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Original Article

Comparison of Medical Treatments According to the Characteristics of Idiopathic Premature Ventricular Contractions: Beta-blockers or Calcium Channel Blockers?

İdiyopatik Ventriküler Erken Vuru Özelliklerine Göre Medikal Tedavilerin Karşılaştırılması: B-blokerler mi, Kalsiyum Kanal Blokerleri mi?

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ABSTRACT

Objective: Premature ventricular contractions (PVCs) are a common arrhythmic condition. The first approach in patients with symptomatic and frequent PVC is medical treatment, primarily beta-blockers (BB) or calcium channel blockers (CCB), but it is still unclear which of the two should be chosen. This study investigated which drug treatment would be beneficial according to patient and electrocardiography (ECG) characteristics in patients with idiopathic PVC.

Methods: We retrospectively analyzed 156 patients with PVC who came to the cardiology outpatient clinic. Seventy-one patients were responsive to BB, and 85 were responsive to CCB. Their demographic and ECG characteristics were compared.

Results: The male ratio was higher (p<0.001), and the left ventricular ejection fraction was lower in BB responders than in CCB responders (p<0.001). Although the mean heart rate was higher in BB responders (p<0.001), the initial PVC burden was lower in BB responders than in CCB responders (p<0.001). The PVC QRS duration was longer in BB responders than in CCB responders (p<0.001). Similarly, the coupling interval variability was higher in BB responders (p=0.006).

Conclusions: The evaluation of clinical and ECG parameters in patients with frequent idiopathic PVCs may determine whether BBs or CCBs should be chosen as initial treatment. Further prospective studies are needed to verify our findings and establish their clinical applicability.

Keywords: Premature ventricular contraction, ventricular arrhythmia, B-blocker, calcium channel blocker, ambulatory ECG monitoring

ÖZ

Amaç: Ventriküler erken vuru (VEV) sık görülen aritmik bir durumdur. Semptomatik ve sık VEV'si olan hastalarda ilk yaklaşım, başta beta-blokerler (BB) ve kalsiyum kanal blokerleri (KKB) olmak üzere medikal tedavidir. Hangi tedavinin seçilmesi gerektiği henüz netleşmemiştir. Bu çalışmayla hasta ve elektrokardiyografi (EKG) özelliklerine göre VEV'li hastalarda hangi ilaç tedavisinin faydalı olacağını araştırmayı amaçladık.

Yöntemler: Kardiyoloji polikliniğine başvuran 156 VEV hastası retrospektif olarak incelendi. BB'ye yanıt veren 71 hasta ile KKB'ye yanıt veren 85 hasta klinik ve EKG özellikleri açısından karşılaştırıldı.

Bulgular: BB'ye yanıt veren grupta erkek cinsiyetin daha fazla olduğu (p<0,001) ve sol ventrikül ejeksiyon fraksiyonu düzeylerinin KKB'ye yanıt veren gruba göre daha düşük olduğu saptandı (p<0,001). BB'lere yanıt veren grupta ortalama kalp hızı seviyeleri daha yüksek iken (p<0,001), başlangıç VEV oranı BB'ye yanıt veren grupta, KKB'ye yanıt veren gruba göre daha düşüktü (p<0,001). VEV QRS süresi, BB'ye yanıt veren grupta, KKB'ye yanıt veren gruba göre daha uzundu (p<0,001). Benzer şekilde, BB'ye yanıt veren grupta eşleşme aralığı değişkenlik düzeyleri daha yüksek bulundu (p=0,006).

Sonuçlar: Sık idiyopatik VEV'si olan hastalarda klinik ve EKG parametrelerinin değerlendirilmesi, BB ve KKB arasından hangi başlangıç tedavisini seçmemiz gerektiği konusunda bize yol gösterebilir. Gözlemlerimizi doğrulamak ve klinik uygulanabilirliğini belirlemek için daha ileri prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Prematür ventriküler kontraksiyon, ventriküler aritmi, B-bloker, kalsiyum kanal blokeri, amblatuvar EKG takibi

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INTRODUCTION

Premature ventricular contractions (PVCs) seem common regardless of the existence of structural heart disease[1]. The incidence of PVC is estimated to range between 4% and 50%, even in individuals without structural heart disease[2-5]. These PVCs, considered idiopathic, generally have a good prognosis[6]. However, PVCs can result in various symptoms such as palpitations, shortness of breath, atypical chest pain, and syncope[7], but they can also lead to dilated cardiomyopathy, left ventricular (LV) dysfunction, and heart failure[6,8,9]. Pharmacological medical treatment is usually first-line in patients with symptoms or who have (or are at risk of) cardiomyopathy from ventricular arrhythmia[10].

Triggered activity is considered the most common mechanism in idiopathic PVCs. Therefore, it seems reasonable to use a beta-blocker (BB) or non-dihydropyridine calcium channel blocker (CCB) as the first-line therapy. However, the effects of these drugs on PVC burden are moderate[11]. Considering the side effects and possible complications of these drugs, it is crucial to determine which drug is preferred for treating PVCs. Moreover, it is unclear whether there is a difference in the effectiveness of these medical treatments according to PVC properties.

This study aimed to clarify the first-line therapy in patients with frequent PVCs without structural heart disease.

MATERIALS and METHODS

Study Population

We retrospectively analyzed 156 patients who visited the cardiology outpatient clinic between 2018 and 2022. They were diagnosed with PVC via electrocardiography (ECG) and underwent ambulatory 24-hour rhythm Holter monitoring. We divided the patients into those who underwent BB or CCB treatment. Seventy-one patients were BB responders, and 85 were CCB responders; they were compared according to demographic and ECG characteristics. The absence of structural heart disease was demonstrated by echocardiography, exercise (treadmill) stress test, coronary computed tomography, cardiac catheterization, and/or cardiac magnetic resonance imaging (MRI). Patients with a previous history of coronary artery disease or delayed contrast enhancement with cardiac MRI, LV dilatation due to causes other than PVC, and reduced LV ejection fraction (LVEF) were excluded from the study. Patients with Brugada syndrome, arrhythmogenic right ventricular (RV) cardiomyopathy, or long QT syndrome were also excluded from the study. The demographic data of the patients, laboratory tests, echocardiography measurements, ambulatory rhythm Holter records, and ECG results were collected from the hospital database. Frequent idiopathic PVC was defined as ≥5% PVC on 24-hour ambulatory ECG (Holter) monitoring. The medical treatments received by the patients for idiopathic PVC were classified according to the Vaughan-Williams classification[12]. Response to medical treatment was defined as ≥80% reduction in PVC burden with 24-48 hours of Holter monitoring at the 3rd-month follow-up. BB responders were defined as those who did not respond to CCB or other antiarrhythmic drugs at different times, or who could not use these drugs due to side effects but responded to BB treatment. The reverse held for CCB responders.

The study protocol was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022/0410, date: 29.06.2022) and the Ministry of Health. In addition, data collection, and analysis were independently performed by individuals. The 1975 Helsinki revisions were taken into account when conducting the study.

ECG Analysis

The 12-lead ECG data were manually analyzed with regard to the normal beat and PVC. The QRS width and duration of the normal beat and PVCs were measured (average of three beats). The PVC source was assessed using the 12-lead ECG recordings. The ECGs were taken at a speed of 25 mm/s, calibration of 10 mm/mV, and lowpass filter of 40 Hz. RR intervals and corrected QT intervals were evaluated during normal sinus rhythm. The QRS duration was determined as the distance from the onset of the Q wave to the endpoint of the S wave. The coupling interval of the PVC was defined as the distance from the beginning of a normal QRS complex to the onset of PVC. The compensatory interval (ComI) of the PVC was defined as the time from PVC to the following normal sinus QRS. The coupling interval dispersion of the PVC was described as the difference between the longest and shortest coupling intervals in different derivations. If the RR interval between two sinus beats involving the PVC was exactly twice the normal RR interval, it was defined as full compensation[13]. The origin of PVC was classified as follows: 1) RV outflow tract (inferior axis, left bundle branch block, and V2 transition ratio <0.60), 2) LV outflow tract (inferior axis, left or right bundle branch block, and V2 transition ratio ≥0.60), 3) RV non-outflow tract (non-inferior axis and left bundle branch block),

and 4) LV non-outflow tract (non-inferior axis and right bundle branch block morphology).

Ambulatory Rhythm Holter-ECG Monitoring

All patients underwent 24-hour ECG (Holter) recording. The initial PVC burden was defined as the ratio of PVC obtained in a 24-hour rhythm Holter to the total QRS number before treatment. Patients with ≥5% PVC in the 24-hour rhythm Holter were included in the study. If the selected treatment reduced the PVC burden by ≥80% at the 3rd-month control 24-48 hour rhythm Holter recording, it was accepted as clinical success. Coupling interval variability was described as the difference between the coupling interval values of PVC pulses in the same ECG lead. Non-sustained ventricular tachycardia was defined as three or more consecutive PVCs at a heart rate of >100 beats/min.

Statistical Analysis

Statistics were conducted utilizing the Statistical Package for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the data. Continuous data with a normal distribution are expressed as the mean ± standard deviation, non-parametric data with a non-normal distribution are expressed as the median (interquartile range), and categorical variables are expressed as number and percentage (%). Differences between categorical variables were determined by the chi-square test. Student's t-test or the Mann-Whitney U test was utilized to compare continuous variables. Significance was assumed as $p<0.05$ value.

RESULTS

The study analyzed 156 patients with idiopathic PVCs who were divided into two groups according to the treatment response. Seventy-one patients responded to BB treatment, and 85 patients responded to CCB treatment. Their demographic characteristics are shown in Table 1. There was no statistically significant difference between the groups concerning age, smoking, body mass index, smoking, hypertension, and diabetes mellitus. The sex frequency was compared, and the males were significantly more among BB responders than among CCB responders [56 (79) vs. 45 (53), $p<0.001$]. LVEF levels were significantly lower in BB responders than in CCB responders (57.5±9.3 vs. 61.8±2.9, $p<0.001$) (Figure 1). Possible PVC-related symptoms were examined (palpitations, fatigue, chest pain, and dyspnea), and there was no difference between the groups ($p>0.05$).

The rhythm Holter and ECG recordings of patients with idiopathic PVC were compared according to the treatment response (Table 2). Although mean heart rates were higher in BB responders than in CCB responders (74.3±7.3 vs. 68.5±10.2; $p<0.001$), the initial PVC burden was significantly lower in BB responders [6 (5-8) vs. 10 (5-16), $p<0.001$] (Figure 2). The groups were also compared in terms of coupling interval, Coml, full compensation, QTc of sinus rhythm, and non-sustained VT frequency, and there was no significant difference between them ($p>0.05$). The PVC QRS durations were higher in BB responders than in CCB responders (153.2±12.9 vs. 141.2±13.6, $p<0.001$) (Figure 2).

Similarly, coupling interval variability levels were higher in BB responders (44.3±19.3 vs. 36.1±17.2, $p=0.006$) (Figure 2). Finally, the treatment responses of the patients were compared according to PVC localization, and no significant difference was found ($p>0.05$).

DISCUSSION

In this study, we investigated which drug therapy is more effective according to PVC characteristics and patient demographics. We made the following findings. First, according to the analysis of demographic characteristics, BBs may be more beneficial than CCBs in males and those with a relatively lower LVEF. Second, our comparative analysis of the ECG parameters of individuals with a higher initial PVC burden showed that BB treatment may be more beneficial in those with a high heart rate, prolonged PVC QRS duration, and high coupling interval variability.

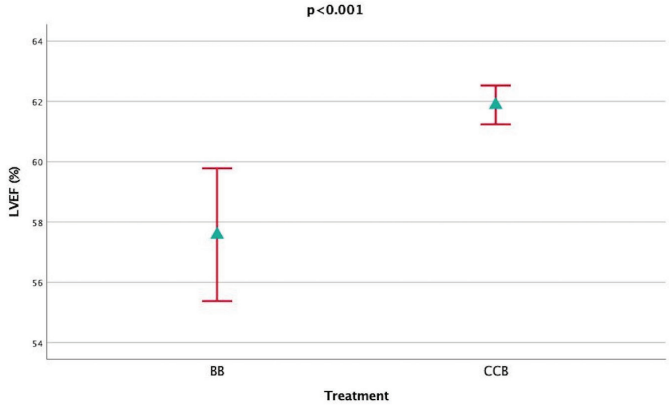

Figure 1. Comparison of BB and CCB responders according to LVEF (57.5±9.3% vs. 61.8±2.9%, $p<0.001$).

BB: B-blocker, CCB: Calcium channel blocker, LVEF: Left ventricular ejection fraction

PVCs are one of the most prevalent arrhythmias in clinical practice. Patients with idiopathic PVCs mostly have a good prognosis. However, symptoms may lead to a decrease in the quality of life and trigger cardiomyopathy in some patients in relation to the PVC burden[14-16]. The goal of treatment is to provide symptomatic relief and to prevent or reverse arrhythmia-induced cardiomyopathy. In medical treatment, which is usually the first-line therapy, a BB, or non-dihydropyridine CCB can be used. These drugs have moderate effects on PVC burden[17].

Table 1. Clinical and demographic characteristics of patients with PVCs who were responsive to BB and CCB therapy.

Clinical characteristics	BB responders (n=71)	CCB responders (n=85)	p-value
Age (years)	55.0±10.4	54.2±14.2	0.667
Male	56 (79)	45 (53)	0.001
BMI (kg/m^2)	22.5±2.2	23.2±2.7	0.075
LVEF, (%)	57.5±9.3	61.8±2.9	<0.001
Smoker	32 (45)	32 (37)	0.348
HT	15 (21)	23 (27)	0.390
DM	12 (17)	7 (8)	0.099
Symptoms, n (%)			
Palpitations	33 (45)	34 (40)	0.416
Fatigue	8 (11)	16 (18)	0.193
Chest pain	22 (31)	33 (38)	0.308
Dyspnea	21 (29)	23 (27)	0.728

Data are presented as mean ± standard deviation or numbers (n) and percentage (%). BB: B-blocker, CCB: Calcium channel blocker, PVC: Premature ventricular contraction, BMI: Body mass index, LVEF: Left ventricular ejection fraction, HT: Hypertension, DM: Diabetes mellitus

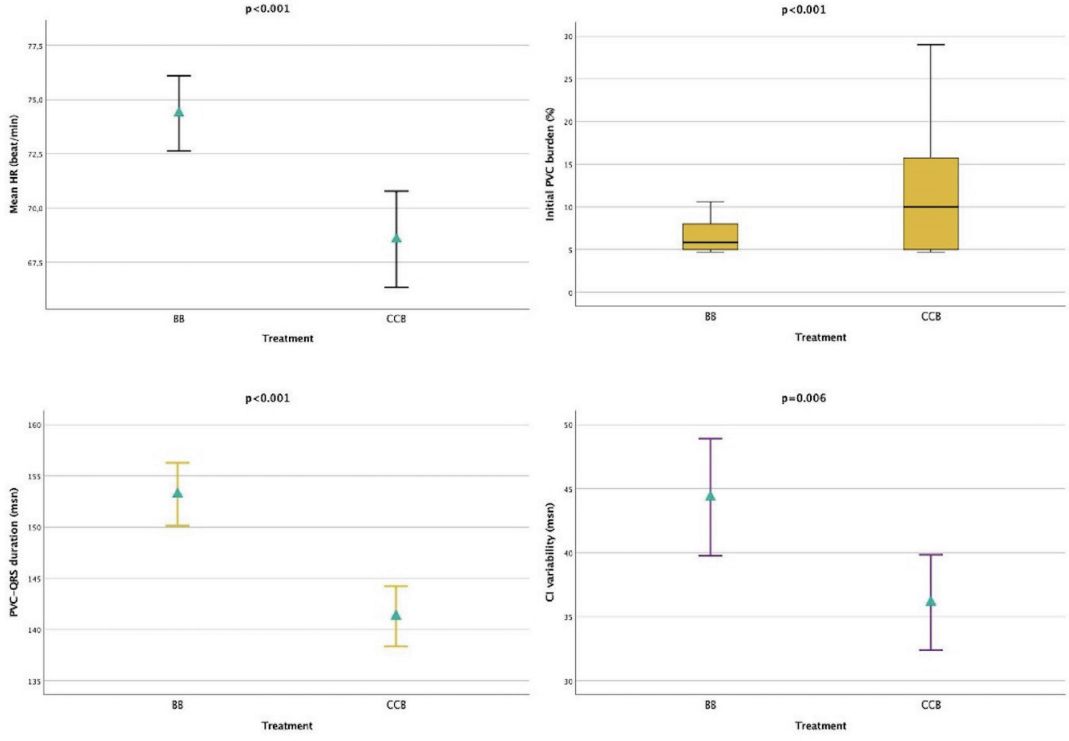

Figure 2. Comparison of BB and CCB responders in terms of mean heart rate, initial PVC burden, PVC QRS duration (width), and coupling interval variability.

BB: B-blocker, CCB: Calcium channel blocker, PVC: Premature ventricular contraction

It is reasonable to use a CCB for treatment if a BB fails, or vice versa, in a patient with a structurally normal heart[18]. However, it is unclear which of these two drug groups affects patients' PVC characteristics and whether there is a priority between these two treatment options.

Reports indicate that sex hormones and differences are associated with ventricular arrhythmias[19,20]. Depending on these differences, the effects of estradiol levels on PVC have been proven. It is also known that this effect occurs through calcium channel inhibition[21]. In our study, the difference in treatment response in terms of sex can be explained by the fact that, in women, estradiol has a calcium channel-blocking effect and a synergistic relationship with CCBs. We also found that BB treatment was effective at lower LVEF levels, and these findings were similar to those of Demir et al.[22] In their study, patients with PVC were divided into two groups: responsive and unresponsive to BBs. The mean LVEF was 57.3%±12.7% in the responsive group, similar to that in our study, and the mean LVEF was higher in the non-responsive group (61.8%±8.0%)[22]. Considering that BB treatment is more effective than CCB treatment in individuals with reduced LVEF[23], it is not surprising to see similar results in our study. In the sympathetic neural system, which is one of the most important neurohormonal adaptations in heart failure, activation starts very early in the course of the disease. Although LVEF levels were within the normal range in patients using BB in the study groups, this system may have already been activated even in small LVEF decreases. Because this system activation is directly related to β-agonist receptors, the circulating adrenergic neurotransmitters may explain the differences in treatment response[24-26]. Another finding from the study of Demir et al.[22] was that the PVC burden was higher in the group that was unresponsive to BB treatment, although the difference was not statistically significant. Similarly, Shinohara et al.[27] found that the group with a high PVC burden did not respond to BB treatment. Our data showed that the low efficacy of BB treatment in the group with high PVC burden is compatible with the literature. Considering the difference in heart rate between the groups and the fact that the percentage of PVCs was lower in the group with a higher heart rate, the main benefit may be related to the successful treatment response, rather than the PVC burden[28]. This also explains why BB therapy benefited patients with a higher mean heart rate.

PVC QRS duration increases as the distance from the PVC focus to the conduction system increases. As reported in previous studies, this provides a distinction in terms of the presence and absence of structural heart disease[29], and the presence of possible structural heart disease changes the effect on treatment in individuals with wide QRS. In addition, an increase in QRS width will cause more discordance in ventricular contraction[30,31], resulting in impaired cardiac mechanical efficiency, increased asymmetric wall thickness, excessive workload in late activated regions, changes in myocardial blood flow, and

Table 2. Comparison of parameters in 24-h rhythm Holter and ECG recordings of patients with PVC who were responsive to BB or CCB treatment.

ECG features	BB responders (n=71)	CCB responders (n=85)	p-value
Mean HR, beat/min	74.3±7.3	68.5±10.2	<0.001
Initial PVC burden, %	6 (5-8)	10 (5-16)	<0.001
Coupling interval, ms	507.2±69.9	516.3±81.9	0.461
PVC QRS duration, ms	153.2±12.9	141.2±13.6	<0.001
ComI, ms	994.9±269.7	1031.4±290.1	0.420
Coupling interval variability, ms	44.3±19.3	36.1±17.2	0.006
Full compensation	43 (60)	61 (71)	0.139
QTc sinus, ms	412.4±20.9	420.9±32.4	0.062
Non-sustained VT	17 (24)	11 (12)	0.075
PVC QRS location			
RVOT	19 (27)	30 (35)	0.253
Non-RVOT RV	8 (11)	12 (14)	0.596
LVOT	21 (29)	34 (40)	0.175
Non-LVOT LV	16 (22)	16 (18)	0.568

Data are presented as mean ± SD, median (interquartile range), or numbers (n) and percentage (%). ECG: Electrocardiography, BB: B-blocker, CCB: Calcium channel blocker, PVC: Premature ventricular contraction, ComI: Compansatory interval, HR: Heart rate, LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract, QTc: Corrected QT, VT: Ventricular tachycardia

local changes in myocardial protein expression. Likewise, the benefit of fascicular PVCs originating from the area close to the conduction system that benefited from CCBs can be considered another factor explaining our findings. All these mechanisms may affect the treatment response by causing structural changes in the myocardium[32]. Idiopathic ventricular tachycardias originating from the ventricle can be classified according to their mechanisms as re-entry (sensitive to verapamil), triggered (sensitive to adenosine), and automatic (sensitive to propranolol)[33]. The coupling interval variability value, which gives information about the mechanism of arrhythmia, was high in the group that benefited from BB treatment in our study. It is not surprising that BB therapy is effective in this PVC group, as the level of coupling interval variability suggests a mechanism associated with automaticity.

The results of our study seem to have important clinical implications because there are many unknowns in the management of PVCs. In particular, it is unclear which patients can benefit from medical treatment and which treatments should be selected. Additional observational and prospective randomized studies are needed to clarify the different types of ventricular arrhythmias and optimize the treatment strategies.

The study has some limitations. First, the results were obtained retrospectively from relatively small study samples. Second, treatment success was defined as ≥80% suppression of PVC burden; however, symptomatic relief analysis was not performed for every patient. Third, long-term follow-up data were unavailable to assess treatment success. Fourth, although the group effects of drugs were examined, the specific drug type, and dose effects were not investigated. Fifth, the long-term effect could not be clarified because records were retrospectively reviewed for up to 3 months. Sixth, no prognostic, or independent predictor was identified due to the retrospective study design.

CONCLUSION

The evaluation of clinical and ECG parameters including sex, LVEF, heart rate, PVC burden, QRS duration, and coupling interval variability in patients with frequent PVCs may help clarify whether BBs and CCBs should be used. At the end of our research, it was seen that there is no one-to-one study on this subject. Using the appropriate medical therapy for patients with PVC may offer an effective and promising strategy to eliminate arrhythmic foci and restore cardiac function. Further prospective studies are needed to confirm our findings and establish their clinical applicability.

Ethics

Ethics Committee Approval: The study protocol was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022/0410, date: 29.06.2022) and the Ministry of Health.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: O.F.B., F.B.C., M.C., Concept: O.F.B., S.F., M.A.T., S.O., M.C., Design: O.F.B., M.A.T., M.C., Data Collection and/or Processing: O.F.B., F.B.C., Analysis and/or Interpretation: O.F.B., S.O., M.C., Literature Search: O.F.B., S.F., F.B.C., S.O., M.C., Writing: O.F.B., S.F., M.A.T., M.C.

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