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Evaluation of the risk of developing atrial fibrillation with new electrocardiographic parameters in patients with primary hyperparathyroidism

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ABSTRACT

Aims: Primary hyperparathyroidism (PHPT) is a clinical entity characterized by hypercalcemia caused by excessive parathyroid hormone (PTH) secretion from the parathyroid gland and is the most common cause of hypercalcemia in outpatient clinics. Atrial fibrillation (AF) is a common arrhythmia encountered in cardiology practice, the prevalence of which increases with concomitant heart disease and age. P-wave peak time (PWPT) is the time from the onset of the p-wave to its peak and is a recently defined electrocardiographic (ECG) parameter. Recently, studies on the relationship between PWPT and cardiovascular events have been published. In this study, we aimed to evaluate the risk of AF in PHPT patients by detecting PWPT, a new ECG parameter.

Methods: The study included 21 PHPT patients and 20 healthy subjects as a control group. The groups were compared in terms of demographic characteristics, laboratory findings, echocardiography, and ECG findings. D2 and V1 leads were used for PWPT, as recommended in the literature.

Results: When the patient group was compared with the control group, no difference was detected in terms of demographic characteristics and laboratory findings. When compared with the control group, patients with PHPT had significantly longer PWPT (PWPTV1 56.07 msec ± 8.33 s vs. 50.25 msec ± 7.00 s $p<0.05$, PWPTD2 54.57 msec ± 6.28 msec vs. 48.05 msec ± 5.91 msec $p<0.01$).

Conclusion: We observed that PWPT was longer in patients with PHPT compared to controls, and our results suggest that PHPT patients are at risk of AF.

Keywords: Primary hyperparathyroidism, hypercalcemia, atrial fibrillation, P-wave peak time

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a clinical picture characterized by hypercalcemia caused by excessive parathyroid hormone (PTH) secretion from the parathyroid gland and is the most common cause of hypercalcemia in outpatient clinics.[1,2] It has been observed more frequently in the last 40 years due to more frequent measurements of serum calcium levels.[3] As a result, PHPT is becoming a relatively more common endocrine disease, with an incidence of 1/1000.[4] Recently, there has been an increased interest in the cardiac evaluation of patients with PHPT, with the publication of studies showing that PHPT increases cardiac mortality and arrhythmias.[5,6]

Atrial fibrillation (AF), the most common rhythm disorder in clinical practice, is of critical importance due to accompanying hemodynamic disorders and thromboembolic events.[7] Although the mechanisms causing AF are not fully understood, many risk factors, including age, hypertension (HT), coronary artery disease (CAD), cerebrovascular disease (CVD), and diabetes, are thought to play a role in the development of AF.[8]

P-wave peak time (PWPT) is the time from the onset to the peak of the P wave. It is considered a new index of atrial depolarization, and recent studies have shown an association between PWPT and CAD severity, left

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ventricular end-diastolic pressure, absence of coronary reflux, and left atrial volume index.[9-11] This new parameter suggests that it can be used as an indicator of the risk of developing AF.[12,13]

In this article, we aim to determine PWPT times in patients with PHPT and evaluate the risk of AF development in patients with PHPT based on this index.

METHODS

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

In October 2020, 21 patients who were followed up with a diagnosis of PHPT in our hospital were included in the study and analyzed prospectively. Physical examination findings, medical history, and laboratory results of the patients in the patient group and the control group were recorded from the patient files. The control group consisted of patients of similar age and gender, normal blood PTH levels, and no suspicion of cardiovascular disease based on history, physical examination findings, electrocardiography (ECG), and echocardiography (ECHO).

Exclusion criteria were hypertrophic cardiomyopathy, severe valvular disease, CAD, hypothyroidism and hyperthyroidism, hypokalemia and hyperkalemia, hypomagnesemia and hypermagnesemia, creatinine clearance (CrCl) <60 ml/min, and body mass index (BMI) <30 kg/m². In addition, patients with AF, conduction abnormalities, atrioventricular block, and pacemaker rhythm were excluded from the study. We were obtained from all patients.

Electrocardiogram Analysis

All standard 12-lead ECGs were obtained in the supine position and at rest using an ECG device (Philips brand) standardized to 1 mV/cm and 25 mm/s paper speed. All ECGs were scanned and transferred to personal computers. ECGs were magnified 5-fold and measured using electronic calipers (Cardio Calipers software version 3.3; Iconico.com, Philadelphia, PA, USA) to make the necessary measurements. To reduce erroneous measurements, ECG assessments were performed by two cardiologists blinded to clinical data. The PWPT in lead D2 (PWPTD2) was measured as the time from the onset of the P-wave to its peak in lead D2, and the PWPT in lead V1 (PWPTV1) was defined as the time between the onset of the P-wave and the lower limit of negative deflection in patients with biphasic or pure negative P-wave morphology (**Figure**).[14]

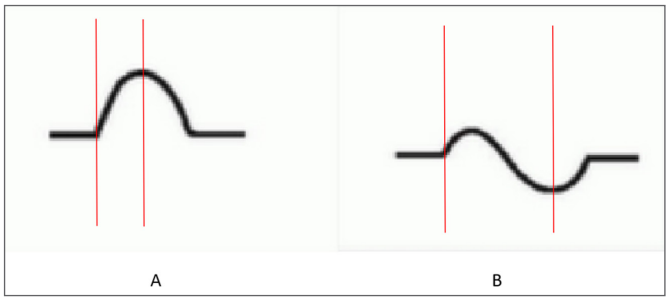

Figure: Measurement of P wave peak time on electrocardiograms
A: Measurement of P wave peak time in the lead D2 (positive wave)
B: Measurement of P wave peak time in the lead V1 (biphasic wave)

Echocardiography Measurements

Patients and healthy volunteers underwent conventional echocardiographic examination with an M4S-RS (1.5-3.6 MHz) cardiac transducer and Vingmed System 5 (General Electronic Horten, Norway) echocardiograph. Left ventricular diastolic (LVIDd) and systolic (LVIDs) diameters, interventricular septum wall (IVSWT), and posterior wall (LVPWT) diastolic thicknesses were measured in the parasternal long axis by M-mode echocardiography according to the standards defined by the American Society of Echocardiography. The ejection fraction was calculated using the Teichholz formula.[15]

Statistical Analysis

Statistical analyses were performed using SPSS Statistics software package version 21.0 (SPSS Inc., Chicago, IL, USA) for Windows. The distribution characteristics of the data were determined using the Kolmogorov-Smirnov test. Independent samples A t-test was used for parametric scale variables. The Mann-Whitney U test was used for nonparametric scale variables. The $\chi 2$ (chi-squared) test was used for univariate analysis of the categorical variables. The variables were reported as means ± SD (standard deviation), whereas the categorical variables were reported as percentages. Correlation analyses were performed using Pearson and Spearman coefficients of correlation. A probability value of $p < 0.05$ was considered significant, and two-tailed p values were used for all statistical analyses.

RESULTS

Baseline clinical and demographic characteristics of the study groups are presented in **Table 1**. There were no statistically significant differences between the patient and control groups in terms of gender, age, smoking status, diabetes, and HT ($p > 0.05$).

The basic laboratory results of the patients are listed in **Table 2**. Total calcium, albumin-corrected calcium, phosphorus, and PTH levels were significantly higher in PHPT patients included in the patient group compared to those included in the control group ($p < 0.01$ for all). Other blood parameters were similar between the

groups. The ECHO parameters of the patient and control groups are shown in **Table 3**. There was no statistically significant difference between the two groups in terms of the ECHO parameters. Heart rate and PR intervals were similar in both groups (77.1±6.1/min vs. 79.2±11.6/min, p=0.442 and 141±14 msec versus 145±16 msec, p=0.891, respectively). PWPTV1 and PWPTD2 were higher in PHPT patients compared to the control group (50.25±7 msec vs. 56.07±8.33 msec p<0.01 and 48.05±5.91 msec vs. 54.57±6.28 msec p<0.01, respectively).

Table 1. Baseline clinical and demographic features of the study groups

Variables	Control group (n=20)	PHPT (n=21)	P value
Age (years)	58.4±10,0	56.7±11.2	.866
Male/female	19/2	18/2	.677
HT	9	8	.925
DM	3	4	.966
Smoke	1	1	.986
SBP (mmHg)	113.5±11	125.2±13.1	.108
DBP (mmHg)	69.7±8.1	72.5±5.9	.606

PHPT; Primary hyperparathyroidism, DM: Diabetes Mellitus, HT: Hypertension,CBP: Sistolic Blood Pressure, DBP: Diastolic Blood Pressure Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables

Table 2. Comparison of baseline laboratory measurements among the study groups

Variables	Control group (N=20)	PHPT (N=21)	P value
Glucose (mg/dl)	98.1±11.2	99.4±12.9	.325
BMI	27.48±2.1	27.05±1.89	.760
Kreatinin (mg/dl)	0.79±0,19	0.86±0.21	,690
AST (U/L)	25.6±7.5	24.8±9.1	.875
ALT (U/L)	22.54±5.9	26.1±8.8	.401
Albumin	3.89±0.89	4.21±0.42	.312
Total calcium (mg/dl)	9.86±0.55	12.01±1.12	.0001
Albumin-corrected calcium (mg/dl)	8.99±0.56	11.01±0.88	.0001
Phosphorus (mg/dl)	3.69±0.52	2.65±0.48	.0001
PTH	38.22±10.1	231.65±165.49	.0001
TSH	2.01±1.15	2.55±1.56	.612
D_Vitamin	21.01±3.2	18.99±9.1	.682
WBC (10^3/µl)	7,78±1,47	7,71±1,73	,847
Hemoglobin (g/L)	13.42±2.1	14.1±.9	.551
Platelet (/mm³)	278.6±72.1	265.6±81.6	.825

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. PHPT; Primary hyperparathyroidism, WBC: White Blood Cell, PTH: Parathyroid Hormone, TSH: Thyroid Stimulating Hormone, BMI; Body Mass Index

Table 3. Echocardiography characteristics of the study population

Variables	Control group (N=20)	PHPT (N=21)	P value
LVEDD (cm)	4.34±1.01	4.62±0.86	.266
LVESD (cm)	3.55±.45	3.21±1.23	.655
IVSD (cm)	.99±.55	1.0±0.21	.769
PWD (cm)	.99±0.45	1,01±0.1	.899
LVEF	59.1±4.1	61.1±3.8	.331

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

Table 4. Electrocardiographic characteristics of the study population

Variables	Control group (N=20)	PHPT (N=21)	P value
Heart rate (beat/min)	77.1±6.1	79.2±11.6	.442
PR interval (ms)	141 ± 14	145 ± 16	0.891
PWPTV1 (ms)	50.25 ± 7	56.07 ± 8.33	<.01
PWPTD2 (ms)	48.05 ± 5.91	54.57 ± 6.28	<.01

PHPT; Primary hyperparathyroidism, PWPTD2; P wave peak time obtained from D2 lead, PWPTV1; P wave peak time obtained from V1 lead, Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables.

DISCUSSION

This is the first randomized study to show that PWPT prolongation detected by ECG analysis was higher in PHPT patients included in the patient group than in those included in the control group.

All hypercalcemia, including PHPT-induced hypercalcemia, is a risk factor for cardiac arrhythmias.[16,17] It is traditionally accepted that hypercalcemia developing in PHPT causes shortening of the QT interval, ST segment depression, and mild prolongation of the PR and QRS intervals.[18] Shortening of the refractory period due to QT shortening may cause complex ventricular arrhythmias or sudden death.[18]

Furthermore, recent studies have shown that PHPT patients have impaired LA function.[19] These adverse effects that can be seen in PHPT are also known as risk factors for the development of AF.[20] Studies investigating the effects of PTH and calcium on the heart have shown that both cause changes in both endothelial cells and myocardial cells. PTH may have such effects through calcium; it can also be seen in connection with its effects directly on cells.[21,22]

Clinical observations of conduction disturbances caused by hypercalcemia are surprisingly rare. Case reports have shown a variety of conduction disturbances in patients with PHPT depending on the severity of hypercalcemia, including atrioventricular nodal conduction defects, sinus node disease, and AF; the reason for the prevalence of these disturbances is unknown.[23]

Curione et al.[24] showed that hypercalcemia develops adverse effects on cardiac electrical stability in patients with PHPT. PWPT indicates the time spent for excitation propagating from the sinoatrial node to the maximum sum of positive deflection from the atria. Prolonged PWPT suggests prolonged intra- or inter-atrial conduction time as a consequence of increased intra-atrial pressure.[25] In some previous studies, an association between PWPT and both CAD and cardiac physiologic/pathologic indices had been shown.[9-11] This new parameter has been claimed to be used to predict the development

of AF in recent studies.[11,12] According to our findings, hypercalcemia may cause prolongation of PWPT by affecting atrial conduction pathways. Therefore, it is not unreasonable to think that increased calcium levels may be a predictor for possible AF development.

PTH is vital for calcium hemostasis. However, it is now known that PTH itself causes hypertrophy of cardiac myocytes and vascular smooth muscle, even in the absence of hypercalcemia. Furthermore, parathyroid hormone increases heart rate, an effect mediated by the direct action of PTH on the sinus node and conduction system.[26] PTH also exerts inotropic effects due to increased coronary blood flow, possibly due to the vasodilator effect of PTH on the coronary circulation.[26] Rienstra et al.[27] found that PTH levels were significantly higher in patients with AF. Lee et al.[28] showed that increased PTH levels increased the incidence of AF in their population-based study. In a study by Pepe et al.[29] more frequent atrial extrasystoles were found in 24-hour ECG monitoring of PHPT patients. When evaluated together with the literature, it can be speculated that the prolongation of PWPT found in our study would increase the risk of AF development, which is consistent with the literature.

The present research bears a few limitations. First, we had no information on how long the patients had lived with PHPT and hypercalcemia before the diagnoses. Second, we did not know the threshold values of PTH or calcium levels, which may lead to significant changes in the heart, as well as the duration for how long PTH or calcium levels must remain high for these significant changes to occur. Most of the studies to that effect included patients with symptomatic diseases. Therefore, an intervention in a presymptomatic stage with a lower level of hypercalcemia may alter the disease trajectory. Finally, although values such as PWPT are secondary markers of arrhythmia, we did not perform long-term clinical follow-ups and rhythm Holter follow-ups to detect the development of arrhythmia.

CONCLUSION

The results of the present study suggest that PWPT obtained from ECG, which is a simple, easily measurable, and inexpensive test, can be used as a marker to predict the risk of AF in PHPT patients. More comprehensive and multicenter studies should be performed to better analyze all possible predictors of AF and accordingly make more robust recommendations for the future.

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, Desicion No: 146).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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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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