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Evaluation of the Tpeak-Tend Interval as an Arrhythmogenicity Index in Graves' Disease

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Abstract

Introduction. Graves' disease is the most common cause of hyperthyroidism. The mortality rate increases by 20% in hyperthyroid patients; cardiac problems are the leading cause of death and arrhythmia is the most common cardiac complication.

Our study **aimed** to evaluate the corrected QT interval (QTc), the Tpeak-Tend interval (Tp-e), and the Tp-e/QTc ratio to predict arrhythmia risk in patients with Graves' disease.

Methods. The study included 64 patients with Graves' disease and 57 euthyroid controls. The 12-lead electrocardiograms of the individuals under study were evaluated. The QTc interval, the Tp-e interval, and the Tp-e/QTc ratio of all participants were determined and statistically evaluated with thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) values.

Results. Tp-e ($p < 0.001$) and QTc ($p < 0.05$) were significantly prolonged in the group of patients with Graves' disease as compared to the control group. Heart rate was higher in patients with Graves' disease as well ($p < 0.05$). Correlation analysis in patients with hyperthyroidism demonstrated that Tp-e (r=0.372, p=0.002), QTc (r=0.291, p=0.020), and fT3 levels were significantly and positively correlated. Similarly, Tp-e (r=0.271, p=0.030), QTc (r=0.259, p=0.039), and fT4 levels were significantly and positively correlated.

Conclusions. We observed a significant prolongation of the Tp-e and QTc intervals with the increase in fT3 and fT4 levels. On the other hand, our study demonstrated that the sensitivity and specificity of Tp-e in the prediction of hyperthyroidism were 70.3% and 70.1%, respectively (AUC=0.724 (CI: 0.629-0.818)), the optimal cut-off value=83.5 ms). The Tp-e interval, which has recently been used as one of the arrhythmogenicity indices, may be an indicator of arrhythmia risk in patients with Graves' disease.

Keywords

Arrhythmia; Graves' Disease; Hyperthyroidism; QTc; Tpeak-Tend Interval

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Introduction

Graves' disease is an autoimmune disorder that affects many systems including the thyroid gland, eyes, and skin. Approximately one in 200 people is diagnosed with Graves' disease in their lifetime [1]. Although Graves' disease is frequently found at the age of 30-50 years, it can be diagnosed at any age [2]. Genetic factors account for 80% of the risk of occurring Graves' disease [3]; the other 20% are associated with environmental risk factors such as tobacco products, psychological stress, infections, excessive iodine intake, and conditions involving physiological changes of sex hormones, such as pregnancy [4]. These factors cause the onset of Graves' disease by breaking the mechanisms leading to immune tolerance in genetically predisposed individuals [5].

Most patients with Graves' disease present with prominent symptoms of hyperthyroidism and several physical examination findings typical of Graves' disease. Common symptoms are palpitations, weight loss, chills, heat intolerance, and anxiety [6]. Physical examination findings are enlargement of the thyroid gland, proptosis, tachycardia, and tremor [6]. The rate of mortality increases by 20% in patients with hyperthyroidism, with cardiac problems as the main cause of death [7]. The most common cardiac complication is atrial fibrillation, seen in approximately 10-25% of patients with overt hyperthyroidism [8]. Ventricular tachycardia and fibrillation leading to sudden cardiac death are dangerous complications of hyperthyroidism as well, although not as common as before [8]. An electrocardiogram (ECG) can be used to predict cardiac arrhythmia in such patients. The two most studied predictors in clinical practice are the QT interval and the corrected QT interval (QTc) [9, 10]. Other recently studied markers such as

the Tpeak-Tend (Tp-e) interval and the Tp-e/QT ratio have been increasingly used as well [10]. The Tp-e is the interval between the peak and the end of the T wave, and it has been reported in previous studies to be able to show transmural repolarization. The Tp-e is independent of the QRS complex, and measuring the Tp-e interval is superior to the QTc duration [11, 12].

To the best of our knowledge, most studies on the risk of arrhythmia in patients with Graves' disease and overt hyperthyroidism have been associated with the QTc interval, and there is no study on the predictive value of the Tp-e interval, which is believed to indicate a greater risk of arrhythmia in this group of patients.

Our study **aimed** to evaluate the markers QTc, Tp-e, Tp-e/QTc, which are used as arrhythmia indices in Graves' disease.

Materials and Methods

Following the approval by the Research Ethics Committee of the Kahramanmaras Sutcu Imam University (dated December 01, 2021, decision No. 03), this study was conducted in our institution between January and April 2022.

Participants

The study included 64 patients with thyrotoxicosis who applied to the Division of Endocrinology and Metabolism, Internal Medicine Department, Necip Fazil City Hospital, Kahramanmaras, Turkey, and were newly diagnosed with Graves' disease based on laboratory findings, and 57 euthyroid, healthy subjects who applied for routine check-up. In patients with thyrotoxicosis, antithyroid peroxidase antibodies and antithyroglobulin antibodies were primarily checked and thyroid Doppler ultrasound was performed. Thyroid scintigraphy was requested for patients whose diagnosis could not be made based on examination results. In this study, we could not use thyroid-stimulating immunoglobulin, which can be used in the diagnosis of Graves' disease, as such analysis is not available in our hospital.

Inclusion Criteria

- patients between 18-65 years of age, who were newly diagnosed with Graves' disease as the experimental group;
- euthyroid, healthy individuals between 18-65 years of age as the control group.

Exclusion Criteria

- patients with coronary heart disease, cardiomyopathy, irregular heart rhythm, valvular heart disease;
- patients with bradycardia, tachycardia, bundle branch block, and ST-T wave changes on the ECG;
- patients with a history of pacemaker;
- patients with diabetes mellitus, hypertension, chronic obstructive pulmonary disease, hepatic or renal failure;
- patients with electrolyte abnormalities;
- patients taking any drug affecting the cardiac conduction system;
- patients with tobacco, alcohol, and drug use;
- patients with other causes of thyrotoxicosis.

Laboratory and ECG Analysis

Arterial blood pressure of all participants was measured using a standard manual sphygmomanometer after the 10-minute rest period. Pulse rate was measured on the radial artery and recorded as beats per 1 minute. All participants were normotensive. Venous blood samples were taken in the morning, after 12 hours of fasting. Thyroid-stimulating hormone (TSH) levels were measured by an immunoradiometric assay and free triiodothyronine (fT3) and free thyroxine (fT4) levels were measured by a radioimmunoassay.

The 12-lead ECGs of the individuals under study were evaluated. A resting ECG was recorded at 50 mm/sec paper speed (Nihon Kohden ECG-1250 electrocardiograph). The Tp-e interval was defined by the tangential method. The QT interval was descriptive of the time from the onset of the QRS complex to the point where the T wave reversed from baseline. The QTc interval was computed by the Bazett's formula [13]. Precordial V5 lead was applied to these measurements.

Statistical Analysis

All analyses were performed using R software, version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean $\pm$ standard deviation, median (interquartile range), and categorical variables were represented as number (n) and percentage (%). Comparisons of continuous variables between the groups were made using the Student's t-test or the Mann-Whitney U test according to the conformity of data distribution to normal distribution. The groups were compared with respect to categorical variables using the Chi-square test. The correlation coefficients of numerical variables with a homogenous distribution were calculated using the Pearson test and those with a non-homogenous distribution - the Spearman test. The cut-off values of independent predictors and predictivity were analysed with the receiver operating characteristic (ROC) curve. The ROC curve analysis and the area under the curve (AUC) were evaluated using the Hanley and McNeil method. An AUC of > 0.9 was considered excellent; 0.8-0.9 - very good; 0.7-0.8 - good; 0.6-0.7 - average; < 0.6 - poor. A two-sided $p < 0.05$ was considered statistically significant.

Results

Baseline clinical and laboratory characteristics of patients with Graves' disease and healthy controls are presented in Table 1. The study included 121 patients, 87 (71.9%) females with a mean age of 43.3 $\pm$ 13.2 years and 34 (28.1%) males with a mean age of 45.8 $\pm$ 15.5 years. The control group included 57 patients and the experimental group included 64 patients. There were no differences between the groups in gender, age, systolic and diastolic blood pressure, fasting glucose levels, cholesterol levels, and serum electrolyte concentrations. The experimental group had lower levels of body mass index (BMI) than the control group ($p < 0.05$).

Table 1. Comparison of basic characteristics and laboratory data between groups.

	Total (n= 121)	Control group (n= 57)	Experimental group (n= 64)	p
Sex (female), n (%)	87 (71.9)	40 (70.2)	47 (73.4)	0.422
Age, years	44.0±13.9	42.7±11.8	45.2±15.5	0.327
BMI, kg/m^2	25.3 (22.7-28.0)	26.0 (23.0-29.0)	24.5 (22.0-28.0)	**0.049**
SBP, mmHg	126 (120-135)	125 (118-130)	128 (120-135)	0.264
DBP, mmHg	86 (78-92)	86 (80-92)	85 (78-92)	0.654
Fasting glucose, mg/dL	92 (84-102)	97 (86-103)	90 (80-100)	0.138
LDL cholesterol, mg/Dl	87 (66-109)	88 (66-109)	86 (65-110)	0.969
Triglycerides, mg/dL	100 (78-120)	99 (88-116)	100 (72-123)	0.967
Calcium, mg/dL	9.0±0.4	9.1±0.4	9.0±0.5	0.174
Potassium, mg/dL	3.9 (3.7-4.0)	3.9 (3.8-4.0)	3.8 (3.6-4.0)	0.085
Albumin, g/dL	4.1 (3.9-4.4)	4.1 (3.9-4.5)	4.0 (3.8-4.3)	0.114
Creatinine, mg/dL	0.8 (0.6-0.9)	0.8 (0.6-1.0)	0.75 (0.6-0.9)	0.231
WBC, x10^2/μL	7.1 (6.2-8.2)	7.0 (5.9-8.0)	7.4 (6.3-8.3)	0.130
Hemoglobin, g/dL	12.3 (11.9-13.6)	12.5 (11.9-14.0)	12.0 (11.8-13.0)	0.073

Notes: SBP - systolic blood pressure, DBP - diastolic blood pressure, LDL - low-density lipoprotein, WBC - white blood cell.

Table 2. Comparison of electrocardiographic indices and thyroid hormone levels between groups.

	Control group	Experimental group	p
TSH, mIU/L	2.7 (1.7-3.0)	0.005 (0.005-0.007)	**<0.001**
Free T3, pmol/L	3.0 (2.6-3.5)	6.3 (4.8-7.9)	**<0.001**
Free T4, pmol/L	1.1 (1.0-1.2)	2.7 (2.0-4.6)	**<0.001**
Heart rate, beat/minute	72 (64-81)	78 (70-88)	**0.022**
Tpeak-Tend	77 (71-85)	88 (81-92)	**<0.001**
QTc	415 (409-421)	418 (410-425)	**0.012**
Tpeak-Tend/QTc	0.19 (0.17-0.20)	0.21 (0.19-0.22)	**<0.001**

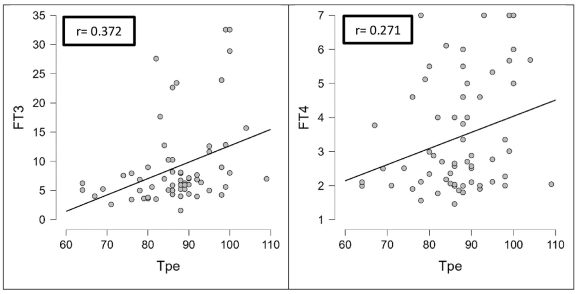

Figure 1. Positive correlation between free triiodothyronine levels (FT3), free thyroxine levels (FT4), and the Tpeak-Tend interval (Tpe).

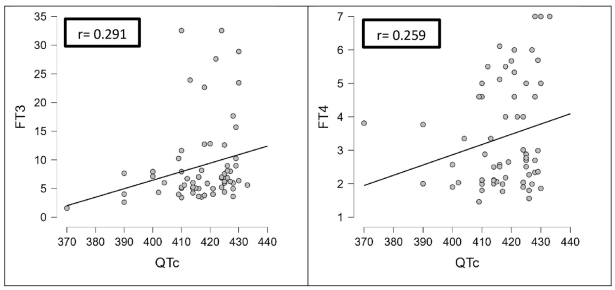

Figure 2. Positive correlation between free triiodothyronine levels (FT3), free thyroxine levels (FT4), and the corrected QT interval (QTc).

The ECG indices and thyroid hormone levels of both groups were compared and displayed in Table 2. Tp-e ($p < 0.001$) and QTc ($p < 0.05$) were significantly prolonged in the experimental group as compared to the control group. Heart rate in patients with Graves' disease was higher as compared to controls ($p < 0.05$). Correlation analysis in patients with hyperthyroidism showed that Tp-e (r=0.372, p=0.002), QTc (r=0.291, p=0.020), and fT3 levels were significantly and positively correlated. Similarly, Tp-e (r=0.271, p=0.030), QTc (r=0.259, p=0.039), and fT4 levels were significantly and positively correlated (Fig. 1, 2). No correlation was found between TSH, Tp-e (r=-0.244, p=0.052), and QTc (r=0.148, p=0.244).

According to Fig. 3, the predictive ability of the ECG parameters was examined by constructing the ROC curves; the sensitivity and specificity of QTc in the prediction of hyperthyroidism were 62.5% and 56.1%, respectively (AUC=0.632 (CI: 0.533-0.731)), the optimal cut-off value=415.5 ms), while the sensitivity and specificity of Tp-e in the prediction of hyperthyroidism were 70.3% and 70.1%, respectively (AUC=0.724 (CI: 0.629-0.818)), the optimal cut-off value=83.5 ms). The Tp-e interval was determined to be superior to QTc in terms of sensitivity, specificity, and predictive value for the diagnosis of hyperthyroidism.

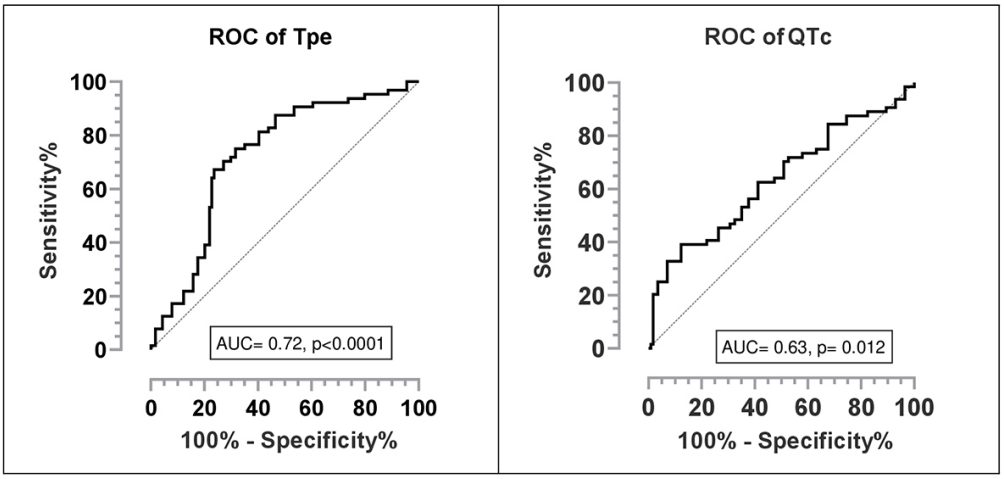

Figure 3. Specificity and sensitivity of the receiver operating characteristic curve for Tpeak-Tend and corrected QT intervals as predictors of hyperthyroid stage.

Discussion

On the ECG, the Tp-e interval is measured from the peak of the T wave to the end of the T wave and forms a subsection of the QT interval. The QT interval demonstrates the whole duration of cardiac ventricular depolarization and repolarization, while the Tp-e interval is thought to demonstrate the distribution of ventricular repolarization [14, 15]. In the last decade, there has been increasing interest in the Tp-e as a risk indicator of arrhythmia and cardiovascular mortality [16]. In individuals with hypertrophic cardiomyopathy, the Tp-e interval was demonstrated to be a better indicator of sudden cardiac death and ventricular fibrillation than QTc [12]. In a Copenhagen study of 138,404 patients, it was shown that a prolongation of the Tp-e interval increased the risk of heart failure, atrial fibrillation, cardiovascular mortality, and all-cause mortality [17]. In our study, we found that both the QTc and Tp-e intervals and the Tp-e/QTc ratio increased in patients with Graves' disease as compared to the control group. Although a positive correlation between these three measurements and fT3 levels was more significant, there was a statistical correlation between both active thyroid hormones. There was no correlation between the indices of arrhythmogenicity evaluated in our study and the level of TSH in patients.

The relationship between Graves' disease and arrhythmia has been investigated in many previous studies. These studies were often performed with QTc. In a Rotterdam study, 939 patients over 55 years of age were evaluated and a significant correlation between hyperthyroidism and QTc prolongation was found [18]. Similar to our study, there was no relationship between TSH levels and QTc duration; however, there was a significant relationship between QTc duration and fT4 levels; fT3 levels of patients were not evaluated. In our study, a more significant relationship was found between arrhythmogenicity indices and fT3 level, rather than fT4 level. Similarly, in another study involving the paediatric age group, hyperthyroidism was shown to be associated with QTc prolongation; however, fT3 levels had no diagnostic value [19]. In fact, fT3 level, which is more active in peripheral tissues [20], can be considered as an expected result in terms of increasing the risk of arrhythmia.

In a study by Akkuş *et al.* on 71 patients, Tp-e values of patients with Graves' disease were evaluated after medical and surgical treatment. The Tp-e/QTc ratio was longer in the group of surgical treatment as compared to the group of medical treatment; however, it was emphasized that the QTc distance was the same in both treatment groups [21]. In our study, both the QTc interval and the Tp-e/QTc ratio increased significantly as compared to the control group. We believe these different results to be due to the different design of the two studies. In a study by Aydin *et al.*, the comparison of the preoperative and postoperative Tp-e levels of hyperthyroid patients revealed an improvement in the Tp-e levels after surgical treatment. It is worth noting that patients in both groups were euthyroid and received medical treatment [22]. Accordingly, Graves' disease may increase susceptibility to arrhythmia independently of thyroid hormone level as well. A study of Aweimer *et al.*, which investigated the relationship between ventricular arrhythmia parameters, including Tp-e and sudden cardiac death, and thyroid hormone levels in both hypothyroid and hyperthyroid patients, supported these findings. A predisposition to arrhythmia was found in both groups. However, sudden cardiac death was associated with prolonged repolarization in the hypothyroid group, whereas this association was not observed in the hyperthyroid group. The authors emphasize that it is necessary to investigate the other mechanisms between hyperthyroidism and arrhythmia [23].

Thyroid hormones affect myocardial contractility, regulation of cardiac output, and heart rate [24]. Today, as with hyperthyroidism, there is a lot of research on arrhythmia in hypothyroidism, with conflicting results of the role of QTc in hypothyroid patients. Some human and animal studies show that hypothyroidism prolongs the QTc period [25, 26], while other studies show that the QTc duration is shorter [27]. In the study of both Tp-e and QTc in hypothyroid patients, there was an increase in both indices;

however, a more significant positive correlation was found between TSH levels and Tp-e interval duration [28]. In our study, in patients with hyperthyroidism, Tp-e demonstrated a more significant correlation than QTc. Hence, we can say that the Tp-e interval is a more significant measurement than QTc in evaluating the risk of arrhythmia in patients with thyroid dysfunction.

Limitations

This research had some limitations. First, the control group was selected from healthy individuals. Instead, selecting a control group from patients with Graves' disease who achieved an euthyroid state would have been more effective for evaluation. Second, a sample size was too small, and therefore, there is a need to conduct this study in a larger population.

Conclusions

In patients with Graves' disease, the Tp-e and QTc intervals are prolonged. These inexpensive and non-invasive methods can be used in the follow-up of patients with Graves' disease to check for arrhythmia. In the literature, it is not yet clear why patients with Graves' disease are at high risk of arrhythmia. More comprehensive electrophysiological studies are needed to elucidate the pathophysiology of the disease.

Ethical Statement

The study was conducted according to the Declaration of Helsinki and approved by the Research Ethics Committee at the Kahramanmaras Sutcu Imam University (dated 01.12.2021, decision No. 03).

Informed Consent

Written informed consent was obtained from all the participants prior to inclusion in the study online.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Financial Disclosure

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