KLİNİK ÇALIŞMA / CLINICAL TRIAL
Ege Klin Tıp Derg 2024;62 (1): 80-86

Relationship Between Heart Rate Variability and Premature Ventricular Contractions

Kalp Hızı Değişkenliği ile Ventriküler Erken Atımlar Arasındaki İlişki

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Geliş Tarihi: 07.02.2024
Kabul Tarihi:22.03.2024

Abstract

Background: Premature ventricular contraction (PVC) is the most often type of ventricular arrhythmias. Heart rate variability (HRV) is an efficient noninvasive methods for assessing autonomic effects on the heart. This study aimed to investigate the relationship between HRV and PVC.

Methods: 80 patients with frequent PVCs and 108 patients without PVC as control group included in this study. Rhythm holter was performed in all participants. Frequent PVCs defined as more than 30 times PVCs in 1 hour, according to the Lown classification. The HRV evaluated by time domain analysis included the standard deviation of all NN intervals (SDNN), standard deviation of the average NN intervals (SDANN), the square root of the mean of the squares of successive differences between adjacent NN intervals (rMSDD), the percentage of normal RR intervals that differ by more than 50 millisecond (PNN50).

Results: Patients with frequent PVCs were older ($p<0.001$) and they had more coronary artery disease ($p<0.001$), hypertension ($p=0.026$) and diabetes mellitus ($p<0.001$). Their ejection fraction ($p=0.001$) and estimated glomerular filtration rate levels ($p=0.001$) were lower. Patients with frequent PVCs had lower levels of SDNN ($p<0.001$) and SDANN ($p<0.001$). PNN50 ($p=0.802$) and rMSDD ($p=0.572$) were not statistically different between groups.

Conclusion: Patients with frequent PVCs have been shown to have impaired HRV, indicated by low SDNN and SDANN levels associated with sympathetic overactivity. HRV measurements in patients with PVCs are a simpler and noninvasive method for the assessment of cardioneural regulation using rhythm holter monitoring.

Keywords: Heart rate variability, premature ventricular contraction, sympathetic system

Öz

Amaç: Ventriküler kaynaklı aritmilerin en sık kaşılaşılan tipi ventriküler erken atımlardır (VEA). Kalp hızı değişkenliği, kalp üzerindeki otonomik etkileri değerlendirmek için en etkili noninvaziv yöntemlerden biridir. Bu çalışmada kalp hızı değişkenliği ile ventriküler erken atımlar arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Sık VEA'sı olan 80 hasta ile VEA izlenmeyen 108 hasta çalışmaya dahil edildi. Tüm katılımcılar ritm holter ile değerlendirildi. Lown sınıflandırmasına göre ritm holterde 1 saat içinde 30'dan fazla VEA izlenmesi sık VEA olarak tanımlandı. Kalp hızı değişkenliği, tüm NN aralıklarının standart sapmasına (SDNN), ortalama NN aralıklarının standart sapmasına (SDANN), bitişik NN aralıkları arasındaki ardışık farkların karelerinin ortalamasının karekköküne (rMSDD) ve 50 milisaniyeden fazla farklılık gösteren normal RR aralıklarının yüzdesine (PNN50) göre değerlendirildi.

Bulgular: Sık VEA'sı olan hastalar daha yaşlı (p<0.001), daha fazla koroner arter hastası (p<0.001), hipertansif (p=0.026) ve diyabetik (p<0.001) idi. Ejeksiyon fraksiyonları (p=0,001) ve glomerüler filtrasyon hızları da daha düşüktü (p=0,001). Sık VEA izlenen hastalarda SDNN (p<0.001) ve SDANN (p<0.001) değerleri daha düşük saptandı. PNN50 (p=0.802) ve rMSDD (p=0.572) değerleri ise gruplar arasında anlamlı farklılık göstermiyordu.

Sonuç: Çalışmamızda sık VEA'lı hastalarda, aşırı sempatik aktiviteyle ilişkili düşük SDNN ve SDANN değerlerinin izlendiği bozulmuş kalp hızı değişkenliği saptadık. Sık VEA izlenen hastalarda ritm holter ile kalp hızı değişkenliği kardiyonöral regülasyonun değerlendirilmesinde faydalı ve invaziv olmayan bir yöntemdir.

Anahtar Kelimeler: Kalp hızı değişkenliği, sempatik sistem, ventriküler erken atım.

Introduction

Premature ventricular contraction (PVC) is the most frequent type of ventricular arrhythmias. The autonomic nervous system is an important regulatory mechanism in arrhythmias, including PVCs and ventricular tachycardia (1). The autonomic nervous system, including sympathetic and parasympathetic system, plays a prominent role in the occurrence of ventricular and atrial arrhythmias (2,3)**.**

Heart rate variability (HRV) shows the influence of the parasympathetic and sympathetic systems on the heart. The balance between parasympathetic and sympathetic activity regulates the cardiac cycle from beat to beat. Heart rate variability is a noninvasive marker for cardiac autonomic modulation. It is also used for assessment of cardiac adaptation mechanisms and cardiac autonomic status (4). HRV is calculated based on oscillations between R-R intervals of the ECG. HRV is associated with cardiovascular diseases, metabolic diseases, age, exercise, circadian rhythm and respiratory rate (5-7)**.** Also, HRV is associated with higher cardiovascular mortality (8). Rhythm holter systems is a noninvasive and basic method to assess HRV.

Whereas, the relationship between PVC and HRV in the population still remains controversial (9,10). This study aimed to investigate the relationship between HRV and PVC.

Materials and methods

80 patients with frequent PVCs and 108 patients without PVC as control group included in this study. Frequent PVCs defined as more than 30 times in 1 hour, according to the Lown classification (10). The exclusion criteria were patients aged <18 years old, incomplete 24 hour rhythm holter datas and patients with atrial fibrillation.

All participants underwent a 24 hour rhythm holter monitoring by using a validated three channel device (Borsam Holter ECG BS6930, Borsam Biomedical Instruments Co., Ltd, China) and the datas were analysed on iTengo Analysis System. All participants were suggested to maintain their regular activities during the rhythm holter examination.

The HRV evaluated by time domain analysis included the standard deviation of all NN intervals (SDNN), standard deviation of the average NN intervals (SDANN), the percentage of normal RR intervals that differ by more than 50 millisecond (PNN50) and the square root of the mean of the squares of successive differences between adjacent NN intervals (rMSDD) (11,12).

This retrospective study was approved by the local ethics committee according to the declaration of Helsinki.

Statistical Analysis

SPSS 13.0 (SPSS Inc., IBM, Chicago, IL, USA) was used for statistical analyses. Kolmogorov-Smirnov test was used to analyze the distribution of the parameters. Categorical variables were expressed as percentages and frequencies. Abnormally distributed parameters are expressed as median and percentiles (25–75) and normally distributed variables as mean±SD. Categorical variables were tested with the Chi-square or Fisher's exact test. Normally distributed continuous parameters were evaluated with 2-tailed Student's t-test and abnormally distributed parameters with Mann-Whitney U test. A p value <0.05 was accepted as statistically significant.

Results

80 patients with frequent PVCs and 108 patients without PVC were included in this study. Patients with frequent PVCs were 61±17 years of age and control group was 56.7±5.5 years of age. Patients with frequent PVCs were older compared to the control group (p<0.001). 55% of the patients with frequent PVCs and 43.5% of the control group was male. There was no significant difference in gender between the groups (p=0.079). BMI was 28.2±3.8 kg/m^2 of the patients with frequent PVCs and 26.2±5.3 kg/m^2 of the control group. The BMI was not statistically significant between groups (p=0.069).

36.3% of the participants were diabetic, 47.5% of the participants were hypertensive and 23.8% of the participants had coronary artery disease in patients with frequent PVCs. 12% of the participants were diabetic, 32.4% of the participants were hypertensive and 6.5% of the participants had coronary artery disease in control group. Diabetes mellitus (p<0.001) and HT (p=0.026) and coronary artery disease (p<0.001) rates were significantly higher in patients with frequent PVCs compared to the control group.

Ejection fraction (EF) was 60 (55-65) % in the patients with frequent PVCs and 60 (60-65) % in the control group. E ussu was 7 (6-9) in the patients with frequent PVCs and 9 (8-11) in the control group. LVEDD was 48 (46-50) mm in the patients with frequent PVCs and 46 (44-48) mm in the control group. LVESD was 32 (29-36) mm in the patients with frequent PVCs and 31 (28-34) mm in the control group. Left atrium was 36 (32-40) mm in the patients with frequent PVCs and 32 (30-36) mm in the control group. Ascending aorta was 33.1±3.2 mm in the patients with frequent PVCs and 31.4±4.6 mm in the control group. EF (p=0.001), E' (p=0.003) were significantly lower and left ventricular end diastolic diameter (LVEDD) (p<0.001), left ventricular end systolic diameter (LVESD) (p=0.047), left atrium (p=0.001), ascending aorta (p=0.004) were higher in the patients with frequent PVCs compared to the control group.

E wave (p=0.407), A wave (p=0.547), and pulmonary artery systolic pressure (PAsP) (p=0.137) were similar between groups. Baseline characteristics and echocardiographic parameters of the groups were given in Table 1.

ACE-I/ARB (p=0.014), beta-blocker (p<0.001), thiazide diuretic (p=0.026), acetylsalicylic acid (p=0.001), diltiazem (p=0.031) and statin (<0.001) usage were higher in the patients with frequent PVCs compared to the control group. Calcium channel blocker (p=0.510) usage was similar between groups.

Glucose was 108 (90-130) mg/dl in the patients with frequent PVCs and 95 (90-105) mg/dl in the control group. HbA1c was 6 (5.6-6.9) in the patients with frequent PVCs and 5.6 (5.3-6) in the control group. eGFR was 79.3±24.2 ml/min in the patients with frequent PVCs and 91.9±20.4 ml/min in the control group. Creatinine was 1.08±0.8 mg/dl in the patients with frequent PVCs and 0.89±0.32 mg/dl in the control group. Urea was 40±22.4 mg/dl in the patients with frequent PVCs and 31.3±12.5 mg/dl in the control group.

Table 1. Baseline characteristics and echocardiographic parameters of the groups

	Patients with Frequent PVCs (n=80)	**Control Group (n=108)**	**P**
Age (years)	61±17	54±19	**<0.001**
Male/female	44/36 (55%-45%)	47/61 (43.5%-56.5%)	0.079
Body mass index (kg/m^2)	28.2±3.8	26.2±5.3	0.069
Hypertension	38 (47.5%)	35 (32.4%)	**0.026**
Diabetes mellitus	29 (36.3%)	13 (12%)	**<0.001**
Coronary artery disease	19 (23.8%)	7 (6.5%)	**<0.001**
Echocardiographic parameters			
Ejection fraction (%)	60 (55-65)	60 (60-65)	**0.001**
E wave	82±26	86±21	0.407
A wave	78±22	67±22	0.547
E' wave	7 (6-9)	9 (8-11)	**0.003**
LVEDD (mm)	48 (46-50)	46 (44-48)	**<0.001**
LVESD (mm)	32 (29-36)	31 (28-34)	**0.047**
Left atrium diameter (mm)	36 (32-40)	32 (30-36)	**<0.001**
PASP (mmHg)	20 (15-30)	20 (15-20)	0.137
Ascending aorta (mm)	33.1±3.2	31.4±4.6	**0.004**

LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PASP: Pulmonary arterial systolic pressure

Total Cholesterol was 198±42mg/dL in the patients with frequent PVCs and 190±45mg/dL in the control group. LDL was 120±37mg/dL in the patients with frequent PVCs and 116±36mg/dL in the control group. HDL was 45 ±11mg/dL in the patients with frequent PVCs and 49±12mg/dL in the control group. Triglyceride was 157±63mg/dL in the patients with frequent PVCs and 122±74mg/dL in the control group. Glucose (p=0.001), HbA1c (p=0.002), creatinine (p=0.001), urea (p=0.001) and triglyceride (p=0.002) were higher and eGFR (p=0.001), HDL (p=0.024) were lower the patients with frequent PVCs compared to the control group. Hemoglobin (p=0.459), hematocrit (p=0.601), platelet (p=0.091), WBC (p=0.075), AST (p=0.629), ALT (p=0.999), total cholesterol (p=0.329) and LDL (p=0.539) were similar between groups. Medications and hematological/biochemical parameters of the groups were given in Table 2.

Table 2. Medications and hematological/biochemical parameters of the groups

	Patients with Frequent PVCs (n=80)	**Control Group (n=108)**	**P**
ACE-I/ARB	26 (32.5%)	19 (17.6%)	**0.014**
Beta-blocker	35 (43.8%)	15 (13.9%)	**<0.001**
Thiazide diuretic	22 (27.5%)	15 (13.9%)	**0.026**
Acetylsalicylic acid	28 (35%)	16 (14.8%)	**0.001**
Diltiazem	4 (5%)	0 (0%)	**0.031**
Statin	20 (25%)	5 (5.6%)	**<0.001**
Calcium Channel Blocker	17 (21.3%)	24 (22.2%)	0.510
Hematological and biochemical parameters			
Glucose (mg/dl)	108 (90-130)	95 (90-105)	**0.001**
HbA1c	6 (5.6-6.9)	5.6 (5.3-6)	**0.002**
Hemoglobin (g/dl)	13.4±2.1	13.6±1.8	0.459
Hematocrit (%)	40±5.8	40.5±5	0.601
Platelet (x1000/uL)	240±63	259±74	0.091
WBC (x1000/mm³)	7.3±2.4	6.7±2	0.075
eGFR (ml/min)	79.3±24.2	91.9±20.4	**0.001**
Creatinine (mg/dl)	1.08±0.8	0.89±0.32	**0.035**
Urea (mg/dl)	40±22.4	31.3±12.5	**0.001**
AST (U/L)	19 (17-25)	20 (20-24)	0.629
ALT (U/L)	16 (12-25)	17 (12-23)	0.999
Total Cholesterol (mg/dL)	198±42	190±45	0.329
LDL (mg/dL)	120 ±37	116±36	0.539
HDL (mg/dL)	45 ±11	49±12	**0.024**
Triglyceride (mg/dL)	157 ±63	122±74	**0.002**

ACE-I: Angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers, WBC: White blood cell count, eGFR: Estimated glomerular filtration rate, AST: Aspartate transaminase, ALT: Alanine transaminase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

SDNN was 138.1±55 ms in the patients with frequent PVCs and 176.3±50.9 ms in the control group. SDANN was 136.5 (96.5-190.3) ms in the patients with frequent PVCs and 203.5 (149.3-280) ms in the control group. PNN50 was 28.6±23.5 % in the patients with frequent PVCs and 27.8±18.6 % in the control group. rMSDD was 76 (48-137) ms in the patients with frequent PVCs and 86.5 (54-124.8) ms in the control group.

PVC was 2015 (1031-5283) in the patients with frequent PVCs and 0 (0-0) in the control group (p<0.539). SDNN (p<0.001) and SDANN (p<0.001) were significantly lower in the patients with frequent PVCs compared to the control group. PNN50 and RMSDD were similar between groups. Heart rate variability parameters of the groups were given in Table 3.

Table 3. Heart rate variability parameters of the groups

	Patients with Frequent PVCs (n=80)	Control Group (n=108)	P
SDNN (ms)	138.1±55	176.3±50.9	<**0.001**
SDANN (ms)	136.5 (96.5-190.3)	203.5 (149.3-280)	<**0.001**
PNN50 (%)	28.6±23.5	27.8±18.6	0.802
rMSDD (ms)	76 (48-137)	86.5 (54-124.8)	0.572
PVC	2015 (1031-5283)	0 (0-0)	<**0.001**

SDNN: Standard deviation of all NN intervals, SDANN: Standard deviation of the average NN intervals, PNN50: Percentage of normal RR intervals that differ by more than 50 millisecond, rMSDD: Square root of the mean of the squares of successive differences between adjacent NN intervals. PVC: Premature ventricular contraction

Discussion

PVC is the most frequent type of ventricular arrhythmias. Although PVC has a benign character, it has been found to be associated with mortality (8). The parasympathetic and sympathetic systems plays an important role in modulation of ventricular arrhythmias (13).

The main findings of the present study are heart rate variability calculated by SDNN and SDANN related with sympathic system activation were lower in patients with frequent PVC compared to the control group. Also, patients with frequent PVCs were older and they had more coronary artery disease, hypertension and diabetes mellitus. Their ejection fraction and estimated glomerular filtration rate levels were lower compared to the control group. HRV, a noninvasive and basic marker for assessing the cardiac autonomic function, describes the oscillations between R–R intervals of ECG. High levels of HRV usually indicate efficient autonomic function in a healthy individuals, while low levels of HRV often indicate an autonomic nervous system dysfunction (14). SDNN and SDANN reflect a more contribution of sympathetic activity to HRV, and lower levels of SDNN and SDANN show an increased sympathetic tone. Whereas, pNN50 and rMSSD are reliable indicators of parasympathetic tone (15-17).

Dong et al evaluated 4754 patients who received 24 hour rhythm holter for palpitation. Patients with PVC ≥1 and patients without PVC were compared. SDNN, SDANN, rMSSD and pNN50 were lower in patients with PVC ≥1 group (18). Zhang et al studied with 106 patients with frequent outflow tract PVCs and 106 healthy individuals. Patients underwent radiofrequency catheter ablation for drug resistant symptoms and intolerant caused by PVCs. These patients had either PVC burden >10% or PVC counts >10 000 beats/24 hour assessed by rhythm holter monitoring.

Significantly lower levels of SDNN and SDANN were observed in the patients with PVCs compared to the healthy individuals. However, there was no statistically significant difference in the levels of pNN50 and rMSSD between groups (19). Askin et al comprised 50 patients with occasional PVCs (5–10 PVCs/hour) and 50 patients with frequent PVCs (>10 PVCs/hour) . HRV parameters of SDANN, SDNN, RMSSD and PNN50 were similar between groups (20). Barutcu et al compared to the 43 patients with frequent PVCs and control group. Frequent PVCs are defined as occurrence at least 30 times during a 1 hour recording according to the Lown classification or at least once during a standard ECG recording. HRV parameters of SDNN, SDANN, PNN50 and RMSSD levels were similar between groups (10). In the present study, patients with PVCs had lower SDNN and SDANN indicating that enhanced sympathetic activity than patients without PVC. PNN50 and rMSSD were lower but not statistically significant between groups. The reason why Zhang et al (19) and Askin et al (20) results were insignificant may be the lower sample size.

Age was similar between groups and not related with PVCs in Askin et al's study (20). By contrast, an analysis of the ARIC study cohort demonstrated that older age associated with the presence of PVC (21,22). Similarly, patients with frequent PVCs were older in our study.

Nowadays, there is no consensus about whether the incidence of PVC is higher in women or men. Dong et al (18) demonstrated that men had a higher incidence of PVC than women. Haruta et al studied with 5685 individuals, indicated no significant difference in the incidence of PVC between the genders (23). Sirichand et al showed that the incidence of symptomatic idiopathic PVCs were higher in women (24). There was not statistically difference between the genders in the present study.

Sympathetic neural factors are important in the initiation and maintenance of a blood pressure (25). In hypertensive patients, the arrhythmogenic substrate of left ventricular hypertrophy may induce the reentry mechanism. The ventricles are sensitive higher blood pressure. Fibrosis, subendocardial ischemia and higher blood pressure stress can trigger abnormal rhythm (26). In our study, patients with frequent PVCs were more hypertensive.

An analysis using the ARIC study cohort showed that a history of coronary artery disease was associated with the presence of PVCs (21,22). The arrhythmogenic substrate of ischemic or fibrotic myocardial area may stimulate the reentry mechanism. Patients with frequent PVCs had more coronary artery disease in our study.

Agarwal et al demostrated that type 2 diabetes mellitus is related with higher prevalence of ventricular arrhythmias independent of chronic heart failure or coronary artery disease. Patients with frequent PVCs were more diabetic in our study (27).

Barutcu et al (10) found that the left ventricular EF was lower and the LVEDD, LEVESD were higher in patients with frequent VPCs compared with the control group. Left ventricular systolic dysfunction may induce sympathetic activation as a compensatory mechanism resulting in frequent PVCs.

Conclusion

Our findings support that the sympathetic overactivity indicated by lower SDNN and SDANN levels is related with frequent PVCs. HRV measurements in patients with PVCs are a simpler and noninvasive method for the assessment of cardioneural regulation using rhythm holter monitoring.

Limitations

The limitations of this study were relatively small sample size and retrospective design. Further, larger and prospective studies are warranted to support our results. Also, we did not evaluated with HRV frequency domain analysis evaluated by high frequency and low frequency power.

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