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Atrial Electromechanical Delay Is Impaired in Patients with Primary Hyperparathyroidism

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Atrial electromechanical delay is impaired in patients with primary hyperparathyroidism

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Abstract

Background: Primary hyperparathyroidism (PHPT) is an endocrine disease that poses a risk for cardiac arrhythmias. Atrial electromechanical delay (EMD) has been known as an early marker of atrial fibrillation (AF). This study aimed to evaluate the atrial EMD in PHPT.

Material and methods: Fifty PHPT patients (45 females, 5 males) aged 30–75 years and 38 controls (35 females, 3 males) aged 31-73 years were included in the study. Atrial EMD parameters were measured by using tissue Doppler imaging (TDI). Inter-atrial EMD was calculated as the difference between PA lateral and PA tricuspid; intra-atrial EMD was calculated as the difference between PA septum and PA tricuspid, and left-atrial EMD was calculated as the difference between PA lateral and PA septum.

Results: Atrial EMD parameters (PA lateral, PA septum, PA tricuspid) significantly increased in the PHPT group compared to the control group ($p < 0.001$, for all). Also, inter-atrial and intra-atrial EMD were higher in the PHPT group than in the control group ($p < 0.001$, for all). In correlation analysis, calcium was closely associated with PA lateral ($r = 0.749$, $p < 0.001$), PA septum ($r = 0.735$, $p < 0.001$), inter-atrial EMD ($r = 0.807$, $p < 0.001$), and intra-atrial EMD ($r = 0.838$, $p < 0.001$). The same correlation relationship was seen between PTH levels with PA lateral ($r = 671$, $p < 0.001$), PA septum ($r = 0.660$, $p < 0,001$), inter-atrial EMD ($r = 0.674$, $p < 0.001$), and intra-atrial EMD ($r = 0.732$, $p < 0.001$).

Conclusions: Atrial EMD parameters were prolonged in PHPT. The measurement of atrial EMD parameters might be used in determining the risk of AF development in PHPT.

Key words: primary hyperparathyroidism; atrial fibrillation; electromechanical delay

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disease characterized 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 hyperparathyroidism, PHPT is associated with increased cardiovascular morbidity and mortality [2].

Atrial fibrillation (AF) is a vital heart rhythm disorder common in clinical practice, which causes haemodynamic disorders, frequent hospitalizations, and thromboembolic events, and it affects 1-2% of the general population [3]. Although the exact mechanisms causing AF are not fully understood, hypertension, heart failure, diastolic dysfunction, endothelial dysfunction, and left ventricular hypertrophy play an essential role in the pathogenesis of AF [3, 4]. Side effects such as hypertension, diastolic dysfunction, endothelial dysfunction, left ventricular hypertrophy can also be seen in PHPT disease [2]. Therefore, these patients may be at increased risk of newly developing AF.

The atrial conduction time (ACT) represents the interval between sinus impulses and atrial mechanical contraction. It may be measured noninvasively by tissue Doppler imaging (TDI) (5) as an alternative to invasive electrophysiological measurements. The prolongation of intra- and inter-atrial conduction time, called atrial electromechanical delay (EMD), is associated with atrial fibrillation frequency and sensitivity [6].

To the best of our knowledge, atrial conduction abnormalities have not been previously evaluated in patients with PHPT. Therefore, we aimed to assess the atrial conduction time in PHPT patients with TDI, a noninvasive method. Also, we wanted to investigate whether there is a relationship between atrial conduction time and parathyroid hormone and serum calcium levels.

Material and methods

The study was carried out in Kayseri State Hospital, Endocrinology and Cardiology clinics from January 2019 to July 2020. Fifty PHPT patients (45 females, 5 males) aged 30–75 years and 38 controls (35 females, 3 males) aged 31–73 years were included in the study.

A detailed medical history from all patients, physical examination, 12-lead electrocardiography, a complete blood count, and a serum biochemistry test were performed. The presence of classical cardiovascular risk factors, including hypertension, diabetes mellitus, and hyperlipidaemia, was assessed. Detailed transthoracic echocardiographic examination was performed on all patients. There were no atrial or ventricular conduction anomalies in both the patient group and the control group in ECG. Also, none of the patients included in the study had a history of paroxysmal AF.

Patients with a history of ischaemic heart disease, patients with non-sinus rhythm and peacemaker presence, patients with segmental or global wall motion disorders, patients with evidence of moderate to severe valvular heart disease on echocardiography, and patients with structural heart disease, multiple endocrine neoplasms, parathyroid cancer, thyroid cancer, or hyperparathyroidism-jaw tumour syndrome, renal failure, and severe comorbidities were excluded from the study.

Type 2 diabetes mellitus (T2DM), hypertension (HT), and hyperlipidaemia were defined as previously described [7].

Echocardiography

Conventional echocardiography was performed with two-dimensional, M-mode, pulsed wave, continuous, colour Doppler and tissue Doppler imaging (TDI) using a Philips Epiq 7 ultrasound system (Philips, Andover, Mass., USA). Simultaneous ECG recording was done. All patients were in sinus rhythm at the time of examination. Conventional echocardiographic images were obtained from the parasternal and apical views according to the guidelines of the American Society of Echocardiography [8]. M-mode echocardiography measured left ventricular (LV) diameters and wall thickness from the parasternal views. Simpson's method was used for the calculation of LV ejection fraction. While the left atrial area was measured from the apical view, LA diameter was measured from the parasternal long-axis view. Mitral inflow velocities were measured from apical views. Isovolumic relaxation time (IVRT) was obtained by

measurements from pulsed-wave TDI velocities in the medial and lateral walls of the apical four-chamber view (an average between the two values).

Atrial electromechanical time measurement

TDI was performed using transducer frequencies of 3.5–4.0 MHz. The spectral pulsed Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was obtained. The minimal optimal gain was used. Myocardial TDI velocities [peak systolic (S'), early diastolic (E'), and late diastolic velocities (A')] were measured with spectral pulsed Doppler from the apical four-chamber view. The ultrasound beam slope did not exceed 15% to acquire the optimal angle of imaging. The monitor sweep speed was adjusted at 50–100 mm/s to optimize myocardial velocities' spectral display. Atrial EMD was defined as the time interval from the onset of atrial electrical activity (P wave on surface ECG) to the beginning of mechanical atrial contraction (late diastolic A wave) in TDI. All values were averaged over three consecutive beats. Atrial EMD was measured from the lateral mitral annulus, and was called 'PA lateral'; from the septal mitral annulus it was called 'PA septal'; and from the right ventricle tricuspid annulus it was called 'PA tricuspid'. Inter-atrial EMD was calculated as the difference between PA lateral and PA tricuspid, intra-atrial EMD was calculated as the difference between PA septum and PA tricuspid, and left-atrial EMD was calculated as the difference between PA lateral and PA septum [5].

A total of 20 participants, 10 from the patient group and 10 from the control group, were randomly selected to evaluate the intra-observational variability. Measurements were repeated under the same baseline conditions. Intra-observer variability was 4% for lateral PA, 4.4% for septal PA, and 5.1% for tricuspid PA, respectively.

Statistical analysis

Statistical analyses were performed using SPSS Statistics Package version 21.0 (SPSS Inc., Chicago, IL, USA) for Windows. The distribution characteristics of the data were determined by using the Kolmogorov-Smirnov test. The independent samples t-test was used to compare normally distributed quantitative variables, and the Mann-Whitney U test was used to compare non-normally distributed quantitative variables. The χ^2 test was used for univariate analysis of the categorical variables. The variables were given as mean ± SD; categorical variables were

defined as percentage. The median and interquartile ranges were given when the variable did not follow a normal distribution. Correlation analyses were performed using Spearman's coefficient of correlation. A probability value of $p < 0.05$ was considered significant, and two-tailed p-values were used for all statistics.

Results

The baseline characteristics of patients and controls are given in Table 1. The PHPT group's and control group's average ages were 56.9 (49–68) and 56.8 (49–66) years, respectively. There were no significant differences between groups regarding age, gender, hypertension, diabetes mellitus, hyperlipidaemia, and smoking.

Echocardiographic and atrial electromechanically time parameters are shown in Table 2. LV systolic and diastolic diameters, left atrial diameter and area, interventricular septum, posterior wall thickness, and LV ejection fraction were similar in the two groups.

There was no difference between PHPT and healthy subjects in cardiovascular function parameters, except for IVRT, which was significantly longer in PHPT patients and indicated abnormal LV relaxation (86.05 ± 10.39 vs. 100.15 ± 9.93, $p < 0.001$).

Atrial EMD parameters (PA lateral, PA septum, PA tricuspid) significantly increased in the PHPT group compared to the control group (76.62 ± 6.78 vs. 64.13 ± 8.03, 64.13 ± 4.87 vs. 53.97 ± 5.98, 47.09 ± 6.60 vs. 43.55 ± 7.38, $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Also, inter-atrial and intra-atrial EMD were higher in the PHPT group than in the control group (29.52 ± 9.12 vs. 20.57 ± 8.63, 17.03 ± 7.78 vs. 10.42 ± 6.27, $p < 0.001$, $p < 0.001$, respectively). Left atrial EMD was higher in the PHPT group, but it did not reach significance (12.49 ± 7.74 vs. 10.15 ± 8.05, $p = 0.171$) (Fig. 1).

Biochemical parameters are shown in Table 3. Serum phosphorus was significantly lower in the PHPT group than in the control group (median 3.72, interquartile range 3.5-4.0 vs. median 2.62, interquartile range of 2.3-2.9, $p < 0.001$). On the other hand, calcium and parathyroid hormone levels were higher in the PHPT group than in the control group (median 10.86, interquartile range 10.5 to 11.2 vs. median 9.16, interquartile range 8.7 to 9.5: median 251.8, interquartile range 139.7 to 255.5 vs. median 35.6, interquartile range 31.5 to 41.0 $p < 0.001$, $p < 0.001$, respectively). Other blood parameters were similar between the two groups (Tab. 3).

In correlation analysis, calcium was closely associated with PA lateral ($r = 0.749$, $p < 0.001$), PA septum ($r = 0.735$, $p < 0.001$), inter-atrial EMD ($r = 0.807$, $p < 0.001$), and intra-atrial EMD ($r = 0.838$, $p < 0.001$) (Fig. 2).

There was the same correlation relationship between PTH levels with PA lateral ($r = 0.671$, $p < 0.001$), PA septum ($r = 0.660$, $p < 0.001$), inter-atrial EMD ($r = 0.674$, $p < 0.001$), and intra-atrial EMD ($r = 0.732$, $p < 0.001$) (Fig. 3).

Discussion

This study is the first to show that both intra-atrial and inter-atrial conduction times were prolonged in PHPT patients. Also, we found that both intra-atrial EMD and inter-atrial EMD were significantly correlated with calcium and PTH levels.

As is known, PHPT is an endocrinological disease that is typically characterized by high or non-suppressed parathyroid hormone levels (PTH) together with elevated serum calcium levels [1]. As far as we know, in the literature there are no ECG and echocardiography studies conducted to assess atrial arrhythmia risk in PHPT patients. Although hypercalcaemia is well known to cause cardiac conduction disturbances and arrhythmias, surprisingly, follow-up studies of this disease's long-term cardiovascular results have not been conducted. Due to the physiological effects of both parathyroid hormone (PTH) and calcium on the cardiomyocyte, cardiac conduction system, and pancreatic beta cells, disorders such as hypertension, arrhythmias, left ventricular hypertrophy, heart failure, glucose metabolism disorder, and metabolic syndrome can be seen throughout the disease [9]. Furthermore, studies investigating the effects of PHPT on the cardiovascular system have shown impairment in endothelial and vascular functions [10]. In addition to all these effects, increased sympathetic activity and activation of the renin-angiotensin and aldosterone system (RAS) due to increased catecholamines have been shown in PHPT [11, 12].

Furthermore, recent studies have shown impairment in LA functions of PHPT patients [13]. These undesirable effects that can be seen in PHPT are also known as risk factors for AF development [4]. The studies searching for PTH and calcium effects on the heart have shown that both cause changes in both endothelial cells and myocardial cells. PTH may have such effects on calcium; it may also be seen in connection with its effects on the cells directly [14, 15]. Hypercalcaemia poses a risk for cardiac arrhythmia regardless of whether it occurs due to

PHPT or other reasons [16, 17]. Although there are concerns over the development of more ventricular arrhythmia in PHPT, atrial arrhythmia may also be observed in the course of the disease.

Non-invasive measurement of atrial EMD by TDI has been found to be successful in evaluating the risk of AF as an alternative to invasive electrophysiological measurements [5]. Cui QQ et al. showed that the atrial conduction delay measured by TDI was significantly longer in patients with paroxysmal AF compared to the control group [18]. Roshanalli et al. showed that the atrial electromechanical interval is a predictor of AF developing after coronary artery bypass grafting, and preoperative administration of amiodarone to patients with a longer atrial electromechanical interval reduces the incidence of postoperative AF [19]. Previous studies have shown that atrial EMD is prolonged in many clinical disorders such as mitral stenosis, diabetes mellitus, hypertension, psoriasis, and inflammatory bowel disease [20–24]. Also, the incidence of AF in these diseases has increased significantly compared to the normal population. In conclusion, atrial EMD is prolonged in paroxysmal AF and is considered a predictor of new-onset AF [25]. Our study showed that intra-atrial and inter-atrial EMD, a technique that predicts the risk of future AF development, was significantly longer in patients with PHPT compared to controls.

We also found a significant correlation between both inter-atrial EMD and intra-atrial EMD and calcium. In previous studies, the increase in calcium release from the sarcoplasmic reticulum in atrial myocytes was related to AF development [26, 27]. Although hypercalcaemia is well known to cause cardiac conduction disturbances and arrhythmias, clinical observations of conduction disturbances caused by hypercalcaemia are surprisingly rare. Case reports have shown various conduction disorders such as atrioventricular nodal conduction defects, sinus node disease, and atrial fibrillation, depending on the severity of hypercalcaemia in patients with PHPT; the reason for the prevalence of these disorders is unknown [28]. It is known that cardiac relaxation is impaired in individuals with hypercalcaemia as a result of its deleterious effects on the myocardium through the excessive increase of intracellular calcium or calcium accumulation in the myocardium [29]. Also, Curione et al. showed that hypercalcaemia developed adverse effects on cardiac electrical stability in patients with PHPT [30]. According to our results, hypercalcaemia may cause prolongation in atrial EMD by causing involvement in atrial conduction paths in addition to myocardial involvement. Therefore, we may think that hypercalcaemia plays an essential role in the prolongation of atrial EMD. This suggests that the

increase in calcium levels in PHPT patients may be determinant for the possible development of AF.

Another significant result of our study is that we found that PTH levels are associated with atrial EMD. PTH is vital for calcium haemostasis. However, PTH itself is now known to cause hypertrophy of cardiac myocytes and vascular smooth muscle even without hypercalcaemia. Moreover, parathyroid hormone accelerates the heart rate, an effect mediated by PTH's direct effect on the sinus node and conduction system. PTH also exerts inotropic effects, possibly due to increased coronary blood flow due to the vasodilatory effect of PTH on the coronary circulation [31]. Furthermore, biochemical blood measurements have revealed high cytokine levels in patients with elevated PTH levels [32]. This suggests that there is also an inflammatory process in PHPT patients. Because of all these effects, the possibility of developing arrhythmia secondarily to PTH increase may scale up.

Furthermore, serum PHT levels have been associated with AF in recent studies [33–36]. Rienstra et al. have found that PTH levels were significantly higher in patients who develop atrial fibrillation [35]. Lee et al. showed in their public-based study that the increase in PTH levels increased AF incidence [36]. In the study conducted by Pepe and Cipriani et al., more frequent atrial extrasystole in 24-hour ECG monitoring of PHPT patients was determined. Such arrhythmias were shown to be reduced with a decrease in post-parathyroidectomy PTH levels [37]. The relevant effects of PTH consequently lead to the occurrence of electrical and structural remodelling in myocardial cells. These effects cause hypertrophy, fibrosis, and functional disorders in the cardiovascular structures in time and are suggested to have facilitated atrial arrhythmia. Therefore, we can think that PTH plays a vital role in prolonging atrial EMD, a well-known AF predictor. This suggests that the increase in PTH levels in PHPT patients may determine the possible development of AF.

Although our study is not a follow-up study, we have observed that intra-atrial and inter-atrial EMD, a technique that predicts cardiac arrhythmias, was significantly longer in patients with PHPT. It was also found that there is a significant correlation between both inter-atrial EMD and intra-atrial EMD and calcium and PTH levels. In other words, both high PTH and high calcium levels seem to have the potential to cause arrhythmogenic effects. When our outcomes are considered with the literature, it suggests that PHPT patients are at risk for atrial fibrillation. As the European Society of Cardiology emphasized in the latest AF guidelines [38], it is very important to identify and manage risk factors and comorbidities that predispose to AF prior to the development of atrial remodelling and fibrosis. Identifying individuals, e.g. with PHPT, at

higher risk of developing AF in the community could facilitate early AF detection. Thus, we think the results of this study are clinically important.

This study has the following limitations: it is hard to estimate how long the participants have been exposed to calcium and PTH. Furthermore, as the number of participants is low, it is impossible to determine the PTH cut-off value concerning 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 hypercalcaemia. We looked at atrial EMD, a useful marker for AF development, but the development of AF has not been directly investigated. Long-term follow-up is required to identify cases that will cause AF.

Author's contribution

S.K and Y.Y devised the project, the main conceptual ideas, and collected the data. All authors worked on the literature review and discussion. S.K and D.E wrote the manuscript.

Conflicts of interest

The authors reported no potential conflict of interest.

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Figure 1. Change PA lateral–PA tricuspid, PA septal–PA tricuspid, PA lateral–PA septal between study groups. PHPT — primary hyperparathyroidism

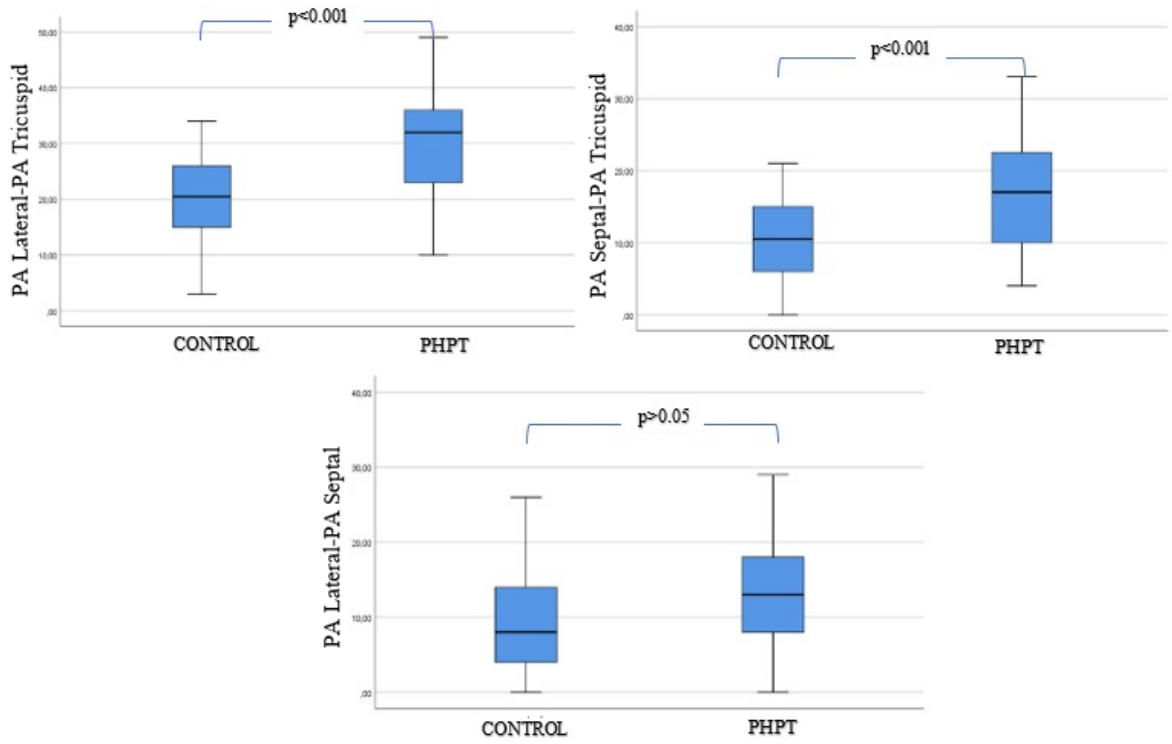

Figure 1: Change PA Lateral-PA Tricuspid, PA Septal-PA Tricuspid, PA Lateral-PA Septal between study groups

Figure 2.A. Correlation between PA lateral and calcium count; **B.** Correlation between PA septum and calcium count; C. Correlation between PA lateral–PA tricuspid and calcium count; **D.** Correlation between PA septal–PA tricuspid and calcium count

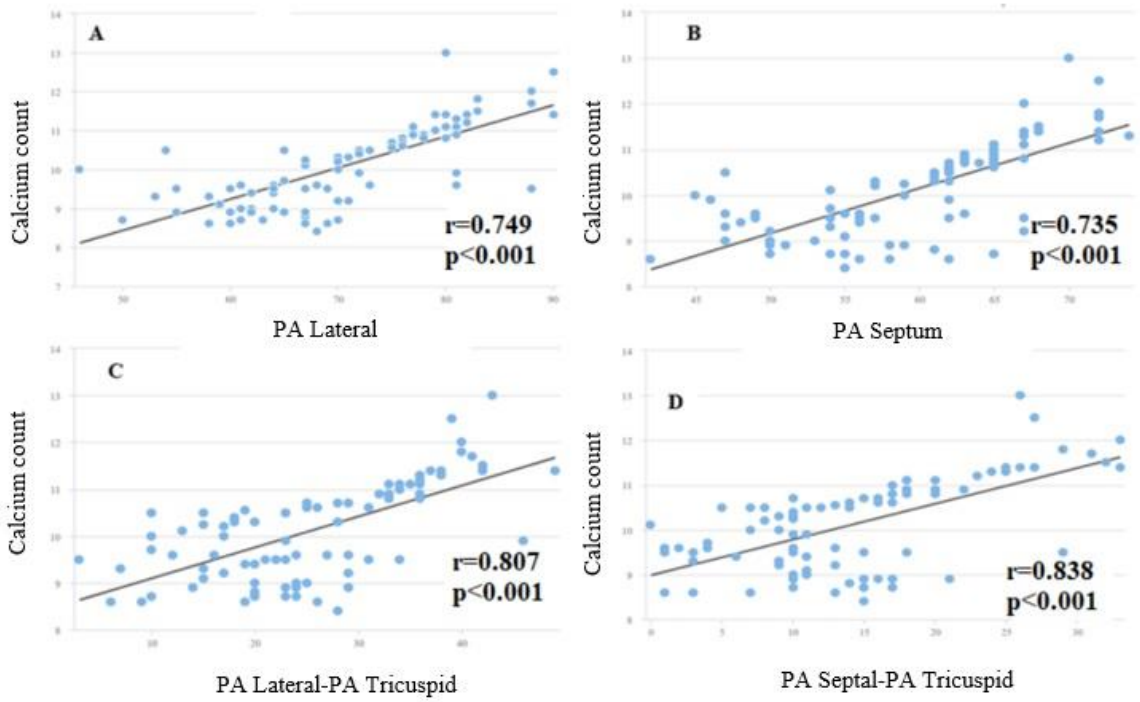

Figure 2. (**A**) Correlation between PA Lateral and calcium count. (**B**) Correlation between PA Septum and calcium count. (**C**) Correlation between PA Lateral-PA Tricuspid and calcium count. (**D**) Correlation between PA Septal-PA Tricuspid and calcium count.

Figure 3.A. Correlation between PA lateral and parathormone (PTH) level; **B.** Correlation between PA septum and PTH level; **C.** Correlation between PA lateral–PA tricuspid and PTH level; **D.** Correlation between PA septal–PA tricuspid and PTH level

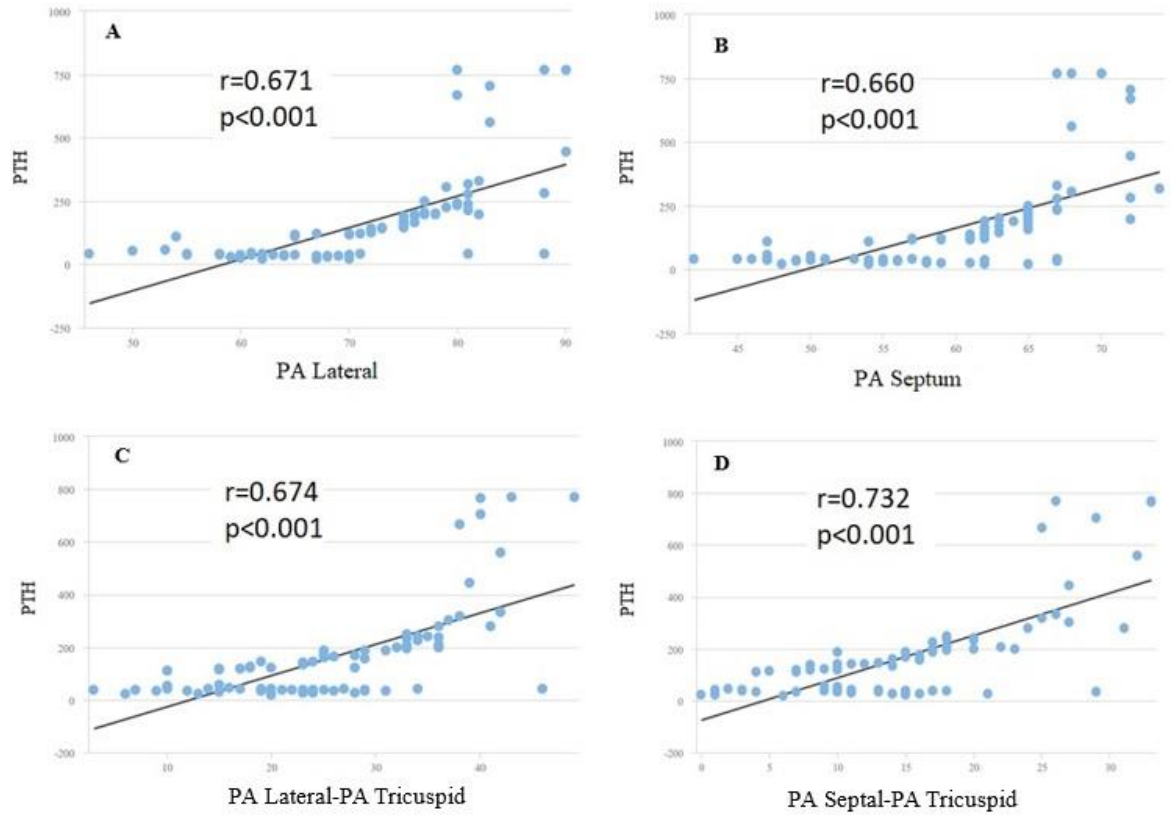

Figure 3. (**A**) Correlation between PA Lateral and PTH level. (**B**) Correlation between PA Septum and PTH level. (**C**) Correlation between PA Lateral-PA Tricuspid and PTH level. (**D**) Correlation between PA Septal-PA Tricuspid and PTH level.

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

Variables	**Control group (n = 38)**	**PHPT (n = 50)**	**p value**
Age (years)	56.9 (49-68)	56.8 (49-66)	0.990
Male/female	3/35	5/45	0.734
HT	16 (42%)	22 44%)	0.859
DM	3 (7.8%)	5 (10%)	0.734
Smoking	1 (2.6%)	2 (4%)	0.726
Hyperlipidemia	8 (21%)	10 (20%)	0.903

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. PHPT — primary hyperparathyroidism; DM — diabetes mellitus; HT — arterial hypertension

Table 2. Echocardiography characteristics of the study population

Variables	Control group (n = 38)	PHPT (n = 50)	p value
LA diameter [cm]	3.37 (3.1–3.6)	3.46 (3.2–3.7)	0.241
LA area [cm^2]	21.2 ± 2.1	22 ± 2.1	0.095
LVDD [cm]	4.71 ± 0.31	4.73 ± 0.45	0.816
LVESD [cm]	3.05 ± 0.35	2.99 ± 0.37	0.405
IVSD [cm]	1.06 (0.9–1.1)	1.08 (0.9–1.2)	0.584
PWD [cm]	1.03 ± 0.07	1.07 ± 0.14	0.192
LVEF (%)	66.89 ± 4.07	65.17 ± 4.32	0.061
PA lateral [ms]	64.13 ± 8.03	76.62 ± 6.78	< **0.001**
PA septum [ms]	53.97 ± 5.98	64.13 ± 4.87	< **0.001**
PA tricuspid [ms]	43.55 ± 7.38	47.09 ± 6.60	< **0.001**
PA lateral–PA tricuspid (inter-atrial delay)	20.57 ± 8.63	29.52 ± 9.12	< **0.001**
Pa septal–PA tricuspid (intra-atrial delay)	10.42 ± 6.27	17.03 ± 7.78	< **0.001**
PA lateral–PA septal (left-atrial delay)	10.15 ± 8.05	12.49 ± 7.74	0.171
Mitral E velocity	77.2 ± 11.2	73.3 ± 12.2	0.121
Mitral A velocity	59.8 ± 15.6	63.6 ± 9.9	0.167
DT [ms]	166.47 ± 24.38	173.56 ± 36.58	0.303
IVRT [ms]	86.05 ± 10.39	100.15 ± 9.93	< **0.001**
(S') [cm/s]	10.89 ± 3.02	10.86 ± 2.40	0.956
(E') [cm/s]	13.52 ± 3.20	12.37 ± 2.68	0.068
(A') [cm/s]	9.78 ± 2.76	10.62 ± 2.09	0.107

PHPT — primary hyperparathyroidism; LA — left atrium; LVDD — LV end-diastolic dimension; LVSD — LV end-systolic dimension; IVSD — interventricular septum thickness; PWD — posterior wall thickness; LVEF — LV ejection fraction; DT — deceleration time; IVRT — isovolumic relaxation time. Inter-atrial delay — PA lateral–PA tricuspid; Intra-atrial delay — PA septum–PA tricuspid; Left-atrial delay — PA lateral–PA septum; S' — systolic velocity from the mitral annulus; E' — early diastolic velocity from the mitral annulus; A' — late diastolic velocity from the mitral annulus

Table 3. Comparison of baseline laboratory measurements among the study groups

Variables	Control group (n = 38)	PHPT (n = 50)	p value
BMI	27.57 ± 1.82	27.35 ± 2.11	0.619
Systolic blood pressure [mmHg]	119.52 ± 10.53	121.01 ± 11.69	0.536
Diastolic blood pressure [mmHg]	73.47 ± 7.30	74.01 ± 6.43	0.710
Glucose [mg/dL]	92.71 ± 14.01	97.28 ± 15.70	0.161
Creatinine [mg/dL]	0.84 ± 0.20	0.76 ± 0.22	0.074
AST [U/L]	19.31 ± 6.12	19.60 ± 7.05	0.843
ALT [U/L]	18.39 ± 7.12	19.70 ± 9.82	0.491
Albumin [g/L]	3.97 ± 0.52	4.11 ± 0.28	0.214
Calcium count [mg/dL]	9.16 (8.7–9.5)	10.86 (10.5–11.2)	**< 0.001**
Phosphorus [mg/dL]	3.72 (3.5–4.0)	2.62 (2.3–2.9)	**< 0.001**
Vitamin D	20.97 ± 6.06	18.71 ± 7.57	0.135
PTH, [ug/L]	35.6 (31.5–41.0)	251.8 (139.7–255.5)	**< 0.001**
WBC [10^3/uL]	7.68 ± 1.44	7.53 ± 1.69	0.653
Haemoglobin [g/L]	14.03 ± 1.56	13.90 ± 1.20	0.639
Platelet [/mm^3]	265.97 ± 69.38	256.56 ± 68.86	0.528

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. PHPT — primary hyperparathyroidism; BMI — body mass index; PTH — parathyroid hormone; WBC — white blood cell