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Evaluation of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio in primary hyperparathyroidism before and after parathyroidectomy

Zeki Çetinkaya[1], Şaban Keleşoğlu[2], Ferhat Gökay[3], Yücel Yılmaz[4]

[1]Department of Cardiology, Elazığ Fethi Sekin City Hospital, Elazığ, Turkiye
[2]Department of Cardiology, Faculty of Medicine, Erciyes University, Kayseri, Turkiye
[3]Department of Endocrinology and Metabolism, Kayseri City Hospital, University of Health Sciences, Kayseri, Turkiye
[4]Department of Cardiology, Kayseri City Hospital, University of Health Sciences, Kayseri, Turkiye

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ABSTACT

Aims: This study aimed to evaluate Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios, which are new ventricular repolarization (VR) parameters in primary hyperparathyroidism (PHPT) patients, and also investigate the potential effect of parathyroidectomy (PTx) on these parameters.

Methods: In total, 27 patients with PHPT who underwent PTx and 25 control subjects were selected for our study. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios of patients planned for PTx were compared to healthy matched controls. Electrocardiographic parameters measured 6 months after the surgery were also compared with preoperative values for each patient.

Results: Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in PHPT patients compared to the control group ($p<0.001$, for all).It was observed that the parameters mentioned after surgery decreased significantly, and there was no statistical difference when compared to the control group.The correlation analysis revealed a significant and positive correlation between corrected calcium (CCa) and PTH levels with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio (for Ca; $r=0.515$, $p=0.006$; $r=0.398$, $p=0.040$; $r=0.797$, $p<0.001$ respectively vs. for PTH; $r=538$, $p=0.04$; $r=0.422$, $p=0.028$; $r=0.812$, $p<0.001$ respectively).

Conclusions: This study showed that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were prolonged in PHPT.These values, which are accepted as an indicator of sudden cardiac death after PTx, decreased significantly. In addition, both high PTH and high calcium(Ca) levels appear to have the potential to cause arrhythmogenic effects separately.

Keywords: Primary hyperparathyroidism, ventricular repolarization, parathyroidectomy, ventricular arrhythmia

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disease characterised by excessive release of parathyroid hormone (PTH), resulting in dysregulation of calcium (Ca) metabolism.[1] Although clinical practice focuses more on adverse effects such as renal complications and osteoporosis in PHPT, PHPT has been shown to be associated with increased cardiovascular morbidity and mortality.[2] Accordingly, there has recently been increased interest in cardiac evaluation in patients with PHPT.Parathyroidectomy (PTX) surgery is the first choice and most effective treatment method in symptomatic patients with PHPT and asymptomatic patients with significant hypercalcemia (>1.0 mg/dL/0.25 mmol/L).[3]

Electrocardiographic data has shown that shortening the QT interval, a well-known risk factor for arrhythmias, is common in PHPT patients; however, the exact prevalence of short QT interval, and more importantly, arrhythmias in PHPT patients is unknown.

In ECG, research on ventricular recovery and augmented dispersion of repolarization are useful markers for ventricular arrhythmias. Some ventricular repolarization markers are useful to predict arrhythmias, including the QT interval, QT dispersion, and T-wave alternans.[4,5]

Recent studies have suggested that new indexes such as Tpeak-Tend (Tp-e) interval and Tp-e interval/QT interval (Tp-e/QT) ratio may be associated with ventricular arrhythmias in various clinical scenarios.[6-8]

Corresponding Author: Zeki ÇETİNKAYA, zeki2387@gmail.com

The aim of this study was to evaluate Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios, which are new arrhythmia markers in PHPT patients by electrocardiographic and compare these parameters with those of control subjects. We also aimed to investigate the potential effect of PTx on these parameters.

METHODS

The study was carried out with the permission of Kayseri City Hospital, Clinical Researches Ethics Committee (Date:03.09.2020, Decision No: 146). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population and Study Protocol

38 PHPT patients who underwent PTx between January 2019 and November 2020 were included in the study.At the beginning of the study, physical examination findings, a detailed medical histories and laboratory characteristics of the study patients and control groups were recorded. The control group consisted of 25 people with normal blood PTH levels and comparable with the patient group in terms of age,gender, and cardiovascular risk factors. The electrocardiographic examination was performed in all patients at baseline and six months after surgery. Five patients did not come for control six months later, so they were excluded from the study.

Other exclusion criteria were: uninterpretable ECG (left bundle branch block, the presence of a pacemaker, those with U waves and negative T waves in the ECG),those with severe valvular disease, known coronary artery disease and heart failure, hypothyroidism and hyperthyroidism, creatinine clearance (CrCl)≤60 ml/min. None of the registered patients were using any medication that affected the QT interval.

After 11 patients were excluded from the study, the data of the remaining 27 patients were used in the analysis. Cardiovascular risk factors such as hypertension (HT) and diabetes mellitus (DM) were defined as previously described (9). Smokers were current smokers and had been using for at least 10 years.

Corrected calcium (CCa) levels were used for calcium levels in the study group (Corrected calcium=serum calcium+0.8 X (4-serum albumin)

Electrocardiogram (ECG) Analysis

All standard 12-lead ECGs were acquired at rest in the supine position simultaneously using a recorder (Philips brand machine) set at 25 mm/s paper speed and 1 mV/cm standardization. All ECGs were scanned and transferred to personal computers an electronic caliper (Cardio Calipers, version 3.3 software; Iconico.com, Philadelphia, PA, USA) was used under magnification to record the measurements. Assessments of the ECG were done by two cardiologists blinded to the clinical data and to diminish the error measurements. Patients whose ECGs showed U waves and negative T waves were excluded from the study.

The Tp-e interval was defined as the distance between the peak of the T-wave and the end of the T-wave. All Tp-e intervals were measured using the best available T-wave in lead V5 (10). When the lead V5 result was not suitable for analysis, the V4 and V6 were used.

The QT interval was measured from the beginning of the QRS complex to the end of the T wave in precordial lead V6, which best reflects the transmural axis of the left ventricle (11) ,and corrected for heart rate using the Bazett formula: $cQT = QT\sqrt{(R–R\ interval}$. The Tp–e/QT ratio and Tp-e/QTc (Tp-e divided by QT and Tp-e divided by QTc) were calculated from these measurements. Interobserver and interobserver coefficients of variation were less than 5%, respectively.

Echocardiography

Conventional echocardiography was performed with 2-dimensional, M-mode, pulsed wave, continuous, colour Doppler and tissue Doppler imaging (TDI) using the Vivid 7 Pro ultrasound system (Vivid 7 pro, GE, Horten, Norway, 2-4 MHz phased array transducer ultrasound system). Conventional echocardiographic images were obtained from the parasternal and apical views according to the guidelines of the American Society of Echocardiography (12). Left ventricular (LV) diameters and wall thickness were measured from the parasternal views by M-mode echocardiography. The Simpson's method was used for the calculation of the LV ejection fraction. The left atrial area and diameter were measured from the parasternal long axis view. Mitral inflow velocities were measured from apical views. Conventional echocardiography evaluations were performed by a cardiologist blinded to the clinical data.

Statistical Analysis

Statistical analyzes were performed using SPSS Statistics Package version 21.0 (SPSS Inc, Chicago, IL, USA) for Windows. The normal distribution of variables was analyzed using the Kolmogorov-Smirnov method. Continuous data means and standard deviations were evaluated and recorded. The chi-square test was used for categorical variables and was calculated as a percentage. Descriptive data was given as mean±standard deviation, depending on normality of distribution. Median and interquartile range were given when the variable did not follow a normal distribution.The independent sample t-test was used for the comparison of normally distributed quantitative variables, and the Mann-Whitney U test was used for the comparison of non-normally distributed quantitative variables.

ANOVA test was performed to analyse the variables between control group, PHPT patient data, and patient data after PTx. Variability between groups was performed by the LSD test. Correlation analyses were performed using Pearson's and Spearman's coefficient of correlation. A probability value of $p<0.05$ was considered significant, and 2-tailed p values were used for all statistics.

RESULTS

A total of 52 participants were selected in the current study.The PHPT group consisted of 27 subjects (2 men,25 female), and the control group included 25 individuals (3 men, 22 female). Baseline demographic features and laboratory measurements of the study groups are presented in **Table 1**. The study population was similar regarding sex distribution, age, smoking status, frequencies of HT and DM were not significantly different between patients and the control group ($p>0.05$). As expected, patients with PHPT had higher serum PTH levels and CCa levels compared to the control group, while serum phosphorus levels were significantly lower ($p<0.001$, for all). Other blood parameters were similar between groups.Serum PTH and CCa levels significantly decreased, whereas serum phosphorus levels significantly increased after PTx surgery. After surgery, 16 of the patients were receiving vitamin D supplements and 5 patients were receiving bisphosphonate treatment because osteoporosis developed.

The electrocardiographic and echocardiographic parameters of the groups are shown in **Table 2**. There was no statistically significant difference between the echocardiographic parameters of PHPT and the control group.

Heart rate and QRS duration among the electrocardiographic parameters were similar between the groups ($p=0.409$, $p=0.562$ respectively). Although the QT interval and QTc interval were shorter in PHPT patients, it was not statistically significant ($p>0.05$, for both). Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in PHPT patients compared to the control group ($p<0.001$, for all).

The correlation analysis revealed a significant and positive correlation between Ca levels with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio ($r=0.515$, $p=0.006$; $r=0.398$, $p=0.040$; $r=0.797$, $p<0.001$ respectively) (**Figure 1**). There was the same correlation relationship between PTH levels and Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. ($r=538$, $p=0.04$; $r=0.422$, $p=0.028$; $r=0.812$, $p<0.001$ respectively) (**Figure 2**). The change in electrocardiographic parameters of pHPT patients 6 months after PTx compared to baseline is shown in **Table 3**. It was observed that the parameters mentioned after surgery decreased significantly, and there was no statistical difference when compared to the control group (**Table 4**).

Table 1. Baseline demographic features and laboratory measurements of the study groups

Variables	Control group (n=25)	PHPT (n=27)	P Value
Age (years)	51.2 (41-62.5)	54.7 (44-63)	0.279
Male/female	3/22	2/25	0.575
Hypertension (HT)	5 (20%)	8 (29%)	0.423
Diabetes Mellitus (DM)	3 (12%)	5 (18%)	0.515
Smoke	0	1 (3%)	0.331
Body Mass Index (BMI)	26.41±1.83	27.12±2.26	0.480
Sistolic Blood Pressure (CBP) (mm/hg)	125.5±8.2	127.2±10.5	0.521
Dıastolıc Blood Pressure (DBP) (mm/hg)	78.2±7.2	80.7±6.3	0.612
Glucose (mg/dL)	91.3±5.9	96.8±13.2	0.064
Kreatinin (mg/dL)	0.83±0.15	0.81±0.14	0.732
AST (U/L)	22.6±5.1	20.9±7.4	0.333
ALT (U/L)	20.4±6.3	22.7±11.7	0.382
Albumin (mg/dl)	4.3±0.50	4.5±0.3	0.056
Corrected calcium (mg/dl)	9.1 (8.8-9.5)	11.6 (11.2-11.9)	<0.001
Phosphorus (mg/dl)	3.5 (3.3-3.9)	2.4 (2.1-2.9)	<0.001
Parathyroid Hormone (PTH)	37.6 (32.5-42)	265.5 (123-395)	<0.001
Thyroid Stimulating Hormone (TSH)	1.8 (0.9-2.4)	1.9 (0.8-2.4)	0.762
D Vitamin	21.4±6.4	18.0±6.5	0.066
White Blood Cell (WBC) (10^3/uL)	8.4±2.5	7.9±1.8	0.425
Hemoglobin (g/l)	13.7±1.1	14.2±1.2	0.127
Platelet (/mm3)	241.5±78.0	265.2±66.6	0.292
Previous medications, n			
Angiotensin converting enzyme inhibitor	2	3	
Angiotensin–aldosterone antagonists	2	4	
Calcium channel antagonists (dihydropyridine)	1	1	

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables.

Table 2. Electrocardiographic and Echocardiography Characteristics of the study population

Variables	Control group (n=25)	PHPT (N=27)	P value
Electrocardiographic Finding			
Heart rate (beat/min)	76.2±9.3	78.8±12.5	0.409
QRS duration (ms)	84.1±7.8	82.7±9.4	0.562
QT interval (ms)	378.2±20.9	367.6±28.7	0.147
QTc interval (ms)	417.3±16.5	408.7±23.9	0.071
Tp-e interval (ms)	81.9±10.4	92.7±5.2	<0.001
TPe/QTc ratio (ms)	0.19±0.02	0.22±0.01	<0.001
TPe/QT ratio (ms)	0.21±0.03	0.25±0.02	<0.001
Echocardiography Characteristics			
LVEDD (cm)	4.72±0.42	4.70±0.45	0.870
LVESD (cm)	3.13±0.47	2.98±0.30	0.196
IVSD (cm)	1.02±0.19	1.08±0.11	0.146
PWD (cm)	0.97±0.20	1.08±0.10	0.021
LVEF (%)	62.6±2.9	63.1±4.6	0.667

Tp-e= T wave interval from peak to end, c=corrected, LVEDD: Left Ventricular End Diastole Diameter, LVESD: Left Ventricular End Systole Diameter, IVSD: İnterventricular Septal Diameter, PWD: Posterior Wall Diameter, LVEF; Left Ventricular Ejection Fraction

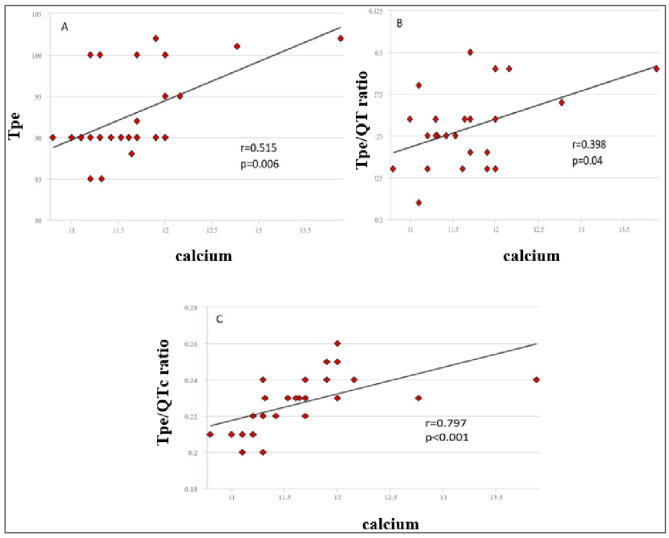

Figure 1. (A) Correlation between Tpe interval and calcium count (B) Correlation between Tpe/QT ratio and calcium count. (C) Correlation between Tpe/QTc ratio and calcium count.

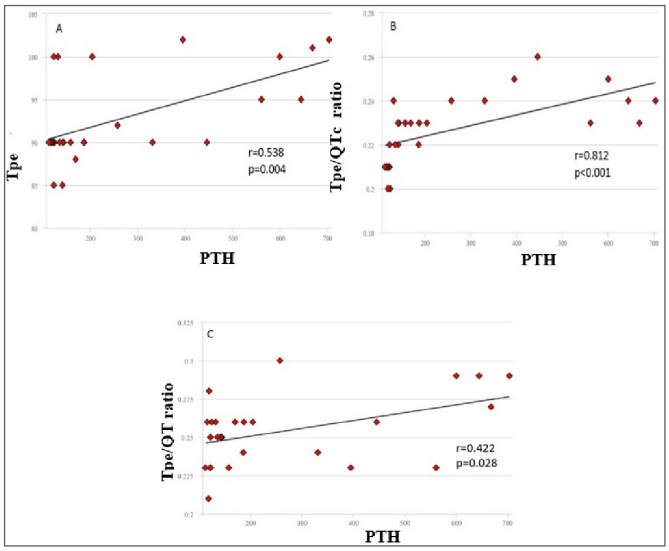

Figure 2. (A) Correlation between Tp-e interval and PTH level (B) Correlation between Tp e/QTc ratio and PTH level. (C) Correlation between Tp–e/QT ratio and PTH level.

Table 3. Laboratory Measurements, Electrocardiographic and Echocardiographic Findings before and after Parathyroidectomy.

Variables	Parathyroidectomy		P value
	Before	After	
Laboratory Measurements			
Corrected calcium (mg/dl)	11.6 (11.2-11.9)	9.2 (9-9.6)	<0.001
Phosphorus (mg/dl)	2.4±0.5	3.3±0.5	<0.001
Parathyroid hormone (PTH)	265.5 (123-395)	44.8 (35-57)	<0.001
D Vitamin	18.0±6.5	21.2±5.9	0.064
TSH	1.92 (0.8-2.4)	2.01 (1.03-2.7)	0.716
Electrocardiographic Finding			
QT interval, (ms)	367.6±29.1	377.6±16	0.124
QTc interval (ms)	408.7±17.1	416.8±12.8	0.053
Tpe interval (ms)	92.7±5.2	84.1±7.3	<0.001
TPe/QT ratio (ms)	0.25±0.02	0.22±0.02	<0.001
TPe/QTc ratio (ms)	0.22±0.01	0.20±0.01	<0.001
Echocardiographic Finding			
LVEDD (cm)	4.70±0.4	4.72±0.4	0.860
LVESD (cm)	2.98±0.30	3.10±0.4	0.300
IVSD (cm)	1.08±0.1	1.06±0.1	0.535
PWD (cm)	1.08±0.1	1.04±01	0.236
LVEF (%)	63.1±4.6	62.4±3.2	0.565

DISCUSSION

This study showed that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were prolonged in PHPT patients without known cardiovascular disease, as compared to controls. In addition, in our study, we found a significant correlation between Tp-e interval, Tp-e/QT ratio , Tp-e/QTc ratio and Ca levels and PTH levels in PHPT patients. One of the most important results of our study is, these values, which are accepted as an indicator of sudden cardiac death (SCD) after PTx, decreased significantly.

As is known, PHPT is an endocrinological disease that is typically characterised by high or non-suppressed PTH levels together with high serum Ca levels.[1] Studies have shown that both PTH and Ca levels affect cardiomyocyte, heart conduction system, smooth vascular and endothelial cells. Excessive secretion of PTH can affect the myocardium and alter the repolarization. Although the effects of PTH on the heart were thought to be due to hypercalcemia, it is now known that PTH itself causes hypertrophy in cardiac myocytes and vascular smooth muscles independent of Ca levels. In addition, it has been reported in the literature that there is a direct relationship between endothelial dysfunction and PTH.[13-17]

Table 4. Post Hoc Test

	Control group	Group 1	P value	Control group	Group 2	P value	Group 1	Group 2	P value
QT (msn)	378.2	367.6	0.097	378.2	377.6	0.923	367.6	377.6	0.110
QTc (msn)	417.3	408.7	0.057	417.3	420.9	0.421	408.7	420.9	0.007
Tpe (msn)	81.9	92.7	<0.001	81.9	84.1	0.321	92.7	84.1	<0.001
TPe/QTc ratio (ms)	0.19	0.22	<0.001	0.19	0.20	0.539	0.22	0.20	<0.001
TPe/QT ratio (ms)	0.21	0.25	<0.001	0.21	0.22	0.394	0.25	0.22	<0.001
Corrected calcium (mg/dl)	9.17	11.6	<0.001	9.17	9.24	0.646	11.6	9.24	<0.001
Phosphorus (mg/dl)	3,5	2,4	<0.001	3.5	3.3	0.116	2.4	3.3	<0.001
PTH	37.6	265.5	<0.001	37.6	44.8	0.823	265.5	44.8	<0.001

Group1. Patients with Primary hyperparatiroidism, Group 2. Patients with Parathyroidectomy. Tp-e= T wave interval from peak to end.

PHPT-induced hypercalcemia is a risk factor for cardiac arrhythmias.[18,19] Hypercalcemia, which develops in PHPT, is conventionally accepted to cause a shortening of the QT interval.[20,21] The shortening of the refractory period due to QT shortening may lead to complex ventricular arrhythmias or SCD.[20,21]

The QTc interval and QT dispersion which show myocardial repolarization status have been used for risk stratification in different patient groups.[22] In recent years, the use of the Tp-e interval and the Tp-e/QTc ratio in determining ventricular arrhythmias and risk of SCD has become increasingly common. Tp-e interval is the duration of the transmural distribution of myocardial repolarization.[23] There is a relationship between the Tp-e and the life-threatening arrhythmic events, and therefore Tp-e helps to predict the risk of developing arrhythmias.[7,24-28] However, QT and Tp-e intervals vary widely between individuals, and the Tp-e interval is affected by the changes in the heart rate. For this reason, the Tp-e/QT ratio has been more consistent among the individuals and their heart rates, regardless of their Tp-e interval values.

Pepe et al.[29] demonstrated that the mean QTc values of patients with PHPT lie within the normal range, but they were significantly lower than the mean QTc values of the control group.They also found that PHPT patients had a higher prevalence of both supraventricular (SVBP) and ventricular premature beats (VPB) in 24-hour ECG monitoring. In addition, they showed that while both SVBP and VPB rates decreased significantly in PHPT patients who underwent PTx after 6 months, QTc values returned to normal levels. As a result, they showed that short QTc caused by hypercalcemia due to PHPT increased the prevalence of SVPBs and VPBs, and these arrhythmic events decreased significantly with PTx.

Similarly, Curione et al.[30] found that QTc was significantly lower in PHPT patients, while QT dispersion was higher. Accordingly, they showed that the possibility of life-threatening arrhythmias in PHPT patients increased. In their other study, Curione et al.31 showed that in PHPT patients who underwent PTx, QT duration and QTc dispersion returned to the normal range after the procedure. They claimed that the surgery performed in this patient group eliminated the myocardial electrical instability.

In our study, we also have found that the QT intervals were shorter in the patient group than in the control group. In addition, similar to the findings of the aforementioned studies, we also did not find any statistically significant difference between the QTc intervals of the patient and the control groups, and the QTc intervals we have found were within normal limits, as well. In addition, we have found that Tp-e intervals, Tp-e/QT ratios and Tp-e/QTc ratios were higher in patients with PHPT compared to the control group. In our previous study, we detected similarly high levels of Tp-e intervals, Tp-e/QT ratios and Tp-e/QTc ratios.[32] Yan et al.[33] showed that a prolonged Tp-e/QT ratio was an independent predictor of nocturnal PVCs in OSA patients. Tashiro et al.[34] claimed that prolonged absolute and corrected Tp-e intervals and an increase in the Tp-e/QT ratio may be useful predictors of life-threatening arrhythmia in children with hypertrophic cardiomyopathy. Yamaguchi et al.[23] suggested that the Tp-e/QT ratio is a better predictor for torsade de pointes compared to the QTc interval. Watanabe et al.[27] have demonstrated that longer Tp-e intervals are associated with spontaneous ventricular tachycardia. On the other hand, Shimizu et al.[35] have demonstrated that the Tpe/QT ratios were higher in patients who developed SCD than those who did not.Hevia et al.[7] revealed that the incidence of recurrent cardiac events is significantly higher in patients with increased Tp-e ranges. Ventricular arrhythmias in PHPT were generally reported in the form of case reports in the literature, and follow-up studies of the long-term cardiovascular consequences of PHPT are not available in the literature. Nilsson et al.[36] and Pepe et al.[29] have reported an increase in VPB in patients with PHPT. In our study, which was also not a follow-up study, we have found that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, which are strong predictors of cardiac arrhythmia, have increased. These rates decreased significantly after PTx. Along with the results reported in the literature, our results suggest that patients with PHPT may be at risk for severe ventricular arrhythmia and SCD and that surgery in these patients may reduce the risk of SCD.

In our study, we have found a correlation between Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio and Ca levels and PTH levels in PHPT patients. This result suggests that PTH levels, together with Ca levels, may have an effect on arrhythmogenesis mechanisms.PTH has chronotropic effects in animal models and affects coronary blood flow and contraction.[37] PTH may cause both hypertrophy and necrosis by directly affecting the cardiac myocytes.38 Hypercalcemia may also affect Tpe and QT durations by electrically shortening the plateau phase of the cardiac action potential and the effective refractory period.[39,40] Considering that PTH has direct cardiac effects, we can speculate that in addition to the arrhythmia-promoting effects of Ca levels, PTH levels may also increase the risk of arrhythmia development.

This study has the following limitations: it is hard to estimate how long the participants have been exposed to Ca and PTH. Furthermore, as the number of participants is low, it is not possible to determine the cut-off value of PTH with respect to the level and exposure period of its cardiac effects. The orbit of the disease may change in presymptomatic patients and with an intervention

in the level of hypercalcemia. We evaluated at the Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, which are good marker for ventricular arrhythmias and SCD, but the development of ventricular arrhythmias has not been directly investigated. Long-term follow-up is required to identify cases that will cause ventricular arrhythmias.

To date, the risk of cardiac arrhythmia in studies conducted in PHPT patients has been investigated over the QT interval. It is well known that shortening the duration of the QT interval is associated with an increased risk of arrhythmia and SCD. It is a matter of debate whether the risk of arrhythmia increases in PHPT patients with a normal QT interval. In this study, we have demonstrated that ventricular repolarization showed an abnormal distribution with an increase in Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in PHPT patients with normal QT interval regardless of the QT interval, and that this group of patients is more susceptible to future ventricular arrhythmias and SCD. We also found that PTx surgery performed in this patient group decreased the mentioned arrhythmia indicators and decreased the risk of possible SCD in these patients.

CONCLUSION

The clinical results of this study should be confirmed with a larger sample size and long-term follow-up. If the results of this research are validated, our study will likely change the PTx proposal, which focuses only on traditional aspects of PHPT, such as skeletal and kidney involvement.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 03.09.2020, Decision No: 146).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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