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Clinical and electrocardiographic predictors of left ventricular diastolic dysfunction in patients with idiopathic premature ventricular contractions

Onur Kaypaklı[1], Fatma Özge Salkın[2]

[1]Department of Cardiology, Hatay Mustafa Kemal University, Faculty of Medicine, Hatay, Türkiye; [2]Department of Cardiology, University of Health Sciences, Adana City Training and Research Hospital, Adana, Türkiye

ABSTRACT

Objectives: Tachycardiomyopathy is a well-known phenomenon with reduction in left ventricular (LV) systolic function. In our study, we aimed to investigate the effects of idiopathic premature ventricular contractions (PVCs) on LV diastolic function in patients with idiopathic PVCs.

Methods: We included 63 patients who are candidates to undergo radiofrequency ablation due to idiopathic PVCs (27 male, 36 female; mean age 47.9±16.6 years). Patients were classified into two groups according to the presence of LV diastolic dysfunction. The percentage of PVC burden was calculated by dividing the daily PVC burden by the total heart beat per day. Coupling interval ratio was calculated with the formula of Coupling interval ratio = (Coupling interval/sinus cycle length) 100.

Results: Age, presence of q wave in D2-D3, daily PVC burden, percentage of PVC burden, left atrial volume index, intervenricular septum thickness, and mitral E/e' ratio were significantly higher; male gender, peak E-wave velocity, lateral and septal annular e' velocity were significantly lower in patients with LV diastolic dysfunction. Daily PVC burden and percentage of PVC burden were positively correlated with mitral E/e' ratio and negatively correlated with lateral annular e' velocity. The coupling interval ratio was positively correlated with mitral E/e' ratio. Age, daily PVC burden, and percentage of PVC burden were independent predictors of increased mitral E/e' ratio. The cutoff value of the percentage of PVC burden was 15.59% for prediction of LV diastolic dysfunction (sensitivity: 88.9%, specificity: 66.7%).

Conclusions: Daily PVC burden, percentage of PVC burden, and coupling interval ratio are correlated with echocardiographic parameters of LV diastolic function.

Keywords: Premature ventricular contractions, coupling interval ratio, left ventricular diastolic function

Idiopathic premature ventricular contractions (PVCs) have been demonstrated to have detrimental effects on cardiac hemodynamics and are associated with a reduction in left ventricular (LV) function [1]. Tachycardia-induced cardiomyopathy or tachycardiomyopathy is a well-known phenomenon that describes LV systolic dysfunction due to PVCs [1]. Previously defined risk factors for LV systolic dysfunction in patients with idiopathic PVCs are high frequency of PVCs, short coupling intervals of PVCs,

Corresponding author: Onur Kaypaklı, MD.,
Phone: +90 326 229 10 00, E-mail: onurkaypakli@hotmail.com

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increased PVC QRS duration, and absence of PVC-associated symptoms such as palpitations [2-4].

Although idiopathic PVCs are usually well tolerated in patients with normal cardiac function, not only LV systolic function but also diastolic function has been adversely affected in recent studies [5-7]. These adverse effects may cause a deterioration of the left atrial (LA) structure and function, and may also trigger new-onset atrial arrhythmias such as atrial fibrillation [8]. In our study, we aimed to investigate the effects of idiopathic PVCs on LV diastolic function and predictors of LV diastolic dysfunction in patients who are candidates to undergo radiofrequency (RF) ablation due to idiopathic PVCs.

METHODS

Study Population

We included 63 patients who are candidates to undergo RF ablation with a 3D electroanatomic mapping system due to idiopathic PVCs (27 male, 36 female; mean age 47.9±16.6 years). Patients older than 18 years old with predominant PVCs exhibiting ECG characteristics suggestive of outflow tract or other typical locations for idiopathic PVCs, frequent PVCs (>10% daily PVC burden) according to 24-hour Holter ECG monitoring, patients with symptoms associated with PVCs were included in the study. In order to eliminate negative effects on LV diastolic function, patients with permanent atrial fibrillation (AF), hypertension, diabetes, renal insufficiency (serum creatinine >1.5 mg/dL), respiratory diseases (chronic obstructive pulmonary disease [COPD], chronic bronchitis, pulmonary embolism), primary pulmonary hypertension, history of coronary artery disease, isolated right heart failure, congenital heart disease, moderate and severe aortic and mitral valve disease were excluded from the study. Patients were classified into two groups according to the presence of LV diastolic dysfunction. All statistical analyses were made between the two groups. The Local Ethics Committee approved the study protocol (decision no.:06, date:12.11.2020), and each participant provided written informed consent. After assessment of detailed medical history and a complete physical examination, the baseline characteristics of patients including age, sex, family history of cardiac disease and medications were recorded for all patients. Electrocardiogram (ECG), fasting blood glucose, renal function tests were performed.

Echocardiographic Assessment

The echocardiographic assessment was performed using parasternal long and short axis, apical two and four-chamber views with a 2.5-3.5 MHz transducer (Philips HD11 ultrasound system, Bothell, USA) [9]. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and LV ejection fraction (LVEF) were assessed using Simpson's equation using the apical 4-chamber view. PW Doppler and color tissue Doppler evaluation were performed to determine LV diastolic functions. Indices of LA volumes for body

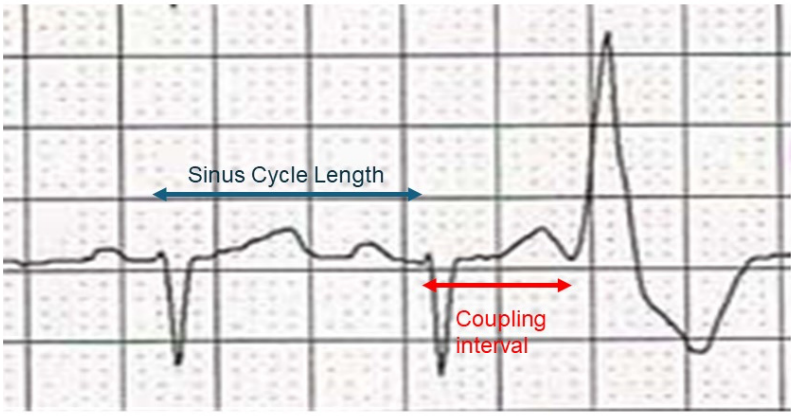

Fig. 1. Calculation of coupling interval ratio.

surface area were also calculated. All echocardiographic measurements were made during sinus rhythm and pre-PVC and post-PVC intervals were not used for measurements. LV diastolic dysfunction was defined as the presence of one of these three criterion: 1] mitral E/A ratio ≤0.8 or ≥2.2] average mitral E/e' ratio >14, 3] Septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s according to the suggestions of ASE/EACVI 2016 guidelines for evaluation of LV diastolic function by echocardiography [10].

24-Hour Holter ECG Monitoring and Electrocardiographic Assessment

24-hour rhythm holter monitorization was made with DMS 300-3A EKG Holter Recorder (DM Software NV, USA). Patients were informed about the device and then were sent to their homes. After 24 hours, the device was removed and the recordings were analyzed and concluded with the program DM Software Cardio Scan 2 premier. Holter parameters were recorded and the data of patients and controls were compared. Total heart beat per day and daily PVC burden were detected. The percentage of PVC burden was calculated by dividing the daily PVC burden by the total heartbeat per day. The QRS duration of PVC was defined as the length of time from the beginning to the end of the QRS complex in the lead with the widest QRS complex. The maximum deflection index was calculated with this formula: (interval between the onset of QRS and earliest point of maximum deflection in V5-V6) / (total QRS duration). The coupling interval of PVCs was measured from the onset of the QRS of the previous sinus beat to the onset of the PVC QRS. Coupling interval ratio was calculated with the formula of: Coupling interval ratio = (Coupling interval/sinus cycle length) × 100 (Fig. 1).

Statistical Analysis

Statistical analyses were conducted using SPSS, version 21.0, (SPSS Inc. Chicago, Illinois). Data are expressed as mean ± standart deviations for continuous variables and percentage for categorical variables. The Shapiro-Wilk test was used to test normality. The Student t-test was used for continuous variables with normal distribution and the Mann-Whitney U test was used for continuous variables with non-normal distribution. Categorical variables and frequencies were compared with the chi-square test. Statistical significance was defined as a P-value <0.05 for all comparisons. Pearson's and Spearman's correlation were used to examine the relationship between continuous variables.

The factors associated with increased mitral E/e' ratio were tested in multivariate linear logistic regression analyses. Variables with a P-value <0.05 in the

Table 1. Comparison of baseline clinical, ECG, and 24-hour holter monitoring parameters in patients with and without left ventricular diastolic dysfunction

	Patients without LVDD (n=37)	Patients with LVDD (n=26)	P value
Age (years)	42.8±16.1	54.0±15.5	**0.022**
Gender (male), n (%)	23 (62)	4 (15)	**<0.001**
Q wave in D1, n (%)	13 (35)	8 (31)	0.717
Q wave in D2-D3, n (%)	5 (13)	9 (35)	**0.047**
PVC QRS width (ms)	173.6±23,0	170.4 ±24.1	0.601
Intrinsicoid deflection time (ms)	96.2±21.4	95.5±25.5	0.993
Maximum deflection index	0.55±0.13	0.56±0.15	0.820
Coupling interval (ms)	461.8±67.8	474.7±82.5	0.523
Coupling interval ratio (%)	62.12±9.78	64.78±11.43	0.354
Daily PVC burden (beats/day)	16793±11848	27488±15490	**0.042**
Percentage of PVC burden (%)	14.9±9.6	23.9±11.3	**0.029**

Data are shown as mean±standart deviation or n (%). LVDD=left ventricular diastolic dysfunction, PVC=Premature ventricular contraction, Coupling interval ratio = (Coupling interval/sinus cycle length) x 100

univariate analysis were tested in the multivariate model. ROC analysis was made to determine the cut-off value of the coupling interval ratio for LV diastolic dysfunction.

RESULTS

Comparison of Baseline Parameters

A comparison of the baseline clinical, ECG, and 24-Hour Holter monitoring parameters is shown in Table 1. Age, Q wave in D2-D3, daily PVC burden, and percentage of PVC burden were significantly higher; male gender was significantly lower ($p<0.05$, for all) in patients with left ventricular diastolic dysfunction. LA volume index, IVS thickness, and mitral E/e' ratio were significantly higher; peak E-wave velocity, lateral and septal annular e' velocity were significantly lower ($P<0.05$, for all) in patients with left ventricular diastolic dysfunction (Table 2).

Bivariate and Multivariate Correlations

Age was positively correlated with mitral E/e' ratio (r=0.301, P=0.045), and negatively correlated with mitral E/A ratio (r=-0.383, P=0,009), lateral annular e' velocity (r=-0.504, P<0.001) and septal annular e' velocity (r=-0.457, P=0.002) in bivariate analysis (Table 3). Daily PVC burden was positively correlated with mitral E/e' ratio (r=0.545, P=0.002), and negatively correlated with lateral annular e' velocity (r=-0.401, P=0.023). The percentage of PVC burden was positively correlated with mitral E/e' ratio (r=0.489, P=0.005), and negatively correlated with lateral annular e' velocity (r=-0.402, P=0.022). The coupling interval ratio was positively correlated with the mitral E/e' ratio (r=0.371, P=0.006), A scatter plot diagram of the relationship between the coupling interval ratio and mitral E/e' ratio is shown in Fig. 2. Multivariate linear regression analysis showed that age (β=0.103, P=0.001), daily PVC burden (β=0.001, P=0.004), and percentage of PVC burden (β=-1.164, P=0.010) were

Table 2. Comparison of the baseline echocardiographic features of the study population

Variable	Patients without LVDD (n=37)	Patients with LVDD (n=26)	P value
LV end-diastolic diameter (mm)	49.2±10.2	50.2±8.8	0.686
LV end-systolic diameter (mm)	34.0±11.6	36.9±10.0	0.313
LVEF (%)	55.4±14.6	51.9±16.1	0.375
LVEDV (mL)	106.3±42.8	120.1±55.5	0.271
LVESV (mL)	54.3±33.3	58.2±36.4	0.667
Peak E-wave velocity (cm/s)	83.5±16.7	70.9±19.8	**0.010**
Peak A-wave velocity (cm/s)	67.1±15.7	78.7±30.1	0.051
MV E/A ratio	1.30±0.3	1.05±0.6	0.063
Lateral annular e' velocity(cm/s)	14.0±2.3	7.9±2.6	**<0.001**
Septal annular e' velocity(cm/s)	10.9±2.2	8.2±2.8	**<0.001**
Mitral E/e' ratio	6.8±1.8	9.5±4.1	**0.005**
IVRT (ms)	79.1±19.,1	87.2±19.6	0.104
IVS thickness (mm)	9.9±1.8	12.6±3.2	**<0.001**
PW thickness (mm)	9.4±2.2	9.7±3.2	0.708
LA end-diastolic diameter (mm)	32.1±5.1	34.4±5.7	0.129
LA volume index (mL/m²)	31.5±16.7	41.2±12.8	**0.040**

Data are shown as mean±standart deviation. LVDD=left ventricular diastolic dysfunction, LV=Left ventricle, LVEF=Left ventricle ejection fraction, LVESV=Left ventricle end-systolic volume, LVEDV=Left ventricle end-diastolic volume, IVRT=Isovolumetric relaxation time, MV=Mitral valve, LA=Left atrium, IVS=interventricular septum, PW=posterior wall

Table 3. Correlation analysis of the continuous variables associated with LV diastolic function

Variables	Mitral E/A ratio	Lateral annular e' velocity	Septal annular e' velocity	Mitral E/e' ratio	LA volume index
Age (r)	**- .383****	**- .504*****	**- .457****	**.301***	.123
Daily PVC burden (r)	.115	**- .401***	- .306	**.545****	.279
Percentage of PVC burden (r)	.065	**- .402***	- .280	**.489****	.295
PVC QRS width (r)	- .230	- .078	- .176	.090	.195
Maximum deflection index (r)	.196	.033	.097	- .093	- .184
Coupling interval (r)	- .014	- .262	- .241	.268	.113
Coupling interval ratio (r)	.266	-.087	- .163	**.371****	.002

Coupling interval ratio = (Coupling interval/sinus cycle length) × 100
*P<0.05, **P<0.01, ***P<0.001

independent predictors of increased mitral E/e' ratio (Table 4).

ROC Curve Analysis to Determine the Predictive Value of Coupling Interval Ratio for LV Diastolic Dysfunction

The cutoff value of the percentage of PVC burden obtained by ROC curve analysis was 15.59% for prediction of left ventricular diastolic dysfunction (sensitivity: 88.9%, specificity: 66.7%). The area under the curve (AUC) was 0.745 (P=0.032) (Fig. 3).

DISCUSSION

To our knowledge, this is the first study to investigate the association of ECG characteristics of PVCs and LV diastolic dysfunction. The main findings of the present study are that: [1] Daily PVC burden, percentage of PVC burden, and coupling interval ratio were correlated with echocardiographic parameters of LV diastolic function such as lateral annular e' velocity and mitral E/e' ratio in bivariate analysis. [2] PVC burden (15.59%) predicts left ventricular diastolic dys-

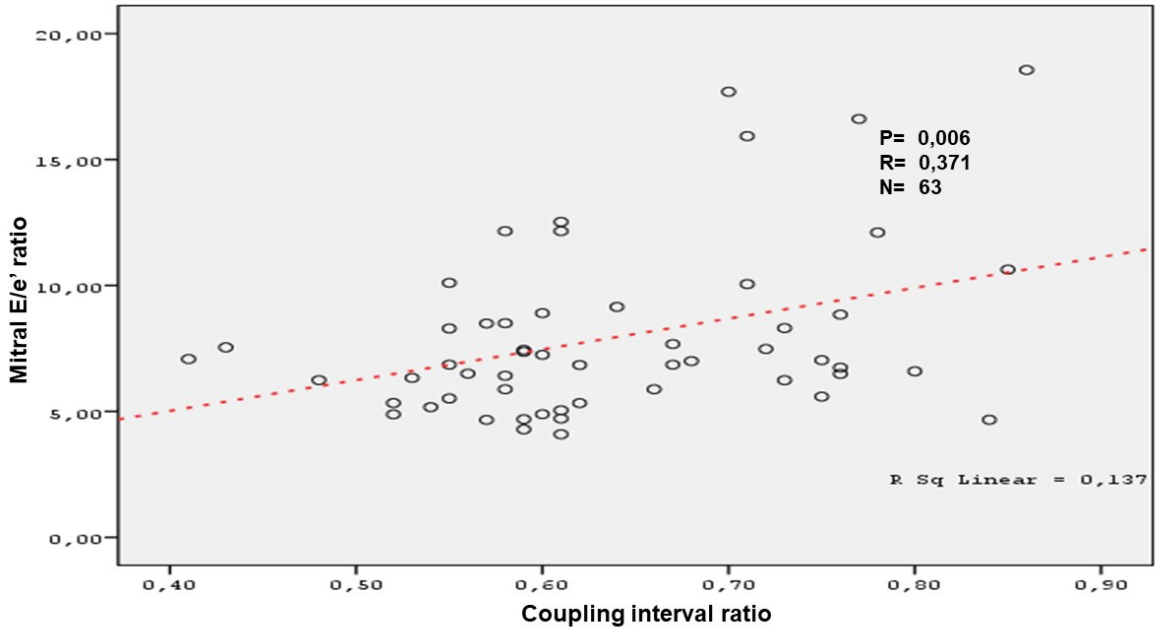

Fig. 2. Scatter plot diagram of the relationship between coupling interval ratio and mitral E/e' ratio.

Table 4. Multivariate linear regression to detect independent predictors of high mitral E/e' ratio

Variables	Standardized β-regression coefficients	P value
Age	0.103	**0.001**
Daily PVC burden	0.001	**0.004**
Percentage of PVC burden	-1.164	**0.010**
Coupling interval ratio	0.154	0.261

Coupling interval ratio: Coupling interval / Sinus Cycle Length, PVC=prematüre ventricular contraction

function with 88.9% sensitivity and 66.7% specificity.

PVCs are the most common cardiac arrhythmias. The patient population with PVCs is expanding with the widespread use of long-term ECG Holter monitoring devices. Detrimental effects of idiopathic PVCs on LV systolic function which is also known as tachycardia-induced cardiomyopathy is well documented. The factors associated with tachycardia-induced cardiomyopathy are widely investigated. Previously defined risk factors for LV systolic dysfunction in patients with idiopathic PVCs are high frequency of PVCs, short coupling intervals of PVCs, increased PVC QRS duration, and absence of PVC-associated symptoms such as palpitations [2-4]. In our study, we found a high PVC burden (15.59%) and a high coupling interval ratio to be associated with a high mitral E/e' ratio. In contrast to the fact that short coupling intervals of PVCs are a well-documented risk factor for tachycardiomyopathy, in our study, we found a long coupling interval ratio to be associated with LV diastolic dysfunction. This may be due to the negative effects of retrograde atrioventricular (AV) conduction and retrograde atrial depolarization on LA electrical and mechanical functions. Longer coupling intervals may increase the chance of retrograde AV conduction by providing enough time for the AV junction to be conductive after the refractory period of the previous sinus beat. Retrograde AV conduction and retrograde atrial

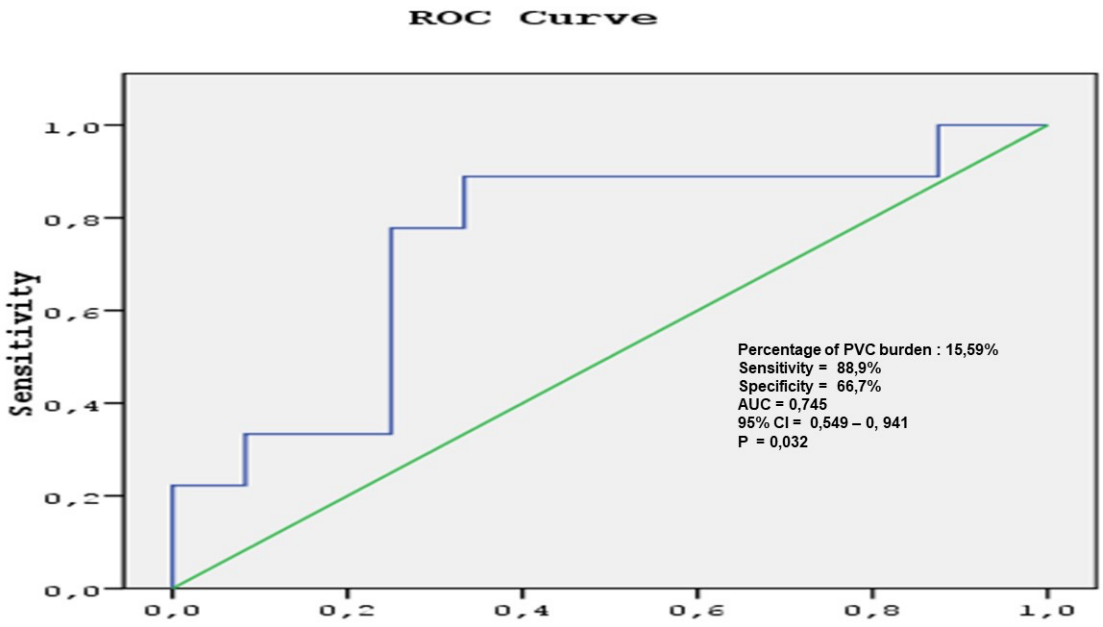

Fig. 3. ROC curve analysis to determine predictive value of percentage of PVC burden for left ventricular diastolic dysfunction. PVC=prematüre ventricular contraction.

depolarization after PVCs may cause dyssynchrony on LA contraction and may also disrupt atrioventricular synchrony if LA construction occurs when AV valves are closed. This condition further increases LV filling pressures. Similarly, in a recent study, the coupling interval ratio was found to be higher in patients who had PVC-related symptoms compared to the patients without symptoms even though PVC burden and age were similar between the two groups [11]. In this case, further studies are needed to clarify the relationship between new-onset AF and longer coupling intervals of PVCs.

Despite their benign nature, the risk of cardiovascular mortality increases with higher burdens of idiopathic PVCs [12, 13]. Interestingly, PVCs have been demonstrated to trigger atrial fibrillation when there is retrograde AV conduction [14, 15]. The study of Ofoma *et al*. [16] which demonstrates the association of PVCs with ischemic stroke also emphasizes the importance of the aforementioned mechanism of AF pathophysiology. Recent studies demonstrated that clinical diagnosis of PVC increases the risk of new-onset AF [17]. In a large population-based study, moderate-to-high burden PVCs (≥1000/day) were found to have a higher risk of developing new-onset AF than the low-burden PVCs (4.91% versus 2.73%, P<0.001) [8]. In our study, we found high PVC burden and high coupling interval ratio to be associated with high LV filling pressures. As increased LV filling pressure is associated with left atrial mechanical and electrical remodeling, AF occurrence can be thought to be the next step in this pathophysiological process.

Limitations

There were some limitations in our study. The sample size is relatively small and our results need to be confirmed in future large multi-center prospective trials. Since our study was not a follow-up study, we could not determine the change of LV systolic and diastolic function after successful PVC ablation procedure.

CONCLUSION

Daily PVC burden, percentage of PVC burden, coupling interval ratio were correlated with echocardiographic parameters of LV diastolic function such as lateral annular e' velocity and mitral E/e' ratio. We suggest that larger and long term studies are needed to determine the relationship between clinical and electrocardiographic factors and AF occurrence in patients with idiopatic PVCs.

Ethics Approval

The study was reviewed and approved by the MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (Decision number: 06 and date: 12.11.2020).

Authors' Contribution

Study Conception: OK, FÖS; Study Design: OK, FÖS; Supervision: OK, FÖS; Funding: N/A; Materials: FÖS; Data Collection and/or Processing: FÖS; Statistical Analysis and/or Data Interpretation: FÖS; Literature Review: OK; Manuscript Preparation: OK and Critical Review: FÖS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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