

The relationship between the TSH values and the Tpeak – Tend interval duration in hypothyroid patients receiving Levothyroxine treatment

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Introduction. Changes in thyroid hormone level can affect the cardiovascular system. The aim of this study was to show how the Tpeak -Tend (Tpe) interval, which is a new marker of ventricular arrhythmia, is affected in patients who have become euthyroid following Levothyroxine treatment for hypothyroidism, as this has not been examined previously in literature.

Materials and Methods. This, cross-sectional study included a total of 119 females aged 18-45 years, separated into 3 groups as hypothyroid, euthyroid and control groups. For evaluation of the QTc and Tpe intervals, examination on precordial V5 lead was made of all the ECGs taken routinely on presentation of the patients.

Results. The Tpe and QTc intervals of the hypothyroid group were determined to be significantly prolonged compared to those of the euthyroid and control groups ($p < 0.001$) and the values of the euthyroid and control groups were similar. A positive correlation was determined between TSH levels and Tpe and QTc intervals. Tpe interval AUC = 0.801 (%95 CI: 0.719 – 0.884) was higher than that of QTc AUC = 0.689 (%95 CI: 0.591 – 0.786).

Conclusions. The Tpe duration was evaluated in respect of the risk of arrhythmia in hypothyroid patients. In patients who had become euthyroid, the Tpe interval was found to be similar to that of healthy individuals and was more predictive than QTc. In the light of these findings it can be recommended that measurement of the Tpe interval should be preferred to QTc as a marker of the arrhythmogenic effect in hypothyroid patients.

Key words: ECG, hypothyroidism, Tpeak Tend interval, L-thyroxine.

INTRODUCTION

Thyroid disease is a widely seen endocrine anomaly and it affects 10%-15% of the adult female population. Although thyroid hormone is active in almost all tissues and metabolic processes, the most evident effects are in the cardiovascular system. The majority of effects can be seen as widespread electrocardiographic changes such as sinus bradycardia, prolonged QT interval, prolonged atrium and ventricular interval action potential transfer time, low voltage and heart block at varying degrees. Despite high levels of plasma norepinephrine seen in hypothyroid patients, due to a reduction in the number of adrenergic receptors and desensitisation of catecholamines, the response rate to endogenous catecholamines is reduced. This autonomic function disorder can be partially corrected with levothyroxine (LT-4) treatment [1, 2].

One of the outcomes of arrhythmic activity is sudden cardiac death, which is the cause of approximately 800,000 deaths per year worldwide [3]. In recent years, the Tpeak-Tend (Tpe) interval on electrocardiography (ECG) has started to be used as a new marker to predict arrhythmia risk and

cardiovascular death. Tpe is the interval between the peak and the end of the T-wave, and in previous studies it has been reported that it can show both transmural repolarisation and is independent of the QRS wave, measurement of the Tpe interval is superior to the QTc duration [4, 5].

To the best of our knowledge, all the studies that have investigated the risk of arrhythmogenicity in hypothyroid patients have been related to the QTc interval and there is no study that has examined the predictive value of a higher Tpe interval for arrhythmogenicity [6-9]. Therefore, the aim of this study was to show how the Tpe interval duration was affected in both hypothyroid patients and patients that had become euthyroid following LT-4 treatment and to evaluate if there were any advantages or disadvantages compared to QTc duration.

MATERIAL AND METHODS

Study population

The study included a total of 119 females, aged 18-45 years, comprising 81 patients and 38 control subjects. The patients were divided into

two groups as hypothyroid (HT) and euthyroid. The HT group included 42 female patients and the euthyroid group, 39 female patients who had received LT-4 treatment for a previous hypothyroid period and now had thyroid function test (TFT) results within the normal reference interval. The individuals selected for all the groups had no known or reported chronic disease, had levels of electrolytes (Na, K, Ca), fasting blood glucose, urea and creatinine within the normal reference intervals of the Biochemistry Laboratory of our hospital, had no history of medication within the last month and did not use tobacco, alcohol or drugs. In addition to these criteria, the control group subjects had no history of thyroid disease and had normal TFT results.

Measurements

Blood samples were taken from all the participants in the morning between 0800 and 1030 after an 8-12-hour period of fasting. In the Biochemistry Laboratory, measurements were taken of blood fasting glucose with the Abbott Architect C16000 (Abbott USA) using the photometric method, of ions with the Abbott Architect C16000 (Abbott USA) using the ion selective electrode method, of hemogram with the Cell-Dyne Ruby (Abbott USA) using the impedance and laser screening measurement method and of TSH and sT3-4 levels with the Abbott Architect C16000 (Abbott USA) analyser. Resting ECG was recorded at 50mm/sec paper rate (Nihon Kohden 1250 ECG machine) and was examined manually. The Tpe interval, which is the distance between the peak point and the end of the T-wave, was determined with the tangential method. The QT interval was defined as the time from the start of the QRS to the point at which the base line of the T-wave reversed. The QTc interval was calculated using the Bazett formula [10]. A precordial V5 probe was used for both measurements.

Statistical analysis

Data obtained in the study were analysed statistically using SPSS version 21 software. Conformity of the data to normal distribution was assessed visually (histogram and probability graphs) and with analytical methods (the Kolmogorov-Smirnov test), and variance homogeneity with the Levene test. In descriptive analyses, variables with normal distribution were stated as mean \pm standard deviation (SD), and variables not showing normal

distribution as median, minimum and maximum values. The One-Way ANOVA test was applied to evaluate the differences in parametric data between groups. Parameters not showing normal distribution were compared within the groups using the Kruskal-Wallis test. The statistical significance was calculated with the Spearman test of numerical variables with normal distribution and the correlation coefficients of numerical variables which did not meet at least one of the normal distribution criteria were calculated with the Pearson test. The cutoff 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 with the Hanley and McNeil method. A value approaching 1.0 in the AUC was interpreted as an increase in predictive excellence. In all the statistical evaluations, a total Type-1 error level of 5% was set as significance.

RESULTS

The age, pulse rates, fasting blood sugar electrolytes (Na⁺, K⁺, Ca⁺⁺) and mean Wbc, Hgb and Hct were similar in all the study groups ($p > 0.05$). The baseline characteristics of the study and control groups are presented in Table 1. Differences were determined between the groups in respect of mean durations of Tpe (ms) and QTc (ms) ($p < 0.001$). The Tpe and QTc intervals of the hypothyroid group were determined to be statistically significantly prolonged compared to the other two groups ($p < 0.001$). The Tpe and QTc intervals were similar in the euthyroid and control groups ($p > 0.05$) (Table 2, Figure 3). The TSH levels of the hypothyroid group were determined to be statistically significantly higher than that of the other two groups ($p < 0.001$). The TSH levels were similar in the euthyroid and control groups ($p > 0.05$). The sT4 levels calculated in the euthyroid and control groups were determined to be statistically significantly higher than those of the hypothyroid group ($p < 0.001$). The levels of FT4 measured in the euthyroid and control groups were similar ($p > 0.05$) (Table 2).

In the correlation analysis, there was determined to be a correlation between Tpe ($r = 0.603$, $p < 0.001$), QTc ($r = 0.544$, $p < 0.001$) and TSH value (Figure 2. A-B). When the predictive ability of the ECG parameters was examined by drawing the ROC curves, the sensitivity and specificity of QTc

in the prediction of hypothyroidism were 71% and 63% respectively (AUC = 0.689, optimal cutoff value = 420.5 ms), and the sensitivity and specificity of Tp-Te in the prediction of hypothyroidism were 77% and 66% respectively (AUC =

0.801, optimal cutoff value = 77.5 ms) (Figure 1, Table 3). The Tpe interval was determined to be superior to QTc in respect of sensitivity, specificity and predictive value for the ECG markers in hypothyroidism.

Table 1
Demographic and biochemical characteristics of the controls and the patients groups

Variables Total	Control (n = 38)	Euthyroid (n = 42)	Hypothyroid (n = 39)	P
Age(years)	32.92 ± 3.38	33.71 ± 5.64	34.79 ± 4.10	0.193
Pulce (bpm)	73.39 ± 10.21	72.52 ± 8.41	70.77 ± 5.39	0.598
Glucose (mg/dL)	86.58 ± 7.36	88.88 ± 9.67	90.08 ± 6.29	0.151
Wbc (10 ³ /μL)	8.81 (5.4-10.2)	8.83 (5.1-9.9)	8.81 (5-10.1)	0.590
Hgb (g/dL)	13.29 ± 0.69	13.33 ± 0.65	13.09 ± 0.58	0.223
Na (mmol/L)	138.16 ± 2.02	138.81 ± 2.06	138.72 ± 2.37	0.355
K (mmol/L)	4.05 ± 0.27	4.06 ± 0.20	3.99 ± 0.25	0.357

Values are presented as mean ± standard deviation or median (maximum-minimum), WBC: White Blood Cell, Hgb: Hemoglobin, Na : Sodium, K: Potassium

Table 2
Thyroid function tests and echocardiographic characteristics of the controls and the patients groups

Variables total	Control (n = 38)	Euthyroid (n = 42)	Hypothyroid (n = 39)	P
TSH (uIU/mL)	1.95 ± 0.99	2.24 ± 1.11	7.43 ± 1.16	0.000
fT4 (ng/dL)	0.89 ± 0.18	0.92 ± 0.21	0.5 ± 0.05	0.000
QTc (ms)	415.45 ± 10.47	417.05 ± 10.2	423.03 ± 7.92	0.000
Tpe (ms)	72.42 ± 9.30	75.64 ± 7.36	84.05 ± 8.10	0.000

TSH (0.27–4.2 μIU/mL): Thyroid Stimulating Hormone; FT4 (0.8–1.67 ng/dL): free Thyroxine, Tpe: Tpeak-Tend; QTc: corrected QT

Table 3
Performance of variables in predicting hypothyroid stage

	Tpe (ms.)	QTc (ms.)
P value	p < 0.001	p < 0.01
AUC (%95 CI)	0.801 (0.719 – 0.884)	0.689 (0.591 – 0.786)
Cut off value (ms.)	77.5	420.5
Sensitivity	77	71
Specificity	66	63

AUC: Area under the ROC curve, Tpe: Tpeak-Tend, QTc: corrected QT

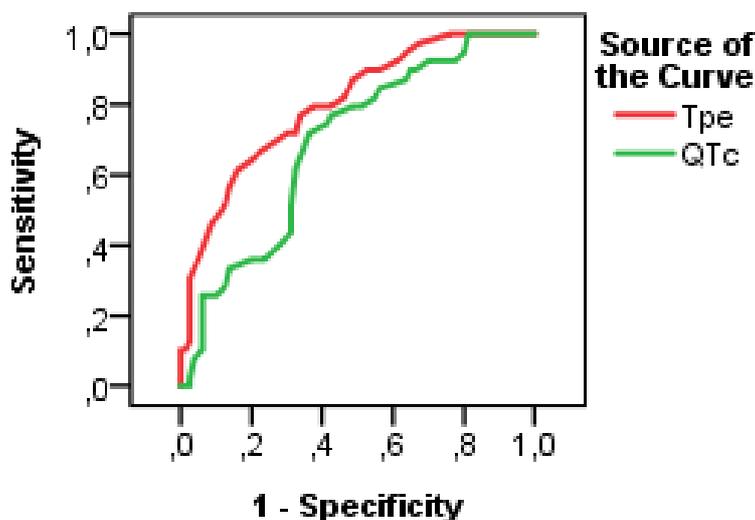


Figure 1. Performance of variables in predicting hypothyroid stage.

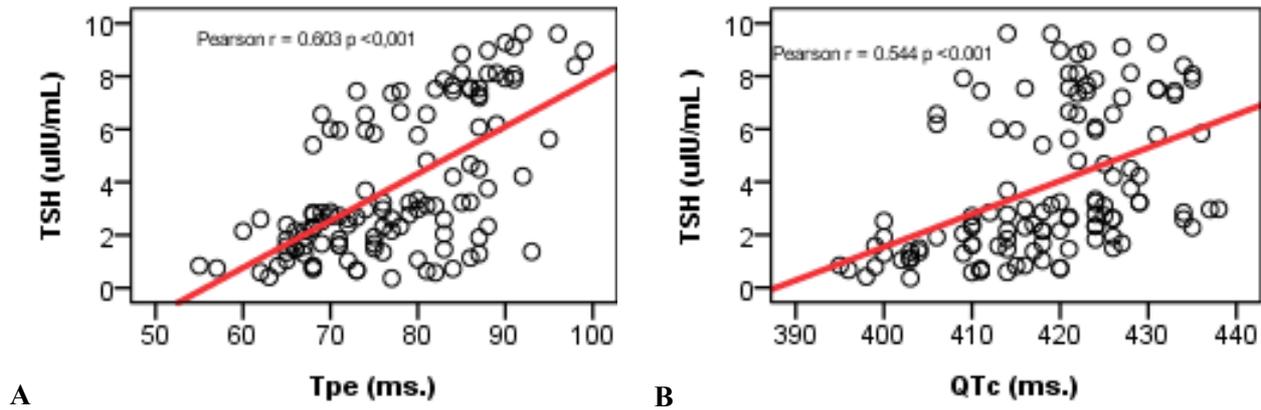


Figure 2. Correlation between Tpe (Tpeak-Tend) and TSH (Thyroid Stimulating Hormone) (A). Correlation between QTc (corrected QT) and TSH (B).

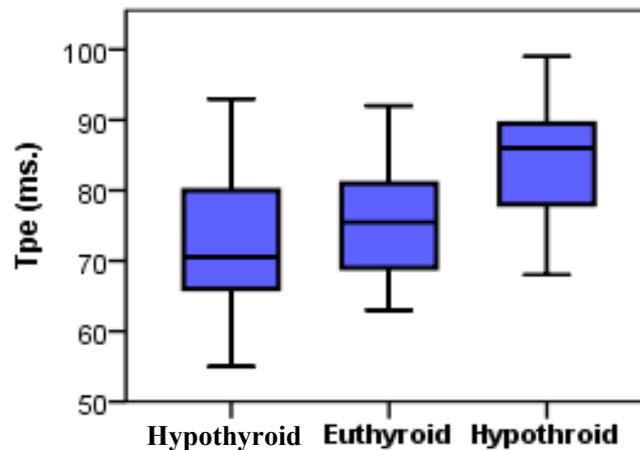


Figure 3. Comparison of Tpe (Tpeak-Tend) interval between the study groups.

DISCUSSION

To the best of our knowledge, this is the first study in literature to have investigated how the Tpe interval duration which is a new and highly predictive arrhythmogenicity index, is affected in patients with primary hypothyroidism and in patients treated with LT-4 who have become euthyroid. The results of the study demonstrated that the Tpe and QTc interval durations measured in the hypothyroid patient group were statistically significantly prolonged compared to the euthyroid and control groups, which had similar values. The Tpe interval duration was more associated with hypothyroidism than QTc and had a high correlation with TSH. The Tpe and QTc values of the euthyroid group were similar to those of the control group.

In a study of subclinical hypothyroid patients, Gurdal *et al.* calculated the Tpe interval duration to be prolonged in the patient group compared to the control group. The significant difference in Tpe between the groups was interpreted as an increase

in the risk of ventricular arrhythmia [11]. In the current study, the Tpe interval was found to be significantly prolonged in the subclinical hypothyroid group compared to the euthyroid and control groups, which was consistent with the findings of Gurdal *et al.* The significant difference determined in the hypothyroid patients of the current study may show cardiac involvement for hypothyroid patients.

There are few case reports and studies in literature related to the change in QTc following LT-4 replacement in patients with primary hypothyroidism. The common evidence in these studies is that the prolonged ventricular repolarisation duration seen in hypothyroidism, and the QTc interval which is the conventional measurement of this, can be corrected with LT-4 treatment alone [6, 7, 12]. As in similar studies, the QTc duration in the current study patients who had become euthyroid with sufficient dosage of LT-4 treatment was seen to be similar to that of the control group, and for the first time in literature, so was the Tpe duration. Therefore, using the Tpe interval duration, it may

show that the electrical functionality of myocytes can be corrected in patients who had reached an euthyroid level following treatment.

In other studies of hypothyroid patient groups, only QTc was correlated with TSH [6-9]. In a population-based study in Pomerania of a sample of 4310 subjects aged 20-79 years, it was emphasized that there was a positive relationship between TSH level and QTc interval duration [9]. Therefore, in the light of the above-mentioned literature and based on the findings of the current study, there can be considered to be a relationship between prolonged QTc and Tpe interval durations and the TSH level and, thereby, the severity of hypothyroidism.

As a parameter of arrhythmogenicity, measurement of the Tpe interval has been determined to be more predictive than QTc in studies of diseases other than hypothyroidism [13, 14]. For the first time in literature, this study has demonstrated that Tpe may be more predictive than QTc for hypothyroid patients. From these findings, it can be recommended that measurement of the Tpe interval rather than QTc should be preferred as a marker of the arrhythmogenic effect in hypothyroid patients. However, there is a need for further studies on this subject to confirm these findings.

The most important limitation of this study was that in respect of more homogenisation of the Tpe and QTc interval durations, which have the potential to respond to an anthropometric and metabolic, multifactorial negative interaction, the ECGs of the same patients could not be compared in hypothyroid and euthyroid periods (eg, before and after treatment). Other limitations were that it was a single-centre study, the number of patients was low, and the study was cross-sectional in design. Nevertheless, the inclusion of female patients only provided a homogeneous group and it can be considered a strong aspect of the study.

CONCLUSION

The results of this study demonstrated that Tpe interval duration is more predictive than QTc for hypothyroid patients, and the Tpe and QTc intervals were found to be normal in patients who had received LT-4 replacement therapy at a sufficient dose. In the light of these findings, it can be suggested that the measurement of Tpe interval should be preferred to QTc as a marker of the arrhythmogenic effect in hypothyroid patients.

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Declaration of intrrest: The authors declare that there are not conflicts of interest.

Introducere. *Modificările hormonilor tiroidieni pot afecta sistemul cardiovascular. Scopul studiului a fost de a evalua cum intervalul Tpeak-Tend (Tpe) pe EKG (un nou marker privind aritmia ventriculară) este afectat la pacienții care au devenit eutiroidieni după tratamentul cu Levotiroxină fiind hipotiroidieni.*

Materiale și metode. *A fost realizat un studiu transversal ce a inclus 119 femei cu vârste între 18 și 45 ani împărțiți în 3 grupe: hipotiroidieni, eutiroidieni și martori. Au fost analizate intervalul QT și Tpe din derivația precordială V5 din EKG-ul realizat de rutină.*

Rezultate. *Intervalul Tpe și cel QTc la pacienții hipotiroidieni au fost semnificativ statistic prelungite față de pacienții eutiroidieni și martorii sănătoși. S-a observat o corelație pozitivă între nivelurile TSH-ului și intervalul Tpe și QTc. AUC a intervalului Tpe a fost de 0,801, (%95 CI: 0,719 - 0,884) mai mare decât a intervalului QTc, AUC = 0,689, (%95 CI: 0,591 - 0,786)*

Concluzii. *Durata Tpe a fost evaluată cu privire la riscul aritmic la pacienții hipotiroidieni. La pacienții eutiroidieni post terapie durata intervalului Tpe a fost similară cu cea a martorilor sănătoși și cu o valoare predictivă mai bună decât intervalul QT. Se poate recomanda măsurarea intervalului Tpe în locul celui QT pentru evaluarea riscului aritmic la pacienții hipotiroidieni.*

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