Evaluation of Cardiac Electrophysiological Balance in Patients with Subclinical Hypothyroidism

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ABSTRACT

Introduction: Subclinical hypothyroidism (SH) is defined by slightly elevated thyroid-stimulating hormone (TSH) levels with normal free triiodothyronine (fT3) and thyroxine (fT4) levels. SH is related to cardiovascular events, including malignant arrhythmias. Cardiac electrophysiological balance (iCEB) and its corrected form with heart rate (iCEBc) are useful electrocardiographic (ECG) parameters for the prediction of malign arrhythmias. In this study, we aimed to evaluate iCEB and iCEBc in SH patients.

Patients and Methods: A total of 164 patients (n= 82 patients with SH and n= 82 controls) were enrolled in this study. iCEB was calculated by dividing QT by QRS, and iCEBc was calculated by dividing corrected QT (QTc) by QRS. The groups were compared based on ECG parameters. Correlation and multiple linear regression analyses were used to assess the association of ECG parameters with TSH levels.

Results: There were no differences between the groups regarding clinical and laboratory findings. Tp-e, QT, QTc, Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc were significantly prolonged in SH patients compared to controls. In correlation analyses, all of the abovementioned ECG parameters were significantly correlated with serum TSH levels. Multiple linear regression analysis indicated that Tp-e, iCEB, and iCEBc were independently associated with serum TSH levels in SH patients.

Conclusion: To our knowledge, this was the first study to demonstrate that iCEB and iCEBc were both prolonged in SH patients compared to controls, and both of them were independently correlated with TSH levels in such patients.

Key Words: Hypothyroidism; cardiac electrophysiology; cardiac arrhythmia

Subklinik Hipotiroidi Hastalarında Kardiak Elektrofizyolojik Dengenin Değerlendirilmesi

ÖZET

Giriş: Subklinik hipotiroidi (SH) hafifçe yükselen tiroid uyarıcı hormon (TSH) seviyeleri ile birlikte serbest triiyodotironin (sT3) ve serbest tiroksin (sT4) düzeylerinin normal olması olarak tanımlanmaktadır. SH malign aritmileri de içeren kardiyovasküler olaylar ile ilişkilidir. Kardiak elektrofizyolojik denge (KED) ve düzeltilmiş formu düzeltilmiş KED (dKED) malign aritmileri saptayabilen kullanışlı parametrelerdir. Biz bu çalışmada subklinik hipotiroidi hastalarında KED ve dKED düzeylerini araştırmayı hedefledik.

Hastalar ve Yöntem: Bu çalışmaya toplan 164 hasta (82 SH hastası ve 82 kontrol grubu) dahil edilmiştir. KED, QT'nin QRS'e bölünmesi ile, dKED ise düzeltilmiş QT (dQT)'nin QRS'e bölünmesi ile hesaplanmıştır. Gruplar EKG parametreleri açısından karşılaştırılmıştır. Korelasyon ve multiple lineer regresyon analizi EKG parametreleri ile TSH seviyelerinin karşılaştırılması amacıyla kullanılmıştır.

Bulgular: Gruplar arasında laboratuvar ve klinik bulgular açısından fark yoktu. Tp-e, QT, dQT, Tp-e/QT, Tp-e/dQT, KED ve dKED düzeyleri SH hastalarında kontrol grubuna göre belirgin düzeyde uzamıştı. Korelasyon analizinde yukarıda belirtilen tüm ekg parametreleri TSH seviyesi ile önemli oranda ilişkili olarak saptandı. SH hastalarında, multiple lineer regresyon analizinde, Tp-e, KED ve dKED TSH seviyesi ile bağımsız olarak ilişkili olarak saptandı.

Sonuç: Bildiğimiz kadarıyla bu çalışma SH hastalarında KED ve dKED'nin kontrol grubuna göre anlamlı düzeyde uzamış olduğunu ve SH hastalarında her iki parametrenin de TSH seviyesi ile korele olduğunu gösteren ilk çalışmadır.

Anahtar Kelimeler: Hipotiroidizm; kalp elektrofizyolojisi; kardiak aritmi

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INTRODUCTION

Subclinical hypothyroidism (SH) is described as having no overt hypothyroidism symptoms with normal free triiodothyronine (fT3) and thyroxine (fT4) levels in the setting of slightly elevated thyroid-stimulating hormone (TSH). Its prevalence is reported to be approximately 10% in the general population, with more frequently observed in women than in men[1]. SH is a well-known medical condition that is associated with several cardiovascular diseases, including heart failure[2], coronary artery disease[3], hypertension[4], and dyslipidemia[5], which are potential risk factors for malignant cardiac arrhythmias[6-9]. It has been reported that the risk of all-cause mortality, including cardiovascular mortality, is greater in SH patients during the six-years follow-up period[10]. Nevertheless, there are conflicting results on the relationship between SH and arrhythmic events in the literature[11,12].

The electrocardiographic parameters of the spatial dispersion of ventricular repolarization, such as QT, Tp-e, Tp-e/QT, and Tp-e/QTc, all of which can be used to predict the risk of ventricular arrhythmia, have been investigated in SH patients previously[13,14]. It was found that the QT interval was prolonged in SH patients[15], and it was significantly correlated with TSH values[16]. On the other hand, a prior study revealed no statistically significant difference in terms of QRS duration in SH patients compared to controls[17]. The cardiac-electrophysiological balance (iCEB), calculated by dividing QT to QRS on surface electrocardiography (ECG), is a non-invasive index that can be utilized to predict malignant ventricular arrhythmias. Because iCEB is accepted as the equivalent of the cardiac wavelength (λ), which is the multiplication of the effective refractory period (ERP) with conduction velocity (CV), both high and low values of iCEB have been related to ventricular arrhythmic risk[18]. In the current medical database, there is no information about the values of iCEB in SH patients. Therefore, we aimed to investigate whether there were differences between SH patients and controls with respect to iCEB and the corrected iCEB (iCEBc) values.

PATIENTS AND METHODS

Study Population

164 patients were included in the study (n= 82 patients with SH and n= 82 controls). All patients in the SH group were not on thyroid hormone therapy. The exclusion criteria were: history of arrhythmia, hypertension, diabetes mellitus, chronic liver or kidney disease, chronic lung disease, coronary artery disease, severe valvular heart disease, cardiomyopathy, connective tissue diseases, electrolyte imbalance, including hypo- or hypercalcemia, hypo- or hyperpotassemia, hypo- or hypomagnesemia, a history of a pacemaker or implantable cardioverter-defibrillator implantation, and those with heart rate below 60 beats/minute or above 100 beats/minute, bundle branch block, or using drugs which affect the cardiac conduction system. Venous blood samples were obtained in the morning following 12-hour fasting in all patients. TSH, fT3, and fT4 levels were determined using Abbott-Architect analyzer (Abbott Laboratories, Abbott Park, III. USA) via chemiluminescent microparticle immunoassay method. The study was approved by our local ethics committee, and it was conducted in accordance with the Helsinki Declaration as revised in 2013.

Electrocardiographic Measurements

All ECG recordings were obtained at 25 mm per second paper speed, 10 seconds segment length, and 512 Hz frequency in the resting state using an ECG machine (Nihon Kohden 1250). All measurements were done manually and were gained as the average of the three consecutive complexes of leads V2 and V5. QT interval was described as the time between the onset of the QRS and the end of the T wave, at which the tangent to the T wave's downslope intersects the isoelectric line. QTpeak was described as the time between the beginning of the Q wave and the peak of the T wave. Bazett's formula was used to calculate the QTc interval. Tp-e interval was accepted as the time from the peak of the T wave to the end of the T wave[19]. Tp-e interval was calculated by the difference between QT and QTpeak. Tp-e intervals were measured from leads V2 and V5 by two cardiologists, and a maximum value of Tp-e was accepted by agreement. In the presence of negative or biphasic T waves, QTpeak was calculated to the nadir of the T wave. T waves with amplitudes less than 0.1 mV or not visible were not measured. The Tp-e/QT and Tp-e/QTc ratios were computed from the values derived. iCEB was calculated by dividing the QT to QRS, and iCEBc was calculated by dividing the QTc to the QRS.

Echocardiography

Echocardiographic examinations were performed with the Philips Epiq 7 device (EPIQ 7 Ultrasound Device®, Philips, USA) unit with a 2.5 MHz FPA probe in lateral decubitis position. According to the American Society of Echocardiography guidelines, standard techniques were used for two-dimensional, color, pulsed, and continuous-wave Doppler examinations[20]. Left ventricular (LV) mass was gained from the Devereux formula: LV mass= 1.04 × [(LV interventricular septal thickness + LV posterior wall thickness + LV diastolic diameter)3 – (LV diastolic diameter)3] – 13.6. and the LV mass index was obtained by dividing the LV mass by body surface area. The mitral inflow conventional Doppler examination was used to calculate early (E) and late (A) diastolic wave velocities. Pulsed wave tissue-Doppler imaging velocities were calculated by placing sample volume at the junction of the mitral annular level. Isovolumetric relaxation time (IVRT) and isovolumetric contrac-

tion time (IVCT) were obtained from the mitral inflow profile by placing the sample volume at the LV outflow tract. IVRT reflects the time between the closing of the aortic valve and the opening of the mitral valve, and IVCT reflects the time between the closing of the mitral valve and the opening of the aortic valve. The myocardial performance index (MPI) was established using the formula MPI= (IVCT+IVRT)/ET as described by Tei et al.[21]. All measurements were calculated on frozen images gained from three to five cardiac cycles.

Statistical Analysis

All calculations were performed using R-Studio Version 4.0.3 (RStudio, Boston, MA, USA).

The Kolmogorov-Smirnov test was used to assess the normality. Quantitative variables were reported as mean ± standard deviation with a normal distribution and median (25-75th interquartile range) without normal distribution. Categorical variables were reported as numbers and percentages. The independent student's t-test or Mann-Whitney U test was used to calculate the statistical differences of continuous variables between the groups. The Chi-square test or Fisher's exact test was performed to compare categorical variables, as appropriate. Spearman correlation analyses were performed to determine the associations between TSH values and the ECG markers, including QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc. Multiple linear regression analysis was used to determine the association of ECG parameters and covariates with TSH levels. Because multicollinearity was detected for QTc, Tp-e/QT, and Tp-e/QTc (variance inflation factor> 3, tolerance< 0.1), we did not include those parameters in the multiple linear regression model. Similarly, because of multicollinearity and interaction, we used two different models with the same covariates to evaluate the relationship of iCEB and iCEBc with TSH levels in multiple regression analyses. The inter-and intra-observer variability for iCEB was calculated as 2.6% and 2.3%, respectively. A 2-sided p< 0.05 was considered statistically significant.

RESULTS

Baseline clinical and laboratory characteristics of SH patients and the control group were presented in Table 1. There

Table 1. Comparison of basaline characteristics and laboratory data between the groups

	Subclinical hypothyroidism (n= 82)	Control group (n= 82)	p
Age, years	54.1 (10.6)	51.9 (11.4)	0.212
Gender, male, n (%)	28 (34.1)	27 (32.9)	1.000
BMI, kg/m^2	24.1 (1.2)	23.8 (1.1)	0.139
Smoking, n (%)	15 (18.2)	20 (24.4)	0.446
SBP, mmHg	126.7 (9.7)	124.6 (9.1)	0.164
DBP, mmHg	76.2 (4.7)	75.4 (3.6)	0.186
Fasting glucose, mg/dL	91.9 (5.9)	90.8 (4.8)	0.199
Total cholesterol, mg/dL	194.6 (17.7)	191.1 (14.3)	0.181
LDL cholesterol, mg/dL	114.4 (16.8)	112.5 (12.6)	0.404
HDL cholesterol, mg/dL	52.3 (13.5)	54.1 (10.5)	0.351
Triglycerides, mg/dL	120.6 (14.8)	116.3 (18.2)	0.103
eGFR, mL/min/1.73m^2	131 (19)	132 (18)	0.626
Calcium, mg/dL	9.4 (0.5)	9.3 (0.3)	0.145
Magnesium, mg/dL	1.95 (0.12)	1.94 (0.12)	0.451
Potassium, mg/dL	4.1 (0.18)	4.1 (0.18)	0.132
Albumin, g/dL	4.3 (0.3)	4.2 (0.3)	0.265
TSH, mIU/L	9.7 (1.7)	2.6 (0.9)	<0.001
Free T3, pmol/L	5.4 (1.0)	5.6 (1.1)	0.178
Free T4, pmol/L	10.9 (1.5)	11.2 (1.2)	0.109

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL: Low-density cholesterol, HDL: High-density cholesterol, eGFR: Estimated glomerular filtration rate, TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine.

Table 2. Comparison of electrocardiographic indices between the groups

	Subclinical hypothyroidism (n= 82)	Control group (n= 82)	p
Heart rate, beat/minute	70.3 (6.9)	72.3 (6.7)	0.063
PR duration, ms	124.5 (27.8)	120.5 (24.1)	0.322
QRS duration, ms	84 (7.7)	83.9 (6.5)	0.892
Tp-e, ms	88 (7.3)	71 (4.8)	**<0.001**
QT, ms	382 (31)	367 (22)	**<0.001**
QTc, ms	418 (39)	402 (33)	**0.02**
Tp-e/QT	0.23 (0.03)	0.19 (0.02)	**<0.001**
Tp-e/QTc	0.22 (0.03)	0.18 (0.02)	**<0.001**
iCEB	4.6 (0.6)	4.4 (0.5)	**0.014**
iCEBc	5.02 (0.6)	4.83 (0.6)	**0.039**

iCEB: Cardiac electrophysiological balance, iCEBc: Corrected cardiac electrophysiological balance.

were no differences between the groups regarding age, gender, smoking status, blood pressure, cholesterol levels, and serum electrolyte concentrations. The SH group had higher TSH levels than the control group (p< 0.001).

ECG features of both groups were compared and were displayed in Table 2. The Tp-e, QT, QTc, Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc were significantly prolonged in the SH group compared to the control group.

Spearman correlation analysis showed that iCEB (r= 0.36), iCEBc (r= 0.33), Tp-e (r= 0.76), QT (r= 0.36), QTc (r= 0.29), TP-e/QT (r= 0.52), and Tp-e/QTc (r= 0.51) were significantly correlated (all p values< 0.001) with TSH levels (Figure 1-2). Multiple linear regression analysis revealed that iCEB, iCEBc, and Tp-e were independently associated with serum TSH levels, whereas QT was not in both models (Table 3).

DISCUSSION

This study showed that the ECG parameters, including QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc, were prolonged in patients with SH, and all of them were significantly correlated with serum TSH values. Furthermore, Tp-e, iCEB, and iCEBc were independently associated with serum TSH levels.

Several studies have demonstrated that increased dispersion of ventricular repolarization might lead to ventricular arrhythmias[22-24]. Tp-e and QT intervals are considered the indexes of transmural dispersion of ventricular repolarization[25]. Thus, Tp-e, Tp-e/QT, Tp-e/QTc were widely investigated in the literature and also in SH patients [13,26,27]. Hypothyroidism can cause the action potential and the QT interval to be longer[15]. Also, SH patients had altered ECG changes as reported in the literature. Jadhav et al. showed that SH patients had longer QTc intervals than control subjects[17]. Similar results were reported by Galetta et al., in which QT and QTc were significantly prolonged in SH patients[14]. Gurdal et al. investigated ventricular repolarization parameters, except iCEB, in SH patients. They reported that Tp-e, Tp-e/QT, and Tp-e/QTc were prolonged, which was in concordance with our results[13]. However, they failed to demonstrate significant differences in QT and QTc between the groups. We thought that the relatively small sample size might have contributed to these results.

The correlations of TSH levels with ECG parameters in SH patients have been evaluated in previous studies. For example, Bakiner et al. showed that QT and QTc were correlated with serum TSH levels of SH patients[16]. Moreover, Gurdal et al. demonstrated that Tp-e, Tp-e/QT, and TP-e/QTc were found to be associated with serum TSH levels in SH patients[13]. Remarkably, in this investigation, we also showed similar ECG findings to the abovementioned studies.

Cardiac wavelength (λ) is the combination of ERP, and CV[28]. Cardiac wavelength can accurately predict arrhythmic tendency in patients with or without anti-arrhythmic medication[29]. Also, the relationship between cellular depolarization and repolarization is represented by the cardiac wavelength[30]. Unfortunately, cardiac wavelength could only be measured invasively. At this point, iCEB can be used to approximately determine cardiac wavelength by calculating the ratio of repolarization to depolarization times. QRS duration is inversely related to CV, whereas QT is accepted to be correlated with ERP. Therefore, iCEB is considered the derivative of cardiac wavelength (λ= ERP x CV, iCEB= QT/QRS). The prolongation of cardiac wavelength can enhance the risk of torsade de

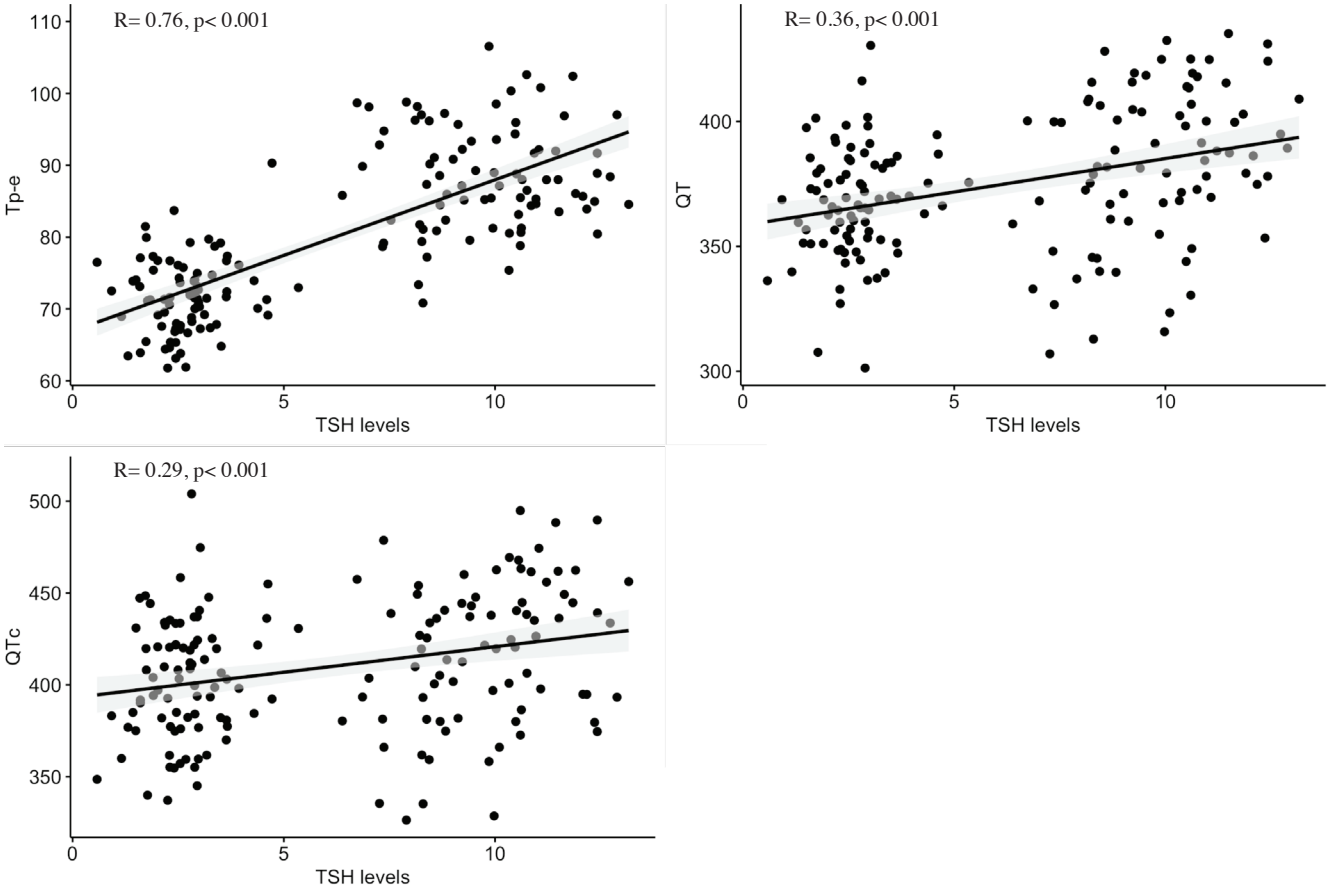

Figure 1. Correlation graphs of Tp-e, QT, and QTc with TSH levels in SH patients.
TSH: Thyroid-stimulating hormone, SH: Subclinical hypothyroidism.

Pointes (TdP). By contrast, a decrease in the duration of cardiac wavelength can also lead to TdP, ventricular tachycardia, or ventricular fibrillation[31]. The balance between cardiac depolarization and repolarization is reflected by iCEB. Therefore, an imbalance in cardiac electrophysiology could be detected by the iCEB, and it might be used to predict the risk of malignant arrhythmias[31]. iCEB was investigated in some previous studies. For example, Askin et al. reported that iCEB levels were higher in patients with slow coronary phenomena[32]. Moreover, Alsancak et al. showed no significant difference in iCEB levels between coronary artery ectasia patients and the control group[33]. Sivri et al. reported that iCEB levels were elevated after hemodialysis in chronic kidney disease patients indicating enhanced arrhythmic risk[34]. Lastly, Ozdemir et al. showed that iCEB levels were significantly higher in healthy smokers than non-smokers[35]. However, to our knowledge, no prior study investigated the iCEB and iCEBc values in SH patients compared to control subjects. For the first time in the current literature, we reported significant correlations of serum TSH values with iCEB and iCEBc in the current study. Additionally, both iCEB and iCEBc were independently associated with serum TSH levels.

Although our findings should be considered only hypothesis-generating, we consider that this study may have significant clinical implications as it may provide useful information for the potential arrhythmia risk in SH patients, which can shed light to physicians on the treatment and follow-up strategy.

Limitations

In this study, our major limitation was its retrospective nature, and the fact that it was conducted in a single center. Because of the lack of data for TSH levels over time, we could not have shown the effect of the changes in TSH levels on iCEB and iCEBc. SH patients were not on anti-thyroid medication, so there was no information about the treatment effect on iCEB and iCEBc in SH patients. In this study, the patients were not followed in terms of arrhythmias. It could be useful to perform a 24-h Holter for evaluating subclinical arrhythmias. Future prospective research with longitudinal study designs and large

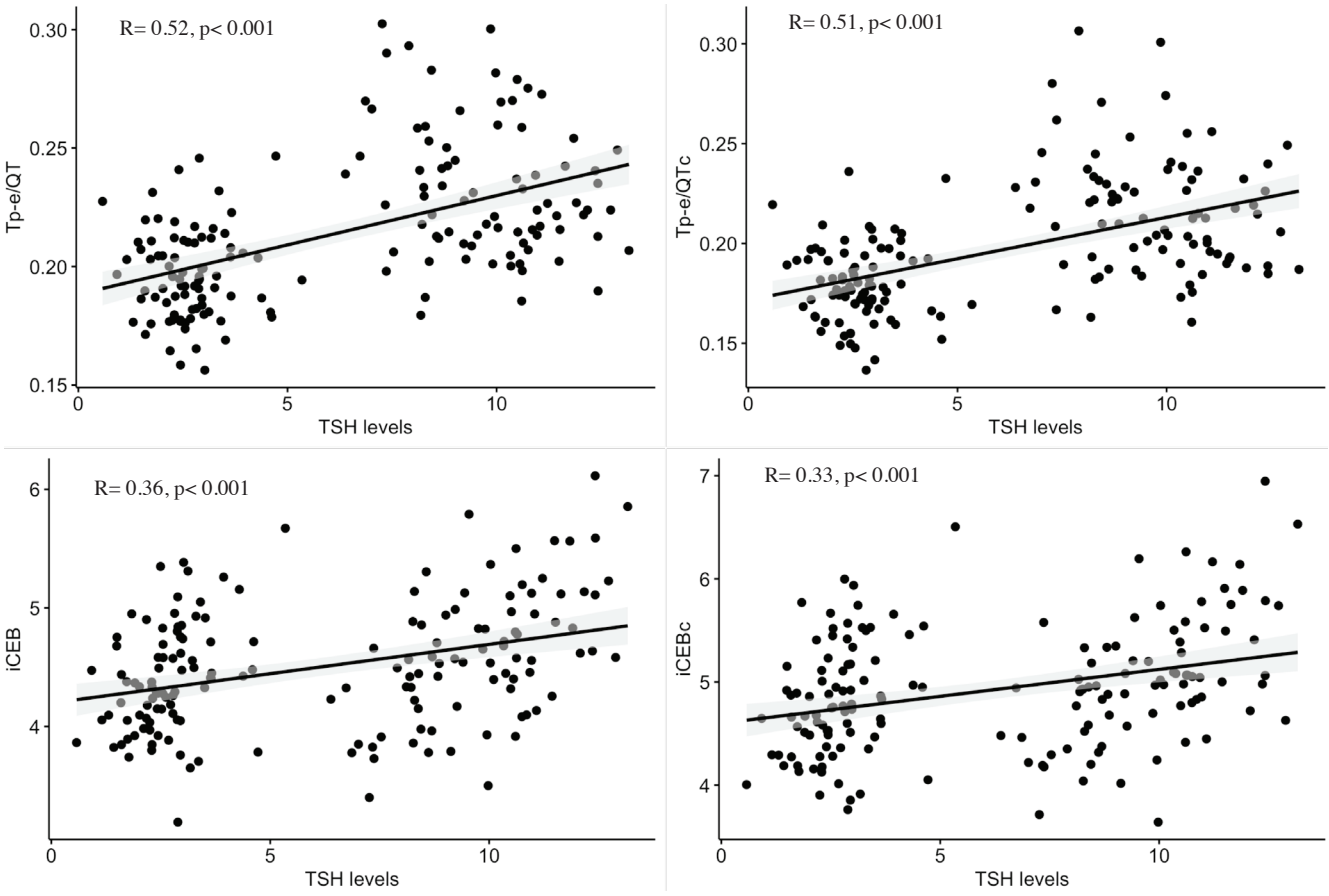

Figure 2. Correlation graphs of Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc with TSH levels in SH patients.
TSH: Thyroid-stimulating hormone, SH: Subclinical hypothyroidism.

Table 3. Multiple linear regression analysis between the variables and TSH levels

	Model 1			Model 2		
	Estimate (95% CI)	**SE**	**p***	**Estimate (95% CI)**	**SE**	**p***
iCEB	1.518 (0.728-2.308)	0.477	**0.02**	-	-	-
iCEBc	-	-	-	1.156 (0.492-1.821)	0.401	**0.004**
QT	0.009 (-0.006-0.023)	0.009	0.332	0.011(-0.003-0.026)	0.008	0.194
Tp-e	0.257 (0.227-0.287)	0.018	**<0.001**	0.259 (0.229-0.290)	0.018	**<0.001**

* Bold values indicate statistically significant difference (p< 0.05).
CI: Confidence interval, SE: Standard error, iCEB: Cardiac electrophysiological balance, iCEBc: Corrected cardiac electrophysiological balance.

sample sizes might give more information about the adverse arrhythmic events in SH patients with higher iCEB and iCEBc levels. Studies that investigate the following of these patients with respect to arrhythmias will be more powerful.

CONCLUSION

This study revealed that iCEB and iCEBc were prolonged in SH patients, and all of them were independently associated with TSH levels.

Ethics Committee Approval: The approval for this study obtained from Van Training and Research Hospital, Clinical Research Ethics Committee (Decision No: 2021/18, Date: 06.10.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - All of authors; Analysis/Interpretation - FŞ; Data Collection - TA, MS; Writing - FŞ; Critical Revision - FŞ, TÇ; Final Approval - TÇ, MS, TA; Statistical Analysis - FŞ.

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