square of successive RR interval differences; pNN50, Percentage of successive RR intervals that differ by more than 50 ms; sNN50, The number of successive RR intervals that differ by more than 50 ms; VLF, Absolute power of the very-low-frequency band (0.0033–0.04 Hz); LF, Absolute power of the low-frequency band (0.04–0.15 Hz); HF, Absolute power of high frequency band (0.15-0.40 Hz); LF/HF, Ratio of LF-to-HF power; cTp-e, Corrected T peak-end interval. *R*-value; 1/0.75: strong positive correlation; 0.75/0.50: moderate positive correlation; 0.50/0.00: weak positive correlation; −1/−0.75: strong negative correlation; −0.75/−0.50: moderate negative correlation; −0.50 to 0.00: weak negative correlation

repolarization and the risk of ventricular arrhythmia.[31] In another study, it was demonstrated by a mechanical method that the degree of increase in transmural myocardial repolarization time might indicate the degree of sustained ventricular tachycardia.[32] In one study, it was shown that the Tp-e interval increased by sympathetic ganglion stimulation but not intravenous norepinephrine infusion.[33] We thought that the Tp-e interval increased by an increase in sympathetic activation or a decrease in parasympathetic activation.

In a published review, a meta-analysis of 155 856 patients and 33 observational studies showed that increased Tp-e interval was associated with a 1.16-fold increase in SCD and malignant ventricular arrhythmias in all groups. This increase was 5.6 times in Brugada syndrome, 1.52 times in hypertension, 1.07 times in heart failure, and 1.06 times in coronary artery disease. In the general population, a prolonged Tpeak-Tend interval predicted the results of malignant ventricular arrhythmia or mortality with a 1.59 odds ratio.[11] In this review, cutoff values of Tp-e interval for malignant ventricular arrhythmias were determined for some diseases and the general population. The cutoff value for the general population was found to be 113.6 milliseconds The lowest value was 95.8 milliseconds in Brugada syndrome and 106.3 milliseconds in heart failure, respectively. Interestingly, there was no statistical significance between the Tp-e interval cutoff value (109.6 milliseconds) detected in ischemic heart disease and the Tp-e cutoff value (113.6 milliseconds) detected in the general population. It is known that ventricular tachyarrhythmias in Brugada syndrome were also affected by autonomic tone, on the other hand, the incidence of MAs is low in BrS aged over 70 years. Malignant ventricular arrhythmias with aging were affected not only autonomic dysfunction but also myocardial degeneration like fibrosis leading conduction disorder.[34]

In one study, increased Tp-e interval, especially Tp-e/QT ratios above 0.25, was found to be closely associated with the emerging malignant ventricular arrhythmias, while no QTc was associated with ventricular arrhythmia in patients with ICD.[35] Several studies have supported this study and demonstrated that increased Tp-e interval times are associated with malignant ventricular arrhythmias.[13] We also found that the Tp-e interval increased with age in healthy male subjects aged between 30 and 79 years. This could help to explain why malign ventricular malign arrhythmias increased with age in healthy subjects or patients with structural heart disease.

Tp-e interval has been investigated in many diseases in which are the incidence of sudden cardiac death and malign ventricular arrhythmias increase. Some of them are HIV patients, patients with liver cirrhosis, patients with celiac disease, migraine attacks, patients with vasospastic angina, and arrhythmogenic right ventricular cardiomyopathy, smokers and many other diseases.[17-19,36-40]

5 | CONCLUSION

Although many conditions affect the Tp-e interval and HRV parameters; as a result, Tp-e interval increases with age, and HRV temporal parameters decrease, in the 30-79 age range of in healthy males, as the decade increases, and it has been found Tp-e interval was significantly correlated with the HRV temporal parameters. We also found that the Tp-e interval increased and HRV temporal parameters decreased with age.

6 | STUDY LIMITATIONS

We could not research malignant ventricular arrhythmias or deaths in groups. Our study was cross-sectional. Studies to follow these individuals for a long time are needed to determine whether malignant ventricular arrhythmia has developed. And also, in addition to Tp-e interval, investigation with parameters such as T-wave heterogeneity and T-wave alternans will provide healthier information.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. There is no source(s) of support in the form of grants, equipment, and drugs. All expenses were paid by the authors.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were following the ethical standards of Turkey's national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study permit was obtained from the hospital management committee. Informed written consent was obtained from each of the patients participating in the study.

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