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The relationship between premature ventricular complexes and index of cardiac-electrophysiological balance

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SUMMARY

OBJECTIVE: Premature ventricular complexes are common in healthy individuals' ambulatory monitoring. The index of cardiac-electrophysiological balance may predict malignant ventricular arrhythmias. This study investigated the relation between Premature ventricular complex burden and index of cardiac-electrophysiological balance in 24-h Holter monitoring.

METHODS: A total of 257 patients who were admitted to a cardiology outpatient clinic without structural heart disease and underwent 24-h Holter monitoring were included in the study. Demographic features, laboratory parameters, and electrocardiographic and echocardiographic values of all patients were obtained from the hospital database. Patients were categorized into the following four groups according to their premature ventricular complex burden: ≤5% premature ventricular complexes as group 1, >6 and ≤10% premature ventricular complexes as group 2, >11 and ≤20% premature ventricular complexes as group 3, and >20% premature ventricular complexes as group 4. QRS, QT, and T peak to end interval were measured by resting electrocardiography. QT interval was corrected using Bazett's formula. T peak to end interval/QT, T peak to end interval/corrected QT interval, index of cardiac-electrophysiological balance, and corrected index of cardio-electrophysiological balance ratios were calculated.

RESULTS: There was no significant difference between groups regarding cardiovascular risk factors. In group 4, beta-blocker usage was significantly higher, and the serum magnesium levels were significantly lower than in other groups. There was no difference in QT duration or index of cardiac-electrophysiological balance values; however, corrected index of cardio-electrophysiological balance was significantly lower in the highest premature ventricular complex group (5.1, 5.1, 4.8, 4.7, p=0.005). In multivariate backward logistic regression analyses, it was found that lower corrected index of cardio-electrophysiological balance, lower serum magnesium levels, lower serum creatinine levels, larger left atrium size, and higher T peak to end interval were associated with higher premature ventricular complexes.

CONCLUSION: Corrected index of cardio-electrophysiological balance is a novel and noninvasive marker that can predict premature ventricular complex burden in patients with structurally normal hearts.

KEYWORDS: Premature ventricular complexes. Index of cardiac-electrophysiological balance. Electrocardiography.

INTRODUCTION

Premature ventricular complexes (PVCs) are a complex clinical entity in structurally normal hearts. Till date, many studies demonstrated different numbers of PVCs in healthy people[1-3]. Previously, the Framingham Heart Study showed that 12% of patients without coronary artery disease experienced PVCs or complex ventricular arrhythmias in 1 h of monitoring[4]. In another study, >200 PVCs per 24 h was found in 3.3% of 1273 healthy volunteers[1]. Detection of PVC burden depends mostly on the follow-up duration. Burden of PVCs of more than 10% in 24 h highly increases the risk of tachycardiomyopathy and heart failure[5].

The index of cardiac-electrophysiological balance (iCEB), which is the ratio of QT/QRS duration on the surface electrocardiography (ECG), was found to be related to Torsades de Pointes (TdP) or non-TdP-like ventricular arrhythmias in an animal model[6]. A change in cardiac-electrophysiological balance affects the heart's systolic and diastolic potentials and changes ECG parameters. Not only QT duration but also QRS duration could have an impact on ventricular arrhythmias. Therefore, iCEB could be used as a new biomarker for predicting arrhythmic potential in normal individuals.

This study aimed to determine the relationship between iCEB and PVC burden in patients with structurally normal hearts.

METHODS

This retrospective study analyzed 257 patients admitted to a cardiology outpatient clinic without structural heart disease and underwent 24-h Holter monitoring. Patients with any known genetic or structural heart disease were excluded. Patients with coronary intervention and/or coronary surgery history, valvular surgery history, ejection fraction (EF) <50%, atrial fibrillation, intracardiac

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implantable devices, thyroid abnormalities, liver or kidney diseases, active infection, presence of malignancy, psychiatric diseases, and taking anti-arrhythmic drugs were excluded from the study. The study was conducted as per the Declaration of Helsinki, and the study protocol was approved by the hospital's ethics committee.

Patients' demographic features, cardiovascular risk factors, and laboratory parameters were collected from the hospital database. Patients' medications at the time of Holter monitoring were also recorded. All patients underwent 24-h rhythm Holter monitoring. Analyses of PVCs and corrections of the automated computer system results were made by a cardiologist. The total number of PVCs was determined by the automated system. Patients were categorized into the following four groups according to their PVC burden: ≤5% PVCs as group 1, >6% and ≤10% PVCs as group 2, >11% and ≤20% PVCs as group 3, and >20% PVCs as group 4.

The iCEB was determined by resting ECG. All the measurements were performed using the MUSE software (GE HealthCare). QRS duration, QT interval, and heart rates were determined. The measurements were performed on lead II and lead V5, and then the longest QT interval was selected for analysis. QT interval was corrected using the Bazett's formula (QTc=QT/(RR1/2)). iCEB and corrected iCEB (iCEBc) were calculated by dividing QT to QRS duration for iCEB and QTc to QRS duration for iCEBc.

Statistical analysis was performed using the SPSS 24.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the distribution pattern of parameters. Continuous parameters with normal distribution were presented as the mean ± standard deviation, whereas parameters with non-normal distribution were presented as median and categorical variables were presented with numbers and percentage values. An analysis of variance test or Kruskal-Wallis tests were used to compare continuous variables according to iCEB groups. A χ^2 test was used to compare categorical variables. Multivariable logistic regression analysis was used to determine the independent parameters related to >20% PVCs. Possible confounding factors for which the unadjusted p<0.10 in univariate regression analysis (age, sex, heart rate, beta blocker usage, creatinine, potassium, calcium, magnesium, corrected iCEB, T peak to end interval, EF, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left atrial [LA] size) were identified as potential risk markers and included in multivariable logistic regression model. The effects of different variables on in-hospital mortality were assessed by Cox regression analysis. A p<0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. There was no significant difference between groups regarding cardiovascular risk factors, including diabetes, hypertension, hyperlipidemia, or smoking status. In the highest PVC group, beta-blocker usage was significantly higher (54.3%, p<0.001), and the serum magnesium levels were significantly lower (1.9 mg/dL, p=0.011) than in other groups. In echocardiographic parameters, EF was similar between groups; however, LA size was increased from group 1 to group 4.

Electrocardiographic parameters of the patients are presented in Table 2. The duration of QRS was significantly different between groups, and group 4 had the highest QRS duration (84.8±11.6, 85.2±13.5, 91.2±13, 94.1±15 ms, p<0.001). There was no difference in QT duration or iCEB values; however, iCEBc was significantly lower in the highest PVC group (5.1, 5.1, 4.8, 4.7, p=0.005) (Figure 1). Tp-e interval was increased from group 1 to group 4, but there was no difference in the Tp-e/QT and Tp-e/QTc ratios between groups.

When we made a multivariate backward logistic regression analyses with a model including age, sex, heart rate, beta blocker usage, creatinine, potassium, calcium, magnesium, iCEBc, T peak to end interval, EF, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and LA size, it was found that lower iCEBc (hazard ratio [HR] 0.552; 95% confidence interval [CI] 0.530–0.925, p=0.024), lower serum magnesium levels (HR 0.043; 95%CI 0.003–0.535, p=0.014), lower serum creatinine levels (HR 0.057; 95%CI 0.005–0.705, p=0.026), larger LA size (HR 1.143; 95%CI 1.053–1.242, p=0.001), and higher Tp-e interval (HR 1.022; 95%CI 1.005–1.040, p=0.014) were associated with higher PVCs (Table 3).

DISCUSSION

This study demonstrated that lower iCEBc, lower serum creatinine levels, lower magnesium levels, larger LA size, and higher Tp-e interval were associated with higher PVCs in patients with structurally normal hearts.

It is well known that an increase or decrease in the QT interval leads to TdP, non-TdP-related ventricular tachycardia (VT), or ventricular fibrillation (VF). However, PVCs and VT/VF can be seen in patients with even normal QT intervals. This may raise the question of whether other factors may be related to arrhythmias in these patients. We speculated that the QRS interval, which shows ventricular depolarization and is similar to conduction velocity, and the QT interval, which is similar to the ventricular refractory period, can be used to determine arrhythmia risk. Therefore, the ratio of QT/QRS, which is called iCEB, may reflect the cardiac-electrophysiological balance and related to cardiac arrhythmias.

Alteration of the cardiac muscle membrane ion current, intracellular calcium metabolism, sympathetic and parasympathetic system balance, and external factors like some drugs are responsible for PVCs in normal hearts[5-7]. In patients with long QT syndrome, it

was found that iCEB was increased compared to genotype-negative family members, while it was decreased in the Brugada syndrome group[8]. This study showed that not only QT interval but also QRS duration is important in arrhythmia risk in patients with genetic diseases. A change in the iCEB value in any direction causes changes in ventricular depolarization and repolarization duration and may

Table 1. Demographic, clinical, and laboratory characteristics of the study population.

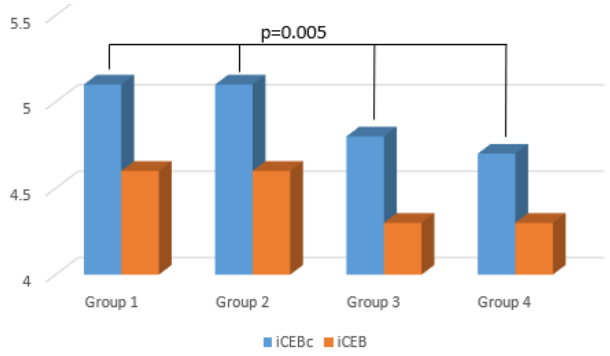
Characteristics	Group 1 (≤5% PVCs) (n=135)	Group 2 (>6% and ≤10% PVCs) (n=40)	Group 3 (>11% and ≤20% PVCs) (n=47)	Group 4 (>20% PVCs) (n=35)	p
Age (years, mean±SD)	51.3±15.9	54.9±19	56.2±15.2	56.2±15.2	0.096
Male, n (%)	61 (45.2)	24 (60)	30 (63.8)	23 (65.7)	**0.036**
SBP (mm Hg, mean±SD)	124±14.4	125.3±15.7	123±14.1	124.3±15.9	0.914
DBP (mm Hg, mean±SD)	72.6±10.4	73±8.9	70.2±9.4	71.1±10.3	0.119
Current smoker, n (%)	3 (2.2)	3 (7.5)	2 (4.3)	3 (8.6)	0.156
Hypertension, n (%)	44 (32.6)	17 (42.5)	15 (31.9)	13 (37.1)	0.661
Diabetes mellitus, n (%)	27 (20)	9 (22.5)	11 (23.4)	8 (22.9)	0.952
Hyperlipidemia, n (%)	13 (9.6)	3 (7.5)	7 (14.9)	6 (17.1)	0.419
Medication, n (%)					
ASA	38 (28.1)	11 (27.5)	20 (42.6)	16 (45.7)	0.092
ACEI/ARB	38 (28.1)	35 (87.5)	32 (68.1)	8 (23.5)	0.965
Beta blocker	71 (52.6)	49 (52.7)	38 (39.6)	19 (54.3)	**<0.001**
Calcium channel blocker	22 (16.3)	3 (7.5)	4 (8.5)	6 (17.1)	0.324
Diuretic	12 (8.9)	7 (17.5)	4 (8.5)	2 (5.7)	0.367
Hemoglobin (g/L, mean±SD)	13.8±1.5	13.9±1.5	13.7±1.6	14±1.4	0.691
WBC (10^3/μL, mean±SD)	7.9±2	7.8±1.8	7.7±1.8	8.3±3	0.553
Platelets (10^3/μL, mean±SD)	251±60.5	241±53.9	248.7±61	238.5±98.7	0.697
Creatinine (mg/dL, mean±SD)	0.8±0.2	0.87±0.2	0.87±0.18	0.8±0.17	**0.027**
GFR (mL/min, mean±SD)	95.8±17.6	90.9±20.5	91±16.2	95±15.6	0.316
Sodium (mmol/L, mean±SD)	140±2.8	140.2±2.9	139.7±2.8	140.4±2.8	0.656
Potassium (mmol/L, mean±SD)	4.5±0.4	4.6±0.3	4.6±0.4	4.4±0.3	0.051
Calcium (mg/dL, mean±SD)	9.2±0.4	9.3±0.4	9.2±0.5	9.1±0.5	0.426
Magnesium (mg/dL, mean±SD)	2±0.17	2.1±0.2	2±0.2	1.9±0.1	**0.011**
AST (U/L, mean±SD)	17.3±6.4	17.6±7.3	17.2±6.2	17.5±6.4	0.996
ALT (U/L, mean±SD)	17.7±9.6	16.1±8.5	16.1±6.3	16.4±11.4	0.653
Total cholesterol (mg/dL, mean±SD)	176.3±41.8	172±32.1	168.5±39.5	164.4±30.2	0.346
HDL-C (mg/dL, mean±SD)	47.5±15.3	47.2±14.3	48.4±12.6	44.5±10.4	0.648
LDL-C (mg/dL, mean±SD)	97±27.6	97.2±24	92.6±30	97.8±24.3	0.769
Triglyceride (mg/dL, mean±SD)	140.1±67	131.1±60.6	135±66.6	115.3±36.7	0.216
Echocardiographic features					
EF (%, mean±SD)	58.6±4.2	58±5	57.1±5.1	57.4±4.1	0.174
LVEDD (cm, mean±SD	4.8±0.5	4.8±0.6	5.1±0.6	5±0.4	**0.003**
LVESD (cm, mean±SD)	3.1±0.5	3.2±0.5	3.5±0.5	3.4±0.5	**<0.001**
LA size (cm, mean±SD)	3.5±0.5	3.6±0.6	3.7±0.5	3.9±0.6	**0.006**

ACEI: angiotensin converting enzyme inhibitor; ALT: alanine transaminase; ARB: angiotensin receptor blocker; ASA: acetyl salicylic acid; AST: aspartate transferase; DBP: diastolic blood pressure; EF: ejection fraction; GFR: glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LA: left atrium; LDL-C: low-density lipoprotein cholesterol; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PVCs: premature ventricular complexes; SBP: systolic blood pressure; SD: standard deviation; WBC: white blood cell. Bold values indicate statistical significance at the p<0.05 level.

Table 2. Electrocardiographic parameters of the groups.

Variables (mean±SD)	Group 1 (≤5% PVCs) (n=135)	Group 2 (>6% and ≤10% PVCs) (n=40)	Group 3 (>11% and ≤20% PVCs) (n=47)	Group 4 (>20% PVCs) (n=35)	p
Heart rate (bpm)	77.2±13.6	75.4±12.9	75.5±14	72.9±13.9	0.390
QRS interval (ms)	84.8±11.6	85.2±13.5	91.2±13	94.1±15	**<0.001**
QT interval (ms)	382.8±39.2	382.7±44.8	386±43	397±48.8	0.343
QTc interval (ms)	429.5±34.8	422.3±40.6	429±39	432.5±42.6	0.666
Tp-e interval (ms)	88.3±22	85.1±26.6	89.9±22.7	100±24.7	**0.032**
Tp-e/QT ratio	0.23±0.06	0.23±0.08	0.24±0.07	0.25±0.07	0.278
Tp-e/QTc ratio	0.2±0.06	0.2±0.07	0.21±0.05	0.23±0.07	0.113
iCEB (QT/QRS ratio)	4.6±.0.6	4.6±0.8	4.3±0.8	4.3±0.8	0.072
iCEBc (QTc/QRS ratio)	5.1±0.7	5.1±0.9	4.8±0.7	4.7±0.9	**0.005**

Bpm: beat per minute; iCEB: index of cardio-electrophysiological balance; iCEBc: corrected index of cardio-electrophysiological balance; ms: millisecond; PVCs: premature ventricular complexes; QTc: corrected QT interval; Tp-e: T peak to end interval. Bold values indicate statistical significance at the p<0.05 level.



iCEB: index of cardio-electrophysiological balance; iCEBc: corrected index of cardio-electrophysiological balance.

Figure 1. iCEB and iCEBc values of the groups.

Table 3. Multivariable Cox-regression analysis of risk factors for premature ventricular complexes burden.

Variables***	Hazard ratio, 95%CI	p
iCEBc	0.552 (0.530–0.925)	**0.024**
Tp-e	1.022 (1.005–1.040)	**0.014**
Creatinine	0.057 (0.005–0.705)	**0.026**
Magnesium	0.043 (0.003–0.535)	**0.014**
LA size	1.143 (1.053–1.242)	**0.001**

CI: confidence interval; iCEBc: corrected index of cardio-electrophysiological balance; LA: left atrium; Tp-e: T peak to end interval. *Model included age, sex, heart rate, beta-blocker usage, creatinine, potassium, calcium, magnesium, corrected index of cardio-electrophysiological balance, T peak to end interval, ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left atrial size. **Selection of covariates for multivariable models is explained in the Methods section. Unless otherwise indicated, hazard is interpreted as the presence (vs. absence) of each categorical variable or an increase of 1 unit of each continuous variable. Bold values indicate statistical significance at the p<0.05 level.

cause PVCs. Therefore, other than well-known ECG parameters like QT interval and Tp-e duration[9], iCEB may add more valuable information about the risk of arrhythmias.

Ventricular repolarization markers such as Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios have been evaluated in many clinical situations[10-14]. The Tp-e interval may represent the transmural distribution of repolarization, and an increased Tp-e interval is associated with malignant ventricular arrhythmias. Furthermore, the Tp-e/QT ratio is found higher in diseases with increased arrhythmogenicity, such as long QT syndrome, Brugada syndrome, short QT syndrome, or organic heart disease[15]. Zhao et al. found that the Tp-e interval and Tp-e/QT ratio were increased in polymorphic VT/VF patients with idiopathic PVCs[16]. In another study, Tp-e interval and Tp-e/QTc ratio have been associated with a high PVC number[17]. Similar to this study, in our study, the Tp-e interval was found to be higher in the highest PVC group compared to the other groups.

In the Atherosclerosis Risk in Communities (ARIC) study, a cross-sectional analysis of the 15,792 individuals, according to 2-min ECG, revealed that increasing age, male sex, lower educational attainment, and lower serum magnesium or potassium levels are directly related to PVC prevalence[18]. Similar to the ARIC study, we found lower serum magnesium and creatinine levels and a higher proportion of males in patients with higher PVCs.

In our study, QRS duration increased from the lower PVC group to the higher PVC group. Although QTc duration was similar between the groups, the ratio of QTc/QRS was lower in the highest iCEBc group. In one study, QRS duration was related to the development of PVC-induced left ventricular dysfunction[19]. In that study, patients who developed cardiomyopathy had significantly longer PVC QRS duration (159 vs. 142 ms; p<0.001) and a longer sinus QRS duration (97 vs. 89 ms; p=0.04).

Limitations

Our study has a few limitations. First, this is a single-center study involving less number of patients. Second, the patients were not followed up, and the PVC burden was determined at a single time. Third, we cannot totally exclude the presence of cardiac disease in the study group because cardiac magnetic resonance imaging was not performed.

CONCLUSION

Corrected index of cardio-electrophysiological balance is a novel, noninvasive marker that may predict PVCs in patients with structurally normal hearts. Beyond the other ECG parameters, iCEBc can be used as a definite marker of electrophysiological balance and arrhythmia risk.

AUTHORS' CONTRIBUTIONS

MKA: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **YD:** Data curation, Investigation, Software, Validation, Writing – original draft. **SY:** Formal Analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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