Atrial Electromechanical Delay Is Impaired in Patients with Primary Hyperparathyroidism

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Abstract

Aim: 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. 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 PHPT group compared to control group ($p<0.001$, for all). Also, inter-atrial and intra-atrial EMD were higher in PHPT group compared to control group ($p<0.001$, for all). In correlation analysis, calcium was well associated with PA lateral ($r=0.748$, $p<0.001$), PA septum ($r = 0.720$, $p <0.001$), inter-atrial EMD ($r = 0.670$, $p <0.001$) and intra-atrial EMD ($r = 0.616$, $p <0.001$). There was the same correlation relationship 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 to determine the risk of development of AF in PHPT

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Conclusions: Atrial EMD parameters were prolonged in PHPT. The measurement of atrial EMD parameters might be used to determine the risk of development of AF 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 has been shown to be associated with increased cardiovascular morbidity and mortality (**2**).

Atrial fibrillation (AF) is an important heart rhythm disorder common in clinical practice, which causes hemodynamic disorders, frequent hospitalizations, and thromboembolic events, and 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 important 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. As an alternative to invasive electrophysiological measurements, it may be measured noninvasively by Tissue Doppler Imaging (TDI) **(5**). The prolongation of intra- and inter-atrial conduction time, called atrial electromechanical delay (EMD), is associated with the frequency and sensitivity of atrial fibrillation **(6).**

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

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.

In addition to a detailed medical history from all patients, physical examination, 12-lead electrocardiography, complete blood count and serum biochemistry test were performed. The presence of classical cardiovascular risk factors, including hypertension, diabetes mellitus and hyperlipidemia, was assessed. Detailed transthoracic echocardiographic examination was performed on all patients.

Patients with a history of ischemic heart disease, 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 tumor syndrome, renal failure, and serious comorbidities were excluded from the study.

There was no significant difference between the patients and the control group in cardiovascular risk factors such as age, gender, hypertension frequency, diabetes mellitus, and hyperlipidemia.

Type 2 diabetes mellitus (T2DM), hypertension and Hyperlipidemia were defined as previously described **(7).**

Echocardiography

Conventional echocardiography was performed with 2-dimensional, M-mode, pulsed wave, continuous, color Doppler and tissue Doppler imaging (TDI) using 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**). Left ventricular (LV) diameters and wall thickness were measured from the para- sternal views by M-mode echocardiography. The Simpson's method was used for the calculation of 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.

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 opti mal 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 4-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 the spectral display of myocardial velocities. 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). All values were averaged over 3 consecutive beats. Atrial EMD was measured from the lateral mitral annulus and called 'PA lateral', from the septal mitral annulus, called 'PA septal', and from the right ventricle tricuspid annulus, 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 analyzes 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 Kolmogorov–Smirnov test. 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. The $\chi 2$ test was used for univariate analysis of the categorical variables. The Variables were given as means ± SD; categorical variables were defined as percentages. Median and interquartile range

were given when the variable did not follow normal distribution. Correlation analyses were performed using Pearson's coefficient of correlation and Spearman coefficient of correlation. A probability value of p <0.05 was considered significant, and 2-tailed p values were used for all statistics.

Results

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

Echocardiographic and atrial electromechanical time parameters are shown in **table 2.** LV systolic and diastolic diameters, left atrial diameter, interventricular septum, posterior wall thickness, and LV ejection fraction were similar in 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<0.01).

Atrial EMD parameters (PA lateral, PA septum, PA tricuspid) significantly increased in PHPT group compared to 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<0.01, p<0.01, p<0.01, respectively). Also, inter-atrial and intra-atrial EMD were higher in PHPT group compared to control group (29,52±9,12 vs 20,57±8,63, 17,03±7,78 vs 10,42±6,27, p<0.01, p <0.01, respectively). Left atrial EMD was higher in PHPT group but it did not reach to significance (12,49±7,74 vs 10,15±8,05, p =0.171) (**figure 1**).

Biochemical parameters are shown in **table 3** . Serum phosphorus were significantly lower in PHPT compared to control group (median 3.72, interquartile range 3.5 to 4.0 vs median 2.62, interquartile range 2.3 to 2.9, p<0.01). On the other hand, calcium and parathyroid hormone were higher in PHPT group compared to 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<0.01, p<0.01, respectively). Other blood parameters were similar between the two groups **(table 3**).

In correlation analysis, calcium was well associated with PA lateral (r=0.748, p<0.001) PA septum (r = 0.720, p <0.001), inter-atrial EMD (r = 0.670, p <0.001) and intra-atrial EMD (r = 0.616, p <0.001) (**figure 2**).

There was the same correlation relationship 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) (**figure 3**).

DISCUSSION

This is the first study to show that both intra-atrial and inter-atrial conduction times were prolonged in PHPT patients. In addition, 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 high serum calcium levels **(1).** As far as we know, there are no ECG and echocardiography studies conducted to assess atrial arrhythmia risk in PHPT patients in literature. Although hypercalcemia is well known to cause cardiac conduction disturbances and arrhythmias; surprisingly, follow-up studies of long-term cardiovascular results of this disease 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 course of 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, increase in 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 known as risk factors for the development of AF**(4)** . The studies searching the effects of PTH and calcium on the heart have shown that both of them 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**). Hypercalcemia poses a risk for cardiac arrhythmia without regarding whether it occurs due to PHPT or other reasons of hypercalcemia (**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 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).** In addition, it has been shown in previous studies that atrial EMD is prolonged in many clinical disorders such as mitral stenosis, diabetes mellitus, hypertension, psoriasis, and Inflammatory Bowel Disease**(20-24**). In addition, 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**). In our study, we 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 found to be related to the development of AF **(26, 27**). Although hypercalcemia is well known to cause cardiac conduction disturbances and arrhythmias, clinical observations of conduction disturbances caused by hypercalcemia 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 hypercalcemia in patients with PHPT, but the prevalence of these disorders is unknown (**28**). It is known that cardiac relaxation is impaired in individuals with hypercalcemia as a result of its deleterious effects on the myocardium through excessive increase of intracellular calcium or calcium accumulation in the myocardium**(29)** . In addition to myocardial involvement, hypercalcemia may also cause involvement in atrial conduction paths, leading to prolongation in Atrial EMD. In addition, Curione M et al. showed that hypercalcemia developed adverse effects on cardiac electrical stability in patients with PHPT **(30).** Therefore, we can think that hypercalcemia plays an important 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 important result of our study is that we found that PTH levels are associated with atrial EMD. PTH is vital for calcium hemostasis. However, PTH itself is now known to cause hypertrophy of cardiac myocytes and vascular smooth muscle even without hypercalcemia. Moreover, parathyroid hormone accelerates heart rate, an effect mediated by PTH's direct effect on the sinus node and conduction system. PTH also exerts inotropic effects, possibly as a result of increased coronary blood flow due to the vasodilatory effect of PTH on the coronary circulation **(31).** Furthermore, it has been shown that blood biochemical measurements have revealed high cytokine levels in patients with high PTH level **(32).** This suggests that there is also an inflammatory process in PHPT patients. Because of all these effects, the possibility of developing arrhythmia secondary to PTH increase may scale up. In addition, serum PHT levels have been shown to be associated with AF in recent studies (**33-36**). Rienstra M 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 the incidence of AF (**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 and such arrhythmias were shown to be reduced with decrease in post- Parathyroidectomy PTH levels (**37).** The relevant effects of PTH consequently lead to the occurrence of electrical and structural remodeling in myocardial cells. All of these effects cause hypertrophy, fibrosis and functional disorders in the cardiovascular

structures in time and are suggested to have facilitated the occurrence of atrial arrhythmia. Therefore, we can think that PTH plays an important role in the prolongation of atrial EMD, a well-known predictor of AF. This suggests that the increase in PTH levels PHPT patients may be determinant for the possible development of AF.

Although our study is not a follow-up study, we have observed that intra-atrial and inter-atrial EMD, which is a technique that predicts the 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 individually the potential to cause arrhythmogenic effects. When our outcomes are considered with literature, it is suggested that PHPT patients are at risk in terms of atrial fibrillation.

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 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 looked at atrial EMD, which is a good 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, Y.Y, devised the project, the main conceptual ideas, and collected the data.

All authors worked on literature review, and discussion. S.K and D.E wrote the manuscript.

Conflicts of interest

No potential conflict of interest was reported by the authors.

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Figure Legent

Figure 1. Change PA lateral-PA Triküspit, PA Septal-PA triküspit, 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 Triküspit and calcium count. (D) Correlation between PA Septal -PA Triküspit and calcium count

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

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TABLES

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
Smoke	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. DM: Diabetes Mellitus, HT: 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
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	**p<0.001**
PA Septum, ms	53.97±5.98	64.13±4.87	**p<0.001**
PA Trikuspit, ms	43.55±7.38	47.09±6.60	**p<0.001**
PA Lateral-PA Trikuspit (Inter-atrial delay)	20.57±8.63	29.52±9.12	**p<0.001**
Pa Septal – PA Trikuspit (Intra-atrial delay)	10.42±6.27	17.03±7.78	**p<0.001**
PA Lateral- PA Septal (Left-atrial delay)	10.15±8.05	12.49±7.74	0.171
Mitral E, cm/S	7.72±1.12	7.33±1.22	0.121
Mitral A, cm/S	5.98±1.56	6.36±0.99	0.167
DT,ms	166.47±24.38	173.56±36.58	0.303
IVRT,ms	86.05±10.39	100.15±9.93	**p<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

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, mm Hg	119.52±10.53	121.01±11.69	0.536
Diastolic blood pressure, mm Hg	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 (mg/dl)	9.16 (8.7-9.5)	10.86 (10.5-11.2)	**p<0.001**
Phosphorus (mg/dl)	3.72 (3.5-4.0)	2.62 (2.3-2.9)	**p<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)	**p<0.001**
WBC (10^3/uL)	7.68±1.44	7.53±1.69	0.653
Hemoglobin (g/l)	14.03±1.56	13.90±1.20	0.639
Platelet (/mm3)	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, BMI; Body Mass Index, PTH: Parathyroid Hormone, WBC: White Blood Cell.

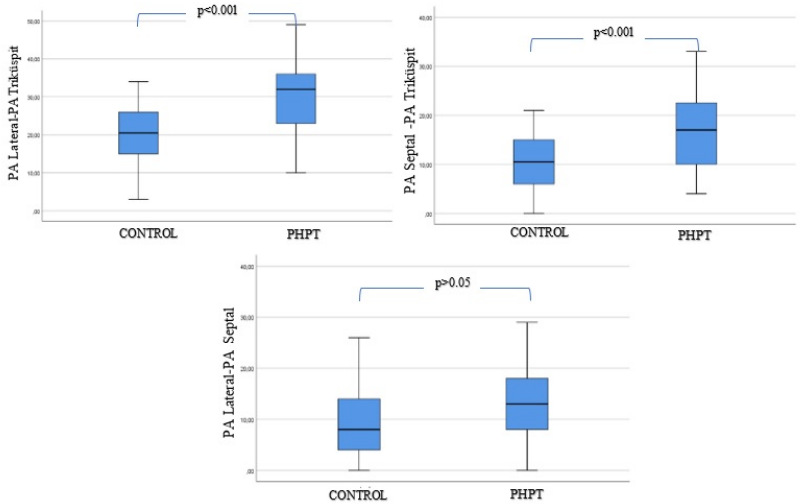

Figure 1: Change PA Lateral-PA Triküspit, PA Septal-PA Triküspit, PA Lateral-PA Septal between study groups

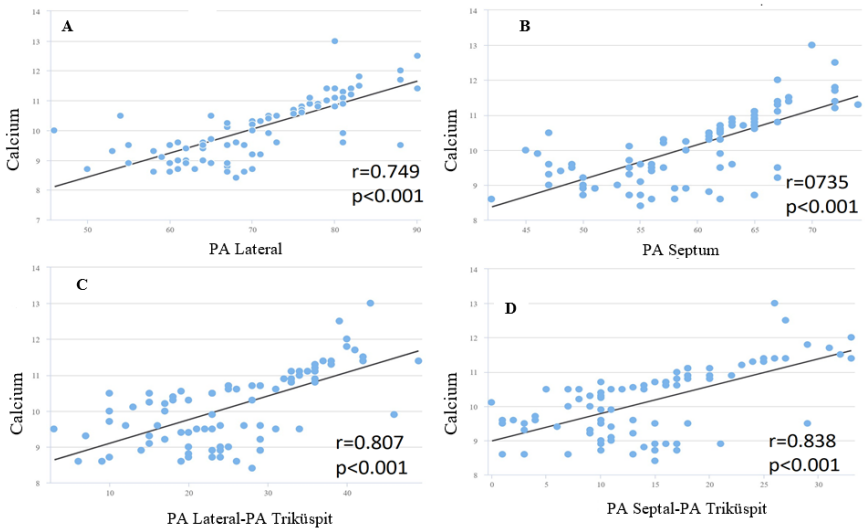

Figure 2. (**A**) Correlation between PA Lateral and calcium count. (**B**) Correlation between PA Septum and calcium count. (**C**) Correlation between PA Lateral-PA Triküspit and calcium count. (**D**) Correlation between PA Septal -PA Triküspit and calcium count

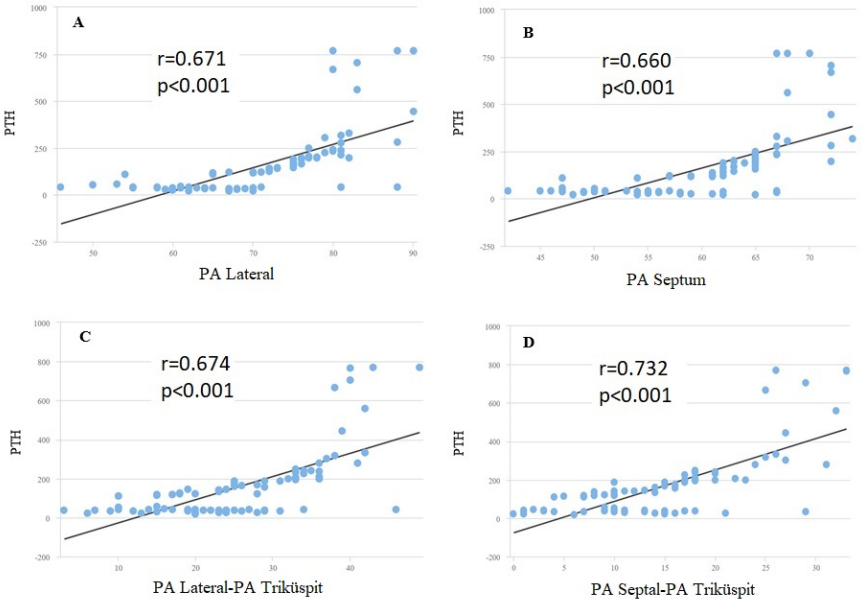

Figure 3. Correlation between PA Lateral and PTH level. (**A**) Correlation between PA-Septum and PTH level. (**B**) Correlation between PA Lateral-PA-Triküspit and PTH level. (**C**) Correlation between PA Septal -PA-Triküspit and PTH level (**D**)