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Relationship between 25-hydroxyvitamin D Level and Idiopathic Premature ventricular Complexes

İdiyopatik Prematüre Ventriküler Atımlar ile 25-Hidroksivitamin D Düzeyi Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Introduction: Idiopathic premature ventricular contractions (PVCs) are the most prevalant ventricular arrhythmias. Vitamin Dand intact parathyroid hormone (iPTH) play role in cardiovascular system, but their affect on premature ventricular complex (PVC) triggering is still uncertain. We investigated the effect of serum 25-hydroxyvitamin D (25[OH]D) and iPTH on PVC burden in our patients.

Method: In this study, a total of 128 patients, who underwent electrocardiography (ECG), 24-hour Holter recordings and transthoracic echocardiographic examination as a study protocol were enrolled. In addition, serum 25(OH)D, iPTH levels were measured. The patients were divided into two groups as 64 of them with PVC and 64 of them as normal healthy controls.

Results: A 64 patients with frequent PVCs (median age 41 [16-84], male 33/64) and Sixty-four controls (median age 38 [19-72], male 34/64), were included in the study. Parathyroid hormone levels were higher (51.70 [18.35-139.30] vs 73.60 [40.40-139.30], p<0.001) and 25(OH)D levels were lower (27.84±6.79 vs. 17.08±6.36, p<0.001) in patients compared to controls. There were no significant differences between the study groups in terms of phosphorus and other blood chemistry parameters, whereas serum calcium levels were lower in the PVC group.

Discussion and Conclusion: High iPTH levels or lower 25-hydroxyvitamin D levels that might be implicated in the pathophysiology of PVC occurrence; even at the normally accepted reference range, may affect ventricular arrhythmias.

Keywords: hypocalcemia, premature ventricular complexes, 25-hydroxyvitamin D, intact-parathyroid hormone

ÖZ

Giriş ve Amaç: İdiyopatik erken ventriküler kasılmalar (PVC'ler) en sık görülen ventriküler aritmilerdir. D vitamini ve parathormon (PTH) kardiyovasküler sonuçlarla ilişkilendirilmiştir, ancak bunların Prematüre ventriküler kompleks (PVC) gelişimi üzerindeki etkileri hala belirsizdir. Çalışmamızda, hastalarımızda serum 25-hidroksivitamin D (25[OH]D) ve PTH'nin PVC riski üzerindeki etkisini araştırdık.

Yöntem ve Gereçler: Çalışmamıza, elektrokardiyografi (EKG), 24 saatlik Holter kaydı ve transtorasik ekokardiyografik inceleme yapılan toplam 128 hasta alındı. Ayrıca serum 25-hidroksivitamin D (25[OH]D), iPTH düzeyleri ölçüldü. Hastalar 64'ü PVC'li ve 64'ünormal sağlık kontrol grubu olmak üzere iki gruba ayrılarak değerlendirildi.

Bulgular: Çalışmaya sık PVC'si olan 64 hasta (ortanca yaş 41 [16-84], erkek 33/64) ve 64 kontrol (ortanca yaş 38 [19-72], erkek 34/64) dahil edildi. Çalışmamızın sonucunda PVC'li hastalar kontrol grubu ile karşılaştırıldığında paratiroid hormon düzeyleri daha yüksek (73.60 [40.40-139.30] 'a karşı 51.70 [18.35-139.30], p<0.001) ve 25-hidroksivitamin D düzeyleri daha düşük (17.08±6.36' a karşı 27.84±6.79, p<0.001) saptandı.. Fosfor ve diğer kan kimyası parametreleri açısından çalışma grupları arasında anlamlı fark bulunmazken, kontrol grubunda serum kalsiyum düzeyleri daha yüksek saptandı.

Tartışma ve Sonuç: PVC oluşumunun patofizyolojisinde rol oynayabilecek yüksek PTH seviyeleri veya daha düşük 25-hidroksivitamin D seviyeleri, normal olarak kabul edilen referans aralığında bile ventriküler aritmileri etkileyebilir.

Anahtar Kelimeler: hipokalsemi, prematüre ventiküler kompleksler, 25-hidroksivitamin D, intakt-paratiroid hormon

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INTRODUCTION

Premature ventricular complex (PVC); traditionally known to be associated with no serious health problems, is the most common rhythm disorder in patients without visual heart disease. However, the innocence of this condition is questioned in publications claiming that sudden death may be associated with PVC-induced arrhythmic events (1,2). Importance of arrhythmia varies according to the clinical consequences it may reveal. Left ventricular systolic dysfunction, that is called PVC-induced cardiomyopathy is a poor sequel associated with frequent PVCs (3,4).

An increased amount of evidence proposes a possible relation between calcium (Ca) homeostasis and many cardiovascular disorders. Ca, which is an important element for skeletal mineralization, is also important for the biological process, including cardiac conduction and contraction. Serum Ca level is regulated by several hormones, including intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D, which have effects on the gut, kidney, and bone. The parathyroid glands secrete PTH with a decrease in serum Ca levels. PTH stimulate the kidneys for reabsorption of secreted Ca. The increase in plasma Ca level is due to the effects of active vitamin D (vitD) on the gastrointestinal tract, bone and kidney, which is regulated by PTH, Ca and phosphate concentrations (5).

Although there are many studies reporting a causal relationship between the increase in daily PVC frequency and the development of LV systolic dysfunction, the relationship of PVCs to calcium homeostasis in individuals with normal LV geometry and systolic performance has not been sufficiently defined. The availability of treatment options, including radiofrequency catheter ablation and vitamin D replacement therapy, enabled us to investigate the relationship between increased PVC frequency and calcium homeostasis, which may be important as an early sign of overt left ventricular systolic dysfunction.

METHODS

Patient selection and study protocol

In this prospective study, a total of 128 subjects over 18 years old, who underwent electrocardiography (ECG), 24-hour Holter recordings and transthoracic echocardiographic examination as a study protocol were enrolled. Thus, a total of 64 patients with PVCs in their 24-hour Holter recordings were enrolled for analysis. In addition, a total of 64 individuals who do not have cardiovascular or any disease and do not have PVCs were included as a control group. Patients with the presence of structural heart disease including left ventricular systolic dysfunction (LV ejection fraction [EF] <50%), known coronary artery disease (previous myocardial infarction, previous coronary revascularization), any type of cardiomyopathy, valvular heart diseases (more than mild severity) and individuals with any type of ventricular tachycardias and supraventricular tachycardias in rhythm Holter recordings were excluded.

Demographic, clinic and laboratory variables of the study participants were noted. Furthermore, venous blood samples were collected from the antecubital veins of the patients without venostasis. Informed consent was obtained from all of the study subjects before enrolment. This study was conducted in line with the principles of the Declaration of Helsinki and ethical approval have been obtained from the Local Institutional Ethics Committee.

Echocardiographic examination

Transthoracic 2D echocardiographic examination was performed in the left lateral decubitus position using commercially available equipment (Philips iE33 2006 (USA). Left ventricular ejection fraction (LVEF) were measured from the apical four-chamber and two-chamber view and calculated by biplane modified Simpson's method. All echocardiographic examinations were

performed by physicians, who were blinded to the ablation outcomes.

Laboratory tests

Venous blood samples were obtained and centrifuged within 2 hours after withdrawal. Serum was stored at -80 °C. The serum 25(OH)D levels were measured with direct enzyme-linked immunosorbent assay (ImmunDiagnostiK, Bensheim, Germany), and intra-assay and inter-assay coefficient of variations (CV) were ≤3.8% and ≤4.1%, respectively. The serum levels of iPTH were measured with immunoradiometric assay Immulite 2000 (Siemens Healthcare Diagnostics Products, Erlangen, Germany). The intra- and inter-assay CV for iPTH were ≤4.2% and ≤3.5%, respectively

Statistical analysis

The Shapiro Wilk test was used to assess the normality of the distribution. Variables were noted as mean±standard deviation or median (minimum-maximum) values. To compare mean differences between groups, independent samples t test or Mann Whitney U test were used according to normality test result. Categorical variables were compared by Chi square test. To determine the association of independent risk factors with PVCs occurence, binary logistic regression analysis was performed. The SPSS 21.0 programme (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for performing statistical analysis. The level of significance was set as p=0.05.

RESULTS

The baseline demographic and clinical characteristics of the study patients is demonstrated in Table 1. Sixty-four controls (median age 38 [19-72], male 34/64) and 64 patients with frequent PVCs (median age 41 [16-84] with 33 of 64 male) were included in the study. There were no significant difference between groups with regard to basal demographic characteristics.

Major cardiovascular risk factors were not significantly different between study groups. While 5/64 of the controls versus 7/64 of the patients (8% vs. 11 %, p = 0.544) were hypertensive, hyperlipidemia was detected in 2 vs 5 (3 % vs 8 %, p = 0.440). Four patients in each group (6 %, p=1.00) were diabetic. Tobacco use was high in both groups with 22 vs. 25 patients in controls and patients, respectively (35 % vs. 39 %, p = 0.629). Controls had a BMI of 25.75±4.12 and patients had a BMI of 25.71±3.76 kg/m2 (p = 0.952). Systolic blood pressure was 130 (100-145) vs. 130 (78-149) (p=0.364), diastolic blood pressure was 80 (60-95) vs. 80 (65-99) mmHg and heart rate was 76 (62-102) vs. 75 (55-95) p = 0.119. The values were not significantly different among groups.

There were no significant difference between patients and controls with regard to blood count and blood chemistry parameters, except iPTH and 25(OH)D levels. iPTH levels were higher (73.60 [40.40-139.30] vs. 51.70 [18.35-139.30], p<0.001) and 25(OH)D was lower (17.08±6.36 vs. 27.84±6.79, p<0.001) in patients compared to controls. Calcium levels were higher (9.70 [9.10-10.30] vs. 9.40 [5.10-10.20], p=0.002) in patients compared to control groups. There were no significant difference in phosphorus or plasma creatinine levels between study groups.

The LVEF was significantly lower among patients compared to controls (57.7 ± 4.8 vs. 62.7±4.3, p<0.001), however none of the study participants demonstrated a LVEF <50%. Left atrium anterioposterior diameter was significantly higher in patients (32 [26-44] vs. 38.50 [31-46], p <0.001).

Table 1. Baseline Clinical, Laboratory, and Follow-Up Characteristics of the Study Groups.

	PVC		p
	Control group (n=64)	**PVC group (n=64)**	
Age (years)	38 (19-72)	41(16-84)	0.055[a]
Gender (F/M)	30/34	31/33	0.860[b]
BMI	25.75±4.12	25.71±3.76	0.952[c]
Heart rate (bpm)	76 (62-102)	75 (55-95)	0.119[a]
SBP (mmHg)	130 (100-145)	130 (78-149)	0.364[a]
DBP (mmHg)	80 (60-95)	80 (65-99)	0.876[a]
Risk Factors			
Hypertension, n (%)	5 (8)	7 (11)	0.544[b]
Hyperlipidemia, n (%)	2 (3)	5 (8)	0.440[d]
Diabates Mellitus, n (%)	4 (6)	4 (6)	1.00[d]
Smoking, n (%)	22 (35)	25 (39)	0.629[b]
Echocardiographic Parameters			
LVEF (%).	62.75±4.26	57.72±4.85	**<0.001[c]**
IVS (mm)	0.80 (0.50-1.20)	0.85 (0.50-1.20)	0.090
PW (mm)	0.75 (0.10-1.10)	0.82 (0.60-1.15)	0,071
LA AP diameter (mm)	32 (26-44)	38.50 (31-46)	**<0.001[a]**
Laboratory tests			
Glucose (mg/dl)	93.50 (64-110)	89 (64-143)	0.108[a]
Hemoglobin (g/dl)	14 (11-17)	14 (10-17)	0.881[a]
Serum creatinine (mg/dl)	0.79 (0.45-9.70)	0.84 (0.50-9.70)	0.251[a]
25(OH)D (ng/ml)	27.84±6.79	17.08±6.36	**<0.001[c]**
iPTH (pg/ml)	51.70 (18.35-139.30)	73.60 (40.40-139.30)	**<0.001[a]**
Calcium (mg/dl)	9.40 (5.10-10.20)	9.70 (9.10-10.30)	**0.002[a]**
Phosphorus (mg/dl)	3.79 (2.25-4.90)	3.87 (2.48-4.90)	0.871[a]

Data were presented as mean±st.deviation(min.:max.), median(min.:max.) and n(%)
a: Mann Whitney U test test,
b: Pearson chi-square test,
c: Independent samples t
BMI, Body mass index; SBP, Systolic Blood Pressure;
DBP, Diastolic Blood Pressure;
LVEF, Left Ventricular Ejection Fraction;
IVS, Inter ventricular septum; PW, Posterior Wall;
LA AP, Left Atrium anteroposterior;
iPTH, intact-parathyroid hormone.

Univariate analysis demonstrated that LVEF, 25(OH)D, calcium, and iPTH were predictors of PVC occurence. Increased calcium level predicted PVC occurence with an odds ratio of (4.93 [2.06-11.82], p<0.001), 25(OH)D levels were associated with an odds ratio for PVC occurence of 0.78 (0.7-0.86, p<0.001) and iPTH levels were associated with an odds ratio of 1.04 (1.01-1.07, p = 0.005). Higher LVEF was associated with lower rate of PVC occurence (OR: 0.82 [0.72-0.92], p <0.001) (Table 2).

Table 2. Univariate Binominal Logistic Regression Analyses Demonstrating Association of Independent Risk Factors with PVCs Occurrence.

Risk Factor	Wald	OR (95%CI)	p Value
LVEF (%)	10.15	0.82 (0.72-0.92)	**0.001**
25(OH)D (ng/ml)	25.58	0.78 (0.70-0.86)	**<0.001**
Calcium (mg/dl)	12.80	4.93 (2.06-11.82)	**<0.001**
iPTH (pg/ml)	7.79	1.04 (1.01-1.07)	**0.005**

LVEF, Left Ventricular Ejection Fraction; iPTH, intact-parathyroid hormone.

DISCUSSION

In this study, we aimed to investigate the association between PVC and calcium homeostasis parameters in subjects with normal LV ejection fraction. The core findings of the current study are: Although all were in normal range; patients with PVCs had significantly larger LA size, higher Ca and PTH levels than control group, also they had lower EF and vitD levels according to control subjects.

Vitamin D metabolites, which affect mineral homeostasis, have cardiovascular system effects in addition to their effects on the skeletal system. VitD receptors have also been demonstrated in cardiomyocytes, vascular smooth muscle cells, and endothelial cells, but our knowledge of the relationship between VitD status and cardiac arrhythmias is limited (6). Chen et al. (7) suggested that vitD deficiency was associated with inflammation and left atrial remodeling. In addition, in an animal study, it was shown that the application of active vitD to left atrium of rabbit, prolonged the duration of the action potential and affected electromechanical properties (8). The role of vitD in aritmia pathogenesis is directly by myocardial substrate modification and indirectly via calcium levels and metabolism at a cellular level (6). In a recent study, the replacement of vitamin D deficiency and correction of hypocalcemia resulted in control of sustained ventricular tachycardia and cardiomyopathy (9). By demonstrating significantly lower vitD and higher PTH levels in our patients with PVCs even in the accepted normal range; we can suggest the association of ventricular arrhythmias with calcium hemostasis. In line with previous findings further exploration of vitD deficiency as a possible causal factor for arrhythmia is needed.

It was shown in a very large survey that shortened and prolonged QT-interval durations, even within a reference range, were associated with increased mortality risk in the general population (10). Cardiac myocyte repolarization altered by shortening of the hypercalcemia-associated QT interval, which can be measured simply by ECG, is a significant risk factor for dysrhythmias (11). In addition, the decreased frequency of PVC after parathyroidectomy made us think that even the calcium levels detected at levels just above the upper limit may have a proarrhythmic role (12). In this context, QT shortening, provacated by exercise stress test, was found to be associated with an increased incidence of PVCs (13). Slight elevation of PTH, regardless of its systemic effect on serum calcium via inositol-1,4,5-triphosphate (IP3) acting on its receptors in the sarcoplasmic cell, may promote arrhythmias secondary to an increase in the amount of free calcium in the cytoplasm. (14). Further calcium release triggered by calcium-sensitive ryanodine receptors increases intracellular free calcium, affecting the cardiac action potential. Accordingly, it leads to automaticity (eg. PVCs), or re-entrant arrhythmias due to the reduction of the effective refractory period (15).

People with more frequent PVCs are usually symptomatic and may have tachycardia-related cardiomyopathy. It has been reported that

when the frequency of PVC exceeds 15-25% of the total heart rate in 24-hour Holter, it is more significantly associated with impairedleft ventricular (LV) function (4). Although the rate of patients with PVCs seen with Holter examination is as high as 40%-75%, most healthy adults have less than 100 PVCs per day. The group we should pay attention to in terms of risk is mainly (multiform) and frequent (>60/hour or >1/min) PVCs, and they constitute 1-4% of healthy individuals (16). In the analysis, which included follow- up of participants known to have previously normal ventricular function, the presence ofa high incidence of PVCs has been associated with high mortality rates in addition to an increased incidence of congestive heart failure (17). Abnormal intracellular calcium cycle due to short coupling intervals, abnormal ventricular filling during the post-PVC pause and increased oxygen consumption, may be other potential mechanisms of PVC-induced cardiomyopathy (16-19).

In our study, we found smaller LV EF, enlarged LA, and larger LV size in patients with PVC compared to the control group; which can be the evidence of a negative effect of PVCs on subclinical LV contractile performance. LA enlargement can be due to following beat after PVC that can cause LA volume overload as a result of the post extra systolic compensatory pause which has a detrimental effect on adverse atrial remodeling.

The results of this study should be interpreted in the context of some limitations. Our most important limitation is that, it does not include long-term follow-up data regarding progressive worsening of LV systolic function from subtle form to apparent heart failure due to frequent PVCs. In our observational study with a small number of patients, a true pathophysiologic causal link between Ca homeostasis and PVCs cannot be mentioned. Although we cannot exclude the relationship between subclinical atherosclerosis and PVC frequency; the possibility of ischemia as the responsible factor for the increased frequency of PVCs was reduced due to the fact that we excluded individuals with a history of coronary artery disease and diabetes, and also no difference seen between the groups in terms of common cardiovascular risk factors such as hypertension, smoking history, and dyslipidemia. This indeed represents the strength of the investigation.

In conclusion, calcium homeostasis parameters that might be implicated in the pathophysiology of PVC occurrence; even at the normally accepted reference range, may affect ventricular arrhythmias. The existence of such a relationship between PVS frequency and vitD status will have potential clinical implications. Identification of risky patients with high PVC burden by means of Holter follow-up and blood VitD levels, which are easily accessible examination methods; and then perhaps clinically useful results can be gained by vitamin D supplementation. However, larger prospective studies with long term results are needed to confirm whether VitD replacement can diminish PVC occurrence and PVC burden before making these decisions.

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