

Original Research

Evaluation of ventricular repolarization parameters in erectile dysfunction: a predictor of cardiac diseases

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Abstract

Background: The purpose of this study is to compare the electrocardiogram (ECG) parameters, which are indicators of ventricular repolarization, between men with erectile dysfunction (ED) and healthy ones. **Methods:** A total of 56 men aged 30–65 years diagnosed with ED were included in the study from March 2021 to November 2021. The control group comprises 59 year-old healthy male volunteers. The International Index of Erectile Function (IIEF-5) questionnaires were used to diagnose ED. The standard 12-lead surface ECG was taken for the whole study group and QT intervals (time between start of the Q, and end of the T wave seen on an ECG, approximating to the time taken from when the cardiac ventricles start to contract to when they finish relaxing), QRS complex (a combination of Q, R, and S waves seen on a typical ECG), and Tp-e intervals (the interval from the peak to the end of the electrocardiographic T wave seen on an ECG) were measured. The corrected QT (QTc) was calculated according to the heart rate using Bazett's formula. The Tp-e/QT and Tp-e/QTc ratios were calculated. **Results:** The mean age in the study group was 51.88 years \pm 1.13 years. Comorbid conditions were similar between the ED and control groups. There was no significant difference between the ECG parameters of the groups (i.e., heart rate, RR interval, QT, QTc and QRS duration). However, the Tp-e interval (76.79 ms \pm 1.41 ms vs 70.46 ms \pm 1.27 ms, $p = 0.0006$), Tp-e/QT (0.21 \pm 0.004 vs 0.19 \pm 0.004, $p = 0.0054$) and Tp-e/QTc (0.21 \pm 0.004 vs 0.17 \pm 0.004, $p < 0.0001$) was significantly higher in the ED group than in the healthy control group. **Conclusions:** The routine cardiac evaluation in cases of a disease knowingly related to cardiovascular diseases, such as ED, provides an opportunity to anticipate possible complications and take precautions. We believe that an inexpensive and non-invasive method such as the ECG is important in this cardiac evaluation. The use of relatively new parameters in routine ECG evaluation such as Tp-e and Tp-e/QT, which show the transmural distribution of repolarization, may also be useful in estimating the risk of arrhythmia.

Keywords: Tp-e interval; Tp-e/QT; Tp-e/QTc; erectile dysfunction; arrhythmia

1. Introduction

Erectile dysfunction (ED) is a pervasive male sexual dysfunction that reduces both sexual and overall quality of life of patients and their partners. ED is known as a condition in which a penile erection sufficient for satisfactory sexual intercourse cannot be achieved and/or maintained [1]. There are many psychogenic, vascular, neurohumoral, and drug-related factors in the pathophysiology of ED [2]. Although its incidence varies among societies, ED occurs in 20% to 30% of the general male population [3]. The relationship between ED and a coronary artery disease (CAD) has been shown in many studies. The development of ED on average 3–5 years before the onset of cardiovascular events can be considered a predictive factor for cardiovascular diseases (CVDs) [4,5]. The pathophysiological mechanism of ED that explains why it is a predictor of CAD events, is the smaller diameter of penile arteries (1–2 mm) being affected by an atherosclerotic plaque burden earlier than coronary arteries with larger diameters (3–4 mm). ED and CVD co-occur once both have common risk factors,

such as diabetes, hypertension (HT), hyperlipidemia (HL), and smoking, and have similar pathophysiological mechanisms, such as impaired endothelial dysfunction, increased oxidative stress, and decreased nitric oxide (NO) release [6].

People with CAD have a higher potential of presenting ventricular arrhythmias compared to the normal population, possibly due to disturbances in the electrical activity of the myocardium exposed to ischemia and inappropriate stimuli arising from necrotic myocardial tissue [7]. Lifestyle changes are the first step toward treating ED. These changes include smoking cessation, physical exercise, and regulation of risk factors. Phosphodiesterase type 5 inhibitors (PDE5i) are commonly used agents in pharmacological treatment.

Electrocardiography (ECG) parameters such as the QT interval, the corrected QT (QTc) and transmural dispersion of repolarization, indicate myocardial repolarization [8]. A prolonged QT interval is a risk marker widely used to detect individuals predisposed to a type of polymorphic



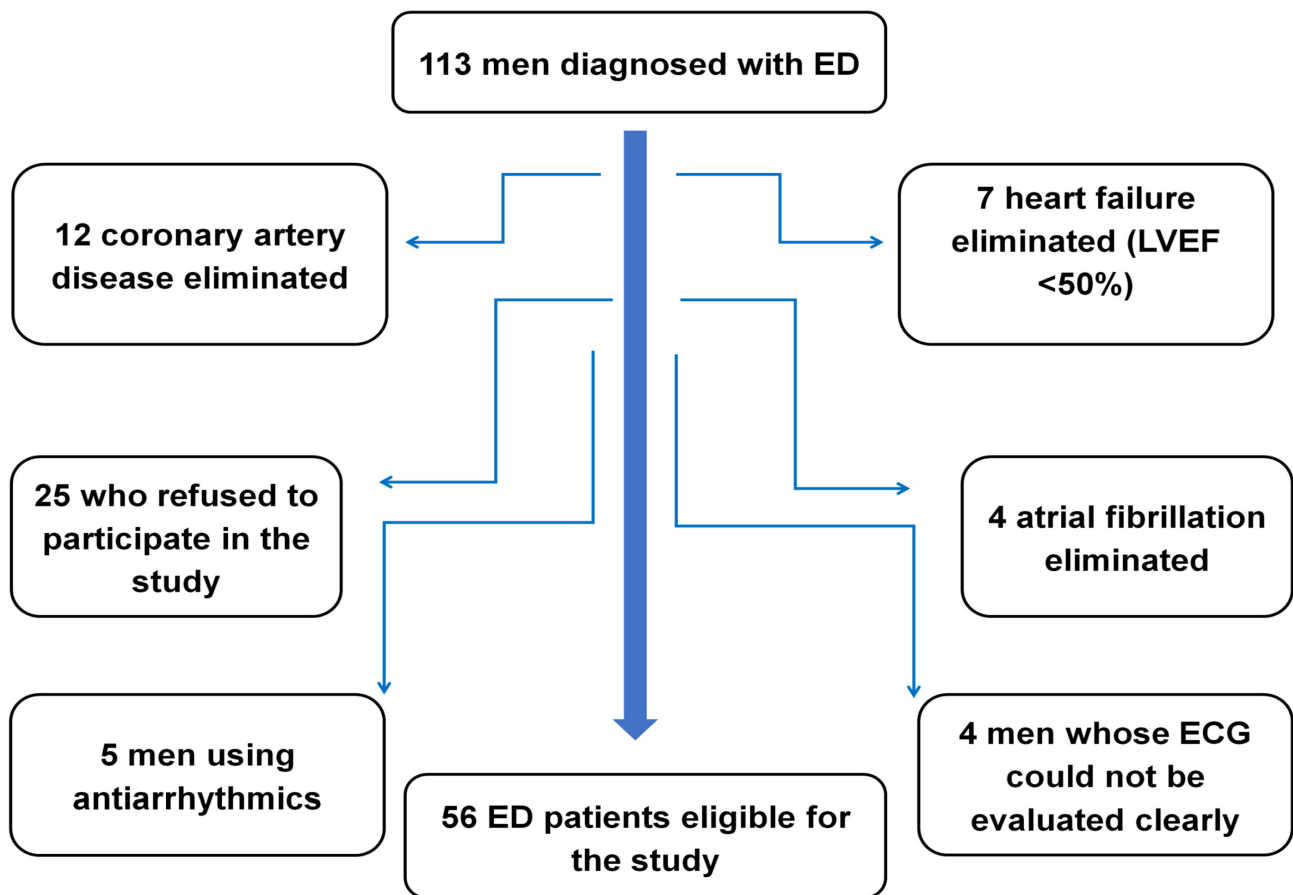


Fig. 1. Patient recruitment algorithm.

ventricular tachycardia (VT), such as Torsades de pointes (TdP) or ventricular fibrillation (VF) [9]. Recent studies have shown that Tp-e and Tp-e/QT can be used to indicate transmural dispersion of repolarization. The Tp-e interval and Tp-e/QT ratio represent valuable electrocardiographic arrhythmic risk indices, possibly corresponding to the spatial distribution of ventricular repolarization [10,11].

To the best of our knowledge, there is no study in the literature evaluating ventricular repolarization parameters in ED patients. Our study aimed to compare ECG parameters (i.e., the QT, QTc, and Tp-e intervals, and the Tp-e/QT and Tp-e/QTc ratios), which show ventricular repolarization of patients with ED, with healthy individuals, and to investigate arrhythmogenesis susceptibility.

2. Materials and methods

2.1 Study population and design

In our cross-sectional and prospective study, 113 male patients aged between 30 years and 65 years who had applied to the urology outpatient clinic from March to November 2021 and were diagnosed with ED were evaluated. A total of 56 patients met the inclusion criteria and were included in the study. The control group comprised 59 year old healthy male volunteers (Fig. 1).

The weight and height values of all individuals participating in the study were used to determine their body mass index (BMI in kg/m^2). The blood pressure was measured at least 10 minutes after resting. Venous blood samples were obtained from each patient at admission to evaluate complete blood count, markers of inflammatory status, and conduct tests of kidney, liver, and thyroid function.

2.2 Exclusion criteria from the study

Patients with known history of CAD (proven by coronary angiography or noninvasive methods), systolic heart failure (left ventricular ejection fraction (LVEF) $<50\%$), use of antiarrhythmic drugs that may affect the QT interval, atrial fibrillation, left bundle branch block, electrolyte disturbances that may cause arrhythmia (hyperkalemia, hypokalemia, hypercalcemia, hypocalcemia, etc.), patients whose ECG cannot be evaluated clearly due to artifact and parasitic appearance, uncontrolled hypertension (HT), thyroid dysfunction, active infection, and history of urological surgery were excluded from the study.

2.3 The evaluation of erectile dysfunction

All male participants included in the study were asked to fill in the International Erectile Function Index (IIEF-5),

which consists of 5 items, after providing a written consent form. Each item in this form is scored from 0 to 5 or from 1 to 5. An overall sexual function score between 1 and 25 is calculated in the total. Those with an (IIEF)-5 score of >21 were defined as men with normal erectile function, while those with an (IIEF)-5 score of ≤ 21 were defined as ED.

2.4 Electrocardiographic evaluation

Twelve-lead surface ECGs were taken during normal breathing patterns in the supine position at an amplitude of 20 mm/mV and 50 mm/sec. ECG recordings were made with a MAC 2000 (GE Medical Systems Information Technologies, Milwaukee, WI, USA) branded device. All ECG recordings were transferred to the hospital automation system and analyzed by magnifying the recording 300 times on the computer system. The ECG parameters included in the evaluation were measured over the V5 precordial lead and the average of three consecutive cardiac beats was calculated. The distance from the beginning of the QRS complex to the point where the T wave intersects with the isoelectric line was measured to obtain QT distance. QTc was calculated based on the heart rate using Bazett's formula ($QTc = QT/\sqrt{RR}$). The Tp-e interval was obtained by measuring the distance from the peak of the T wave to the point where it ends (Fig. 2). The Tp-e/QT and Tp-e/QTc ratios were calculated based on the measurements made. Two different cardiologists performed all ECGs blinded to patient information, and the measurements were averaged. The inter and intra-observer variation coefficients were 4.2% and 4.5%, respectively.

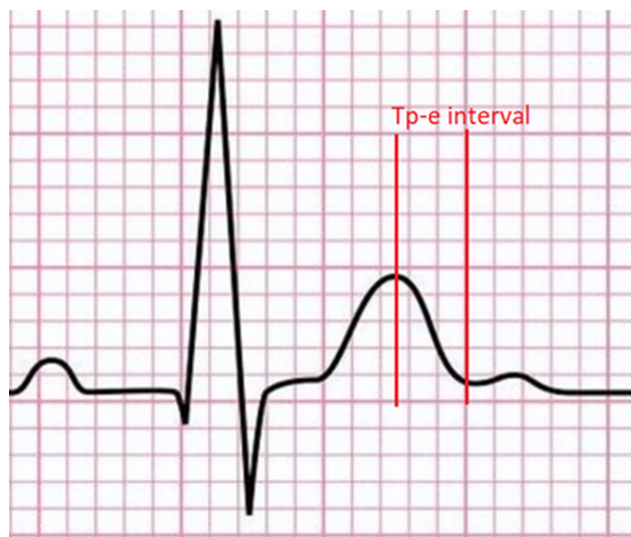


Fig. 2. Measurement of the T peak to end (Tp-e) interval.

2.5 Statistical analyses

The sample size of this study was calculated by assuming desired confidence level (95%), Z score (1.96), and

margin of error (5%; 0.05). We included 115 subjects (56 ED patients, 59 control individuals) in this study.

The statistical analyses were presented as mean \pm standard error of the mean (SEM). An unpaired *t*-test with a one-sided *p*-value was used to compare the patient group with the healthy control group in the GraphPad Prism 6.01 (GraphPad Software, San Diego, CA, USA) software. The significance level was denoted as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$.

In addition to ordinary statistics, the receiver operator characteristic (ROC) curve analysis was applied to the control group and patients to choose a cutoff value that separates “normal” from “abnormal” ECG parameters. The analysis was performed using the GraphPad Prism 6.01 (GraphPad Software, San Diego, CA, USA) software. To help make the decision, a tradeoff of sensitivity versus specificity was plotted as a ROC curve. Sensitivity measures the fraction of people with the disease that the test correctly identifies as positive. In turn, specificity means the fraction of people without the disease that the test correctly identifies as negative. The mean area under the entire ROC curve \pm standard error (SE) of 95% confidence was evaluated, which quantifies the overall ability of the test to distinguish patients from healthy individuals.

3. Results

The mean age of the study group was 51.88 years \pm 1.13 years. Other comorbid conditions (BMI, DM, HT, and smoking) and mean systolic and diastolic blood pressures were similar between the ED and control groups. There was no significant difference between the biochemical parameters of the groups. See Table 1 for the comparison of clinical, demographic, and laboratory parameters.

There was no significant difference between heart rate, RR interval, QT, QTc, and QRS duration. However, the Tp-e interval (76.79 ms \pm 1.41 ms vs 70.46 ms \pm 1.27 ms, $p = 0.0006$), Tp-e/QT (0.21 \pm 0.004 vs 0.19 \pm 0.004, $p = 0.0054$), and Tp-e/QTc (0.21 \pm 0.004 vs 0.17 \pm 0.004, $p < 0.0001$) were significantly higher in the ED group compared with healthy control group. See Table 2 for the comparison of the ECG parameters of the groups.

The area under the curve (AUC) values of Tp-e (0.66 \pm 0.05), Tp-e/QT (0.62 \pm 0.05), and Tp-e/QTc (0.62 \pm 0.05) parameters were significant in ED patients (Table 3). Furthermore, the ROC curves of sensitivity (100%) and specificity (100%) across varying cut-offs surpass the diagonal baseline for these ECG parameters (Fig. 3).

4. Discussion

The main findings of this study are the significantly increased Tp-e/QT and Tp-e/QTc ratios and the increased Tp-e interval in individuals with ED compared with the healthy group. The obtained findings specify the negative impact of ED on parameters that indicate ventricular repolarization. To our knowledge, this is an early report submitted to the

Table 1. Comparison of clinical, demographic, and laboratory parameters in erectile dysfunction (ED) patient and healthy control groups.

Parameters	ED group (n = 56)	Control group (n = 59)	p value
Age (years)	51.84 ± 1.22	51.90 ± 1.06	0.485 ns
Body mass index (kg/m ²)	28.23 ± 0.58	28.19 ± 0.40	0.475 ns
Smoking, (n, %)	18 (32.14)	21 (35.59)	
Hypertension (n, %)	12 (21.42)	12 (20.34)	
Hyperlipidemia (n, %)	10 (17.85)	9 (15.25)	
Systolic BP (mm Hg)	127.60 ± 1.19	126.70 ± 1.30	0.303 ns
Diastolic BP (mm Hg)	79.55 ± 1.54	77.29 ± 1.29	0.130 ns
HbA1c (%)	6.08 ± 0.11	6.00 ± 0.11	0.326 ns
FBG (mg/dL)	99.54 ± 2.64	97.63 ± 3.20	0.324 ns
Creatinine (mg/dL)	0.82 ± 0.02	0.79 ± 0.02	0.238 ns
Sodium (mEq/L)	136.60 ± 0.62	137.70 ± 0.77	0.147 ns
Potassium (mEq/L)	4.50 ± 0.06	4.57 ± 0.07	0.230 ns
Calcium (mg/dL)	9.38 ± 0.08	9.24 ± 0.10	0.159 ns
AST (U/L)	26.29 ± 1.33	26.68 ± 1.30	0.417 ns
ALT (U/L)	21.71 ± 1.28	22.75 ± 1.14	0.274 ns

ns, non-significant; smoking score: 0–1 (nonsmoker score: 0, smoker score: 1); HT score: 0–1 (no HT score: 0, Yes HT score: 1). HL score: 0–1 (no HL score: 0, Yes HL score: 1). BP, blood pressure; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. Comparison of ECG parameters in erectile dysfunction (ED) patient and healthy control groups.

ECG parameters	ED group (n = 56)	Control group (n = 59)	p value
Heart rate (beat/min)	77.77 ± 1.79	75.15 ± 1.87	0.157 ns
RR	0.79 ± 0.01	0.82 ± 0.01	0.103 ns
QT (msec)	371.5 ± 4.05	370.7 ± 3.64	0.447 ns
QTc (msec)	413.6 ± 5.56	416.2 ± 6.16	0.378 ns
Tp-e (msec)	76.79 ± 1.41	70.46 ± 1.27	0.0006 ***
Tp-e/QT	0.21 ± 0.004	0.19 ± 0.004	0.0054 **
Tp-e/QTc	0.21 ± 0.004	0.17 ± 0.004	<0.0001 ****

The degree of significance was denoted as: ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$, ns, non-significant.

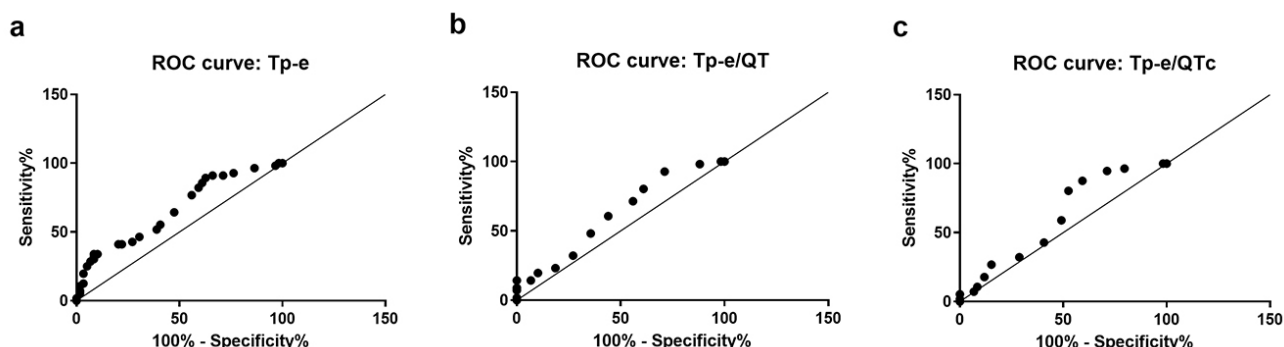


Fig. 3. The relationship between clinical sensitivity (100%) and specificity (100%) for every possible cutoff is shown by receiver operator characteristic (ROC) curves for the ECG parameters (a) Tp-e, (b) Tp-e/QT, and (c) Tp-e/QTc.

Table 3. Area under the receiver operator characteristic (ROC) curves in ECG parameters.

ECG parameters	Area	Significance (<i>p</i>)
Tp-e	0.66 ± 0.05	0.002 **
Tp-e/QT	0.62 ± 0.05	0.024 *
Tp-e/QTc	0.62 ± 0.05	0.033 *

The significance level was denoted as **p* < 0.05 and ***p* < 0.01.

literature on ED-associated increases in ECG parameters.

The non-invasive, easy, and reproducible 12-lead surface ECG is the main diagnostic tool to diagnose ventricular arrhythmias. Physiologically, the susceptibility to ventricular arrhythmias increases in the absence of a normal recovery in myocardial tissue after systole [12]. QT interval, QTc, and T wave are classical ECG parameters that generally provide information about ventricular repolarization [13–15], and their prolongation has been associated with an increased risk of CVDs such as ventricular tachycardia, ventricular fibrillation, TdP, and sudden cardiac death [15]. Recently, electrocardiographic parameters other than QT and QTc intervals, such as the Tp-e interval, have been used to predict ventricular arrhythmias. The TP-e interval has been related to ventricular arrhythmia and sudden cardiac death when prolonged [16,17]. Experimental studies have reported that the epicardial and mid-myocardial action potentials correspond to the peak and the end of the T wave, respectively, and give information on the completion of repolarization [18]. The Tp-e/QT and Tp-e/QTc ratios when compared with total ventricular repolarization time, provide more information on the transmural distribution of repolarization. In addition, the Tp-e interval is also more sensitive. It has also been suggested that the Tp-e/QT and Tp-e/QTc ratios are better predictors of ventricular repolarization than the QT interval [19–21]. Since the Tp-e/QTc index is not affected by variables such as heart rate variability and body surface area, it is considered more relevant as a ventricular repolarization index [18]. The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio increase in heart diseases such as the acute coronary syndrome, long QT syndrome, and Brugada syndrome accompanied by increased malignant ventricular arrhythmias [22,23]. However, these parameters may also increase in many non-cardiac diseases [24–26]. Although the reason for this situation has not been fully explained, microvascular dysfunction, fibrosis, and apoptosis may be responsible for the increased Tp-e interval and Tp-e/QT ratio [27,28].

ED has been associated with chronic heart disease morbidity and mortality, death, stroke, diabetes mellitus, peripheral arterial disease, and chronic kidney failure, as well as with several chronic heart disease risk factors. ED represents one of the first clinical manifestations and an independent predictor of CVDs. ED symptoms have been shown to begin 3–5 years before the CVD is detected [29]. The most likely causes of this association are endothe-

lial dysfunction, impaired NO synthesis, and the same risk factors such as hypertension, smoking, diabetes mellitus, sedentary life, and hyperlipidemia, observed in both cases.

Although there are many studies on the relationship between ED and CVH, there is no study in the literature on ventricular arrhythmia, which is an important cause of mortality in CVDs. Many previous studies have reported increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios in conditions such as DM, HT, and smoking, which are risk factors for CAD [21,30,31]. The common ground in these independent studies is that endothelial damage occurs with similar pathophysiological mechanisms in both ED and CVH. Prothrombotic and proinflammatory molecules such as vWF, selectin, and adhesion molecules released from dysfunctional or damaged endothelial cells increase vascular tone. The presence of the same risk factors and similar pathophysiological mechanisms in the etiology of ED implies a possible risk of ventricular arrhythmia in ED patients.

In a multiethnic study of atherosclerosis (MESA), the prevalence of ED was reported to be associated with eventful atrial fibrillation (AF) [32]. The pathophysiology of AF-related ED may include potential risk of thromboembolism, endothelial dysfunction, inflammatory process, and lack of atrial contribution to the cardiac cycle. Similarly, paroxysmal lone AF was seen more frequently in ED patients than in the normal population [33].

The atrial electromechanical duration has been reported as prolonged in patients with ED [34]. In our study, unlike atrial origin arrhythmias, ventricular repolarization parameters were investigated. In addition to classical parameters such as QT and QTc, which show electrical depolarization and repolarization of the ventricle, relatively new ventricular repolarization parameters such as TP-e, and Tp-e/QT were evaluated.

In our study, the QT and QTc intervals were similar, while the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly longer in ED patients compared to the healthy group. This difference means that ED patients were not only at risk of presenting a CVD but also of presenting ventricular arrhythmias. Therefore, we believe that the assessment of arrhythmia in addition to CVD is also important in the cardiac evaluation of ED patients.

The accuracy of clinical diagnostic assays that aim to discriminate patients from healthy individuals can be calculated through the ROC test. The ROC curve is a unit square plot of sensitivity versus specificity covering different cut-off values [35]. The cumulative accuracy of the assay can be achieved efficiently by measuring the AUC from the ROC curve. It describes the position of the whole curve instead of referring to a particular location, and gives a value ranging from 0 to 1 [35]. If the AUC value is 1, it means excellent correctness, while values equal to 0 indicate an ideal error. When the curve obtained is a 45-degree crossing line, then the AUC is 0.5, indicating that the assay

is unsuitable for diagnosis [36]. Usually, the diagnostic capacity of the assessment is clinically acceptable when the curve exceeds the 45-degree line [36]. Our study revealed AUC values higher than and statistically different from the 0.5 threshold, and ROC curves above the diagonal line indicating the possible diagnostic potential of ECG parameters for ED.

The potential duration of the action of myocytes is maintained by the activation and inactivation of sodium, calcium, and potassium currents through specific ionic channels. Testosterone can shorten the potential duration of the action, and shorten the QT, particularly affecting the L-type calcium channel and the slow latency rectifier K⁺ channel. Thus, it reduces calcium influx and increases potassium influx. This may partly explain the sex difference in QT interval [37,38].

5. Conclusions

In this study, it was shown that while QT and QTc in the ED group were similar to the healthy group, Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio were higher. Routine ECG evaluation may be useful in predicting the risk of ventricular arrhythmia in a disease knowingly associated with cardiovascular diseases, such as ED.

6. Limitations

The study has some limitations. The most important limitation of the research is that the study has small number of patients. In addition, the long-term clinical and rhythm Holter follow-ups could not be performed in this study. Therefore, long-term rhythm Holter monitoring and large patient groups are needed to emphasize the importance of Tp-e interval and Tp-e /QT ratio. Another limitation is the lack of carotid/vertebrobasilar circulation and capillaroscopy imaging approaches. Hence, the correlation between the electrocardiographic data and imaging/capillarography data is missing in this research. To confirm the hypothesis of the study, the next step may be to predict CVD risk in ED patients using coronary calcium score on CT, and, hence, this would be a perspective for further research [39].

Author contributions

İA, AHY, OA—conceptualization; İA, AHY—methodology; İA, RG—software; İA, RG—validation; İA, RG—formal analysis; İA, OA, RG—investigation; İA, AHY, OA—resources; İA, RG—data curation; İA, AHY, RG—writing—original draft preparation; İA, AHY, OA—writing—review and editing; İA, RG—visualization; İA, AHY—supervision; İA—project administration. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

All participants were informed about the study, and a written consent form was obtained. The study was planned according to the Helsinki Declaration criteria and was approved by the local ethics committee (Republic of Turkey Ministry of Health Bilecik Provincial Health Directorate) (Approval no: 2021/016).

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Conflict of interest

The authors declare no conflict of interest.

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