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Received : 29.05.2024
Accepted : 10.09.2024

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Evaluation of P-Wave Dispersion on Surface Electrocardiogram in Patients with Primary Hyperparathyroidism

Objective: It is well established that individuals with primary hyperparathyroidism (PHP) have higher rates of cardiac death and arrhythmias. In cardiology practice, atrial fibrillation (AF) is a prevalent arrhythmia that is addressed due to the rising prevalence of age and concomitant cardiac disease. The difference between the maximum and minimum P wave lengths in surface ECG derivations is called P wave dispersion (PWD). Various studies have shown that P wave dispersion (PWD) is a predictor of AF development. In this study, we aimed to evaluate the risk of AF by detecting PWD in patients with PHP.

Materials and Methods: As a control group, there were 21 healthy people and 26 PHP patients in the study. The groups were contrasted with respect to their ECG, echocardiography, laboratory, and demographic results. The difference between the highest and minimum P-wave durations in any lead is known as PWD

Results: Regarding the laboratory results and demographics, there was no difference found between the patient group and the control group. Total calcium, albumin-corrected calcium, phosphorus and parathyroid hormone (PH) levels were significantly higher in PHP patients ($p<0.05$). The maximum duration of the P wave was significantly longer in patients with PHP compared to healthy participants (108.3 ± 9 vs. 97.8 ± 11 , $p<0.001$). The minimum duration of the P wave was similar between both groups. The PDD duration of patients with PHP was significantly longer (51.16 months \pm 6.72 months compared to 37.85 months \pm 8.12 months, $p<0.01$).

Conclusion: We observed that PWD was longer in patients with PHP compared to controls, and our results suggest that patients with PHP are at higher risk for AF.

Key Words: Atrial fibrillation, P-wave dispersion, primary hyperparathyroidism

Primer Hiperparatroidizimli Hastalarda Yüzeysel Elektrokardiyogramda P Dalga Dispersiyonun Değerlendirilmesi

Amaç: Primer hiperparatroidizm (PHP) bulunan hastalarda kardiyak aritmi ve kardiyak ölümün yüksek oranlarda olduğu iyi bilinmektedir. Atriyal fibrilasyon (AF), kardiyoloji pratiğinde yaygın bir aritmi olup, eşlik eden kalp hastalığı ve yaş ile birlikte prevalansı artmaktadır. Yüzeysel ekg derivasyonlarında maksimum ve minimum P dalga boyları arasında ki farka P dalga dispersiyonu (PWD) adı verilir. Çeşitli çalışmalarda, P dalga dispersiyonunun (PDD) AF gelişiminin öngörücüsü olduğunu göstermiştir. Bu çalışmada PHP hastalarında PDD'yi tespit ederek AF riskini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmaya 26 PHP hastası ve kontrol grubu olarak 21 sağlıklı birey dahil edildi. Gruplar demografik özellikler, laboratuvar bulguları, ekokardiyografi ve EKG bulguları açısından karşılaştırıldı. PDD, herhangi bir derivasyondaki en uzun p dalgası süresi ile en kısa p dalgası süresi arasındaki fark olarak tanımlandı.

Bulgular: PHP grubu ile kontrol grubu karşılaştırıldığında demografik özellikler ve laboratuvar bulguları açısından farklılık saptanmadı. Toplam kalsiyum, albümine göre düzeltilmiş kalsiyum, fosfor ve paratiroid hormon (PH) düzeyleri PHP hastalarında anlamlı derecede yüksekti ($p<0.05$). P dalgasının maksimum süresi PHP'li hastalarda sağlıklı katılımcılara göre anlamlı derecede daha uzundu (108.3 ± 9 vs. 97.8 ± 11 $p<0.001$). P dalgasının minimum süresi her iki grup arasında benzerdi. PHP'li hastaların PDD süresi anlamlı derecede daha uzundu (51.16 msn \pm 6.72 msn'ye karşı 37.85 msn \pm 8.12 msn, $p<0.01$).

Sonuç: PHP'li hastalarda kontrollere göre PDD süresinin daha uzun olduğunu gözlemledik ve sonuçlarımız PHP'li hastaların AF açısından daha yüksek risk altında olabileceğini düşündürmektedir.

Anahtar Kelimeler: Atriyal fibrilasyon, P dalga dispersiyonu, primer hiperparatroidizm

Introduction

Primary hyperparathyroidism (PHP) is an endocrine disorder characterized by excessive secretion of parathyroid hormone (PH) resulting in dysregulation of calcium (Ca) metabolism (1). Although in clinical practice the main target organs in hyperparathyroidism are other, PHP is associated with increased cardiovascular morbidity and mortality (2).

Atrial fibrillation (AF) is a vital heart rhythm disorder. In clinical practice, it is commonly causing hemodynamic disturbances, frequent hospitalizations, and thromboembolic events, affecting 1-2% of the general population (3). Although the mechanisms causing AF are not fully understood, diastolic dysfunction, inflammation, endothelial dysfunction, and catecholamine discharge are implicated in its pathogenesis (3, 4).

The discontinuous and inhomogeneous propagation of sinus impulses is associated with the novel electrocardiographic marker P-wave dispersion (PWD), which is defined as the variation between the maximum and minimum P-wave durations on multiple different surfaces of the ECG (5). Extensive documentation exists regarding the association between interatrial and intra-atrial conduction abnormalities and the initiation of paroxysmal atrial fibrillation (PAF) (6). Clinical decision-making and categorization of patients at increased risk of developing atrial fibrillation (AF) can be influenced by an approximation of the probability that a patient will develop PAF.

To our knowledge, cardiac evaluation using PWD has not been previously performed in PHP patients. Therefore, we aimed to investigate whether AF can be predicted by evaluating PWD in these patients.

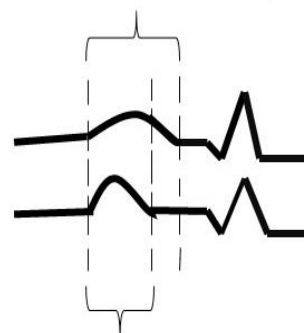
Materials and Methods

Research and Publication Ethics: Approval for the study was granted by Kayseri City Hospital, Clinical research ethics committee; 09/2020-146

Kayseri City Hospital, study number 146, received ethics committee permission on September 3, 2020. The study was conducted in Endocrinology and Cardiology clinics between November 2020 and July 2021. The study included 26 PHP patients and 21 healthy individuals as the control group. In all patients, a comprehensive medical history was taken, a physical examination was conducted, 12-lead electrocardiography was performed, and complete blood count and serum biochemistry tests were carried out. A detailed transthoracic echocardiographic (ECHO) examination was performed on all patients. There were no atrial or ventricular conduction abnormalities on electrocardiogram (ECG) in either the patient group and the control group. In addition, none of the patients included in the study had a history of paroxysmal AF. Individuals with a past medical history of ischemic heart disease, those without sinus rhythm and pacemaker use, those with abnormalities in segmental or global wall motion, those with moderate to severe valvular heart disease, those with structural heart disease, endocrine neoplasms, parathyroid cancer, thyroid cancer, or hyperparathyroidism, those with renal failure, hypertrophic cardiomyopathy, severe valvular disease, coronavirus disease (COVID-19), hypokalemia and hyperkalemia, hypomagnesemia and hypermagnesemia, patients with body mass index (BMI) <30 kg/m², and those with severe comorbidities were not allowed to participate.

Electrocardiogram Analysis: Every typical 12-lead ECG was taken in the supine position and at rest. The ECG machine (Philips brand) was calibrated to record at 1 mV/cm of voltage and 25 mm/s of paper speed. After each ECG was scanned, it was stored on a computer. ECGs were five times magnified and measured using electronic calipers (Version 3.3 of the Cardio Calipers software; Philadelphia, PA, USA, Iconico.com.) in order to achieve the necessary measurements. Significantly concomitant patients were excluded, and ECGs were evaluated by two cardiologists who were blinded to clinical information. The cutoff points were body mass index (BMI) <30 kg/m² and crCl <60 ml/min. This lessened the number of inaccurate readings. The initial atrial deflection crossing the isoelectric line was considered the start of the P-wave, and the atrial deflection returning to the isoelectric line was considered the conclusion of the P-wave. For each of the 12 ECG leads, the P-wave durations (P_{max} and P_{min}) were computed (Figure 1). PWD was defined as the difference between P_{max} and P_{min}.

Maximum P- wave duration (p max)



Minimum P- wave duration (p min)

Figure 1. In each of the 12 ECG leads, the P-wave durations (P_{max} and P_{min}) were computed

Echocardiography: Using a Vingmed System 5 (General Electronic Horten, Norway) and an M4S-RS (1.5-3.6 MHz) cardiac transducer, patients and healthy participants received a traditional ECHO evaluation. ECHO Using M-mode ECHO, the parasternal long axis was measured for left ventricular diastolic (LVIDd) and systolic (LVIDs), interventricular septum (IVSWT), and posterior wall (LVPWT) diastolic thicknesses in accordance with guidelines established by the American Society of Echocardiography. The Teichholz formula was utilized to get the ejection fraction (7).

Statistical Analysis: The statistical analyses were carried out on a Windows platform using the SPSS Statistics software package, version 21.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the data's distribution characteristics. For variables on a parametric scale, a t-test was employed. Mann-Whitney Regarding nonparametric scale variables, the U test was employed. The χ^2 (chi-squared) test was used in a univariate

analysis of the categorical variables. The variables were reported as means ± SD (standard deviation), however the categorical variables were given as percentages. The Pearson and Spearman coefficients of correlation were used to conduct correlation analysis. For all statistical analyses, two-tailed p values were employed, and a probability value of $p < 0.05$ was deemed significant.

Results

Table 1 is a list of the patients basic laboratory results. PHP patients included in the patient group had significantly higher levels of total calcium, albumin-corrected calcium, phosphorus, and PH than those in the control group ($p < 0.01$ for all). The groups' other blood values were comparable.

Table 2 displays the baseline clinical and demographic characteristics of the research groups. Age, gender, diabetes mellitus (DM), smoking status, and hypertension (HT) did not show statistically significant differences between the patient and control groups ($p > 0.05$).

Table 3 displays the ECHO parameter spertaining to both the patient and control groups. Regarding the ECHO parameters, no statistically significant distinction could be made between the two groups. In both groups, heart rate and PR intervals were comparable. The maximum duration of the P wave was significantly longer in patients with PHP than in healthy participants (97.8 ± 11 vs. 108.3 ± 9 , < 0.001). The minimum duration of the P wave was similar between both groups. PWD was significantly longer in patients with PHP than in control subjects (38 ± 12 versus 47 ± 9 , < 0.001). (Table 4)

Table 1. Comparison of baseline laboratory measurements among the study groups

Variables	Control Group (N=21)	PHP (N=26)	p value
Total calcium (mg/dL)	9.55±0.45	11.55±1.01	.0001
Albumin-corrected calcium (mg/dL)	8.99±0.56	11.01±0.88	.0001
Phosphorus (mg/dL)	3.45±0.45	2.45±0.35	.0001
PT	36.32±9.8	222.89±145.52	.0001
D_Vitamin	20.1±2.3	19.25±8.9	.861
Glucose (mg/dL)	90.1±13.1	94.4±11.2	.437
Kreatinin (mg/dL)	0.65±0.21	0.76±0.18	.882
AST (U/L)	32.5±8.2	29.4±10.1	.675
ALT (U/L)	27.4±6.7	28.1±9.4	.507
Albumin	3.89±0.65	4.01±0.43	.553
TSH	1.99±1.21	2.05±1.44	.672
WBC (10 ³ /uL)	9.01±1,44	8.54±1.55	.654
Hemoglobin (g/L)	14.12±2.2	1.65±1.1	.882
Platelet (10 ³ /mm ³)	265.7±72.1	255.4±75.1	.755

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

Table 2. Baseline clinical and demographic features of the study groups

Variables	Control group (n=21)	PHP (n=26)	p Value
Age (years)	55.6±9.2	58.1±8.9	.755
Male/female	14/3	22/4	.455
SBP (mm/hg)	110.5±11	115.1±12.6	.234
DBP (mm/hg)	65.2±7.1	69.4±6.2	.577
HT	6	10	.9945
DM	1	2	.866
Smoke	3	4	.554

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

Table 3. Echocardiography characteristics of the study population

Variables	Control Group (N=21)	PHP (N=26)	p Value
LVEF	57.1±3.2	60.1±3.1	.441
LVEDD (cm)	4.05±1.75	4.35±0.99	.325
LVESD (cm)	3.21±.44	3.43±1.03	.752
IVSD (cm)	1.02±.44	0.85±0.34	.652
PWD (cm)	.94±0.47	1±0.21	.551

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. PHP; Primary hyperparathyroidism, LVEDD: Left Ventricular End Diastole Diameter, LVESD: Left Ventricular End Systole Diameter, IVSD: Interventricular Septal Diameter, PWD: Posterior Wall Diameter, LVEF; Left Ventricular Ejection Fraction

Table 4. Electrocardiographic characteristics of the study population

Variables	Control Group (N=21)	PHP (N=26)	p Value
Heart rate (beat/min)	74.2±8.9	80.3±9.8	0.128
PR interval (ms)	147 ± 11	140 ± 15	0.665
P Max (ms)	97.8±11	108.3±9	<0.001
P Min (ms)	59.4±5.3	59.9±6.3	0.661
PWD (ms)	38±12	47±9	<0.001

PHP; Primary hyperparathyroidism, P max: P maximum; P min: P minimum; PWD: P Wave Dispersion.

Min:minute, ms = millisecond. Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables.

Discussion

In this study, Pmax and PWD on a 12-lead superficial ECG were found to be significantly higher in PHP patients. To the best of our knowledge, no prior research has been done on this topic in the literature.

It is a known fact that hypercalcemia is a risk factor for cardiac arrhythmias (8, 9). The effect of hypercalcemia that develops in PHP on the ECG causes a slight prolongation in PR intervals (10). It has been shown that PHP patients have impaired LA function, and is considered a risk factor for AF (11, 12). Both PH and calcium can cause changes in both endothelial and myocardial cells. It can also be seen in conjunction with both direct and indirect effects of PH via calcium on cells (13, 14). PH can directly affect cardiac myocytes, causing necrosis. In addition, there are studies showing that PH increases markers of systemic inflammation (15). In addition, increased sympathetic activity occurs in PHP due to increased catecholamines (16). Various conduction disturbances, such as atrioventricular nodal conduction defects, sinus node disease, and atrial fibrillation, have been demonstrated in patients with PHP (17). Curione et al demonstrated that hypercalcemia develops adverse effects on cardiac electrical stability in

patients with PHP (18). As a result of the pathologic conditions mentioned above, the atrial forward system is affected and causes inhomogeneous and discontinuous propagation of sinus impulses, resulting in PWD.

PWD is an emerging electrocardiographic marker that is characterized by the discontinuous and heterogeneous propagation of sinus impulses. Moreover, extensive documentation exists regarding the correlation between intra-atrial conduction abnormalities and the initiation of PAF (19-21). Additionally, PWD has been linked to carotid atherosclerosis (22). Additionally, it has been demonstrated that PWD is elevated during coronary sluggish flow (23). It has been documented that PWD is substantially correlated with LV diastolic dysfunction (24). Tukek et al. (25) demonstrated that PAF was associated with a shortened minimal P wave duration in patient with an increased LA diameter. A shortened P-wave duration was identified by Dilaveris et al. (26) as an independent predictor of prevalent AF. A reduced minimal P wave duration was identified by Hashemi et al. (27) as a significant predictor of atrial fibrillation in patients undergoing coronary artery bypass grafting. However, in our study, no significant difference was observed in the minimal P wave duration in PHP patients compared to the control group. This may be due to the small sample size in our study. Our study revealed a rise in PWD, which is consistent with findings reported in the literature. By interfering with atrial conduction pathways, hypercalcemia may induce PWD, according to our findings. Consequently, an increase in calcium and PH levels may therefore serve as a determinant in the potential development of atrial fibrillation.

Hemostasis of calcium depends on PH. It is now understood, therefore, that even in the absence of hypercalcemia, PH itself results in the hypertrophy of cardiac myocytes and vascular smooth muscle. Furthermore, PH increases heart rate; this effect is mediated by PH's direct contact with the sinus node and conduction system. PH may have a vasodilator impact on the coronary circulation, which accounts for its inotropic effects as well as the increased coronary blood flow (28). Studies have shown that there is a connection between AF and serum PH levels.

Rienstra et al. (29) found that PH levels were significantly higher in patients who developed AF. Lee et al. (30) showed that increased PH levels increased the incidence of AF in their population-based study found more frequent atrial extrasystoles in 24-hour ECG monitoring of PHP patients (30-31). When evaluated together with the literature, it is not unreasonable to think that the prolongation of PWD found in our study may increase the risk of AF Progress.

As a result, the current study's findings imply that PWD from ECG, a cheap, easy-to-measure test, can be utilized as a marker to estimate PHP patients' risk of developing AF. It is necessary to do more thorough, multicenter research in order to fully assess all potential AF factors and provide more solid recommendations going forward.

Author's Contribution: Study design and original idea by ZC, ŞK, and YY. Inclusion of participants by MKD, YŞ, ŞK. Collection of data by MKD and ZÇ. ZÇ and ŞK wrote the first draft, but all authors contributed to the final manuscript. ŞK and YY critically reviewed the manuscript for intellectual content. ZÇ and YY are the guarantors of the work, and as such, had full access to

all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data, the support and the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: No potential conflict of interest was reported by the authors.

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