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Original Article

Chicken-egg and Cardiomyopathy Ventricular Extrasystole Paradox

Meltem Altınsoy,[1] Uğur Küçük[2]

[1]Department of Cardiology, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Department of Cardiology, Çanakkale Onsekiz Mart University, Çanakkale, Türkiye

Abstract

Objectives: Left ventricular ejection fraction (LVEF) may decrease due to frequent ventricular extrasystoles (VESs). This study aimed to investigate whether the site of VES origin and other VES characteristics are associated with a decline in LVEF.

Methods: The rhythm Holter records and follow-up files of 400 patients who presented to the outpatient clinic with complaints such as palpitations, presyncope, syncope, and dyspnea between January 2017 and March 2023 and who were prescribed a rhythm Holter as part of their evaluation were retrospectively reviewed. The relationship between reduced LVEF, defined as LVEF <50% on echocardiography, and VES characteristics was examined in patients with normal LVEF and a VES burden above 10%, utilizing 24- and 48-h electrophysiology studies.

Results: The study comprised 34 patients with a mean age of 59.8±17.0 (range: 21–87) years. Among them, 55.9% (19 patients) were female, and the mean ejection fraction (EF) % was 49.5±11.3 (range: 25–67). Patients with EF % <50 (n=18) exhibited significantly higher diastolic diameter (5.3±0.5 vs. 4.7±0.5 cm, respectively; p=0.004), VES burden (32.3 vs. 16.7, respectively; p=0.0001), longer coupling interval (CI) measurements (p=0.018), and QRS duration (p=0.0001) compared to patients with EF % >50 (n=16). A positive correlation was observed between VES load and QRS duration in the group with EF <50% (r=0.664; p=0.002). In patients who developed VES-induced cardiomyopathy (CMP), VES originated from the mitral annulus (p<0.001), whereas VES originating from the right ventricular outflow tract was significantly associated with the non-CMP group (p<0.001).

Conclusion: The burden of VESs may be associated with CMP, as well as longer QRS duration, CI, and exit location.

Keywords: Cardiomyopathies; heart failure; radiofrequency ablation; ventricular premature complexes.

Tavuk-Yumurta ve Kardiyomiyopati Ventriküler Ekstrasistol Paradoksu

Özet

Amaç: Sol ventrikül ejeksiyon fraksiyonu (LVEF), sık ventriküler ekstrasistollerin (VES'lerin) neden olabileceği bir azalmaya maruz kalabilir. Bu çalışma, VES kökeni ve diğer VES özelliklerinin LVEF'de bir azalma ile ilişkili olup olmadığını araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Ocak 2017 ile Mart 2023 arasında polikliniğe başvuran ve değerlendirme sürecinin bir parçası olarak ritim Holter istenen 400 hasta'nın ritim Holter kayıtları ve takip dosyaları retrospektif olarak incelendi. Sol ventrikül ejeksiyon fraksiyonunda (LVEF) azalma olarak tanımlanan LVEF < 50% olan ve % 10'un üzerinde VES yüküne sahip olan hastalarda, normal LVEF'li hastalarda ve VES özelliklerinin ilişkisi, 24- ve 48-saatlik elektrofizyoloji çalışmaları kullanılarak incelendi.

Bulgular: Çalışma, yaş ortalaması 59,8±17,0 (aralık: 21–87) olan 34 hastadan oluşmaktadır. Bunların %55,9'u (19 hasta) kadındı ve ortalama EF % değeri 49,5±11,3 (aralık: 25–67) idi. EF % <50 olan hastalar (n=18), EF % >50 olan hastalara (n=16) göre anlamlı olarak daha yüksek diyastolik çap (sırasıyla 5,3±0,5'e karşılık 4,7±0,5 cm; p=0,004), VES yükü (sırasıyla 32,3'e karşılık 16,7; p=0,0001), daha uzun kuplaj aralığı ölçümleri (p=0,018) ve QRS süresi (p=0,0001) gösterdi. EF < 50% olan grupta VES yükü ile QRS süresi arasında pozitif bir korelasyon bulundu (r=0,664; p=0,002). VES ile ilişkili kardiomyopati (CMP) gelişen hastalarda, VES mitral anulusundan kaynaklandı (p<0,001), RVOT'dan kaynaklanan VES'ler CMP olmayan gruba belirgin şekilde ilişkilendirildi (p<0,001).

Sonuç: Ventriküler ekstrasistollerin (VES'lerin) yükü, kardiomyopati ile ilişkili olabileceği gibi, daha uzun QRS süresi, kuplaj aralığı ve çıkış konumu ile de ilişkili olabilir.

Anahtar sözcükler: Kardiyomiyopatiler; kalp yetmezliği; kateter ablasyonu; ventriküler ekstrasistoller.

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Address for Correspondence:
Uğur Küçük

Department of Cardiology, Çanakkale Onsekiz Mart University, Çanakkale, Türkiye

E-mail: drugurkucuk@hotmail.com

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Introduction

The mortality and morbidity in most cardiomyopathies (CMPs) often result from end-organ damage due to pump failure, decompensation, or fatal arrhythmias.[1] While arrhythmias complicate the course of CMP, they can also be a consequence of it. Distinguishing whether arrhythmia is a cause or a consequence of the clinical presentation is challenging in most patients. Ventricular extrasystole-induced CMP (VES-CMP) specifically refers to left ventricle (LV) dysfunction caused solely by frequent VESs.[2] Recent studies have shown that frequent VESs can adversely affect patients with a structurally normal heart and can lead to reversible VES-CMP.[3] The optimal function of the ventricular pump depends on the synchronous activation of the ventricular myocardium. Mechanical contraction of the ventricular myocardium is inefficient when the myocardium is electrically activated by VESs. Furthermore, when repetitive and sustained over the long-term, this discordant ventricular contraction leads to impairment of LV systolic function, possibly through effects on ventricular remodeling.[4] The same adverse effects of abnormal ventricular activation have been observed in patients with chronic right ventricular (RV) pacing, left bundle branch block.[5,6] Despite high VES burden, some patients do not develop CMP. It is possible for VESs to originate from both right and LVs. VES foci have also been associated with different arrhythmia mechanisms.[7] It is important for early intervention in which patient group will develop VES-CMP, what intensity of VES burden, the origin of VESs, or their electrophysiological characteristics cause myopathic ventricle with a higher risk. In addition, although there is no definite information about which factors are related to reversible recovery and why some patients do not develop VES-CMP despite similar electrocardiographic and electrophysiological features, we aimed to share the experiences of our clinic to contribute to the literature on this subject.

Materials and Methods

A retrospective review was conducted on 400 patients admitted to our hospital between 2017 and 2023 with complaints of palpitations, syncope, presyncope, and rhythm Holter monitoring within the indication. All patients underwent 24-h electrocardiogram (ECG) Holter monitoring at least once before catheter ablation. Patients with left ventricular ejection fractions (LVEFs) below 50% were categorized as having VES-CMP. Coronary angiography was additionally performed in patients with intermediate and high coronary artery risk according to Framingham coronary artery risk classification.[8] Demographic characteristics of the patients were recorded. In routine echocardiographic evaluation, a visual and modified Simpson method was used to calculate LVEF, left ventricular diameters, left ventricular wall thickness, and left atrial diameter quantitatively. In a group of 34 patients, the burden of VESs exceeded 10%. Among them, ten individuals were identified as having VES-CMP. Ischemic CMP was ruled out by coronary angiography in these cases, and subsequent ablation procedures were performed. Subsequently, the characteristics of patients who developed VES-CMP and their prognosis during follow-up were analyzed. Approval for the study was obtained from the local ethics committee (Approval No: 2023/06-06), and all study procedures were conducted in accordance with the Declaration of Helsinki.

ECG Analysis

ECG was recorded at a paper speed of 25 mm/s with an amplitude of 10 mm/mV. VESs were recorded at a paper speed of 50 mm/s, and signals were amplified at 10 mm/mV. The analysis included examination of QRS morphology, QRS width, coupling interval (CI), compensatory pauses, and the presence of notching in the inferior leads if applicable.

Holter Analysis

The analysis involved examining a 24–72-h Holter recording to determine the VES burden, calculated as the ratio of VES to total beats, VES frequency, which represents the number of VES in 24 h, and VES CI, defined as the time interval from the onset of the preceding ventricular complex to the onset of VES.

Electrophysiological Study

Following obtaining written informed consent, standard laboratory protocol, and operator judgment, electroanatomical mapping was conducted to localize and ablate VES foci using a radiofrequency catheter. Mapping of the high right atrium, His bundle, coronary sinus, and RV apex was performed with standard mapping catheters. In addition, VESs originating from the LV were approached by retrograde aortic and/or atrial transseptal passage. If VESs were not observed at baseline, programmed atrial and ventricular stimulation with intravenous isoproterenol was administered to induce VES. Three-dimensional electroanatomical activation mapping was employed to pinpoint the earliest endocardial ectopic ventricular activation, utilizing the Columbus® 3D EP Navigation System from MicroPort® EP, China. Pacing maps were utilized to confirm the localization of the identified VESs. Radiofrequency ablation was then performed using either a 5-mm tipped catheter without irrigation (power 30–50 W, target temperature 60°C) or a 2.5-mm tipped catheter with irrigation (FireMagicTM 3D irrigated ablation catheter, combined with ColumbusTM 3D EP Navigation System; target impedance drop 5–10 ohms).

Anatomical Distribution and ECG Features

The site of origin of the clinically observed dominant VES was determined by analyzing surface 12-lead ECGs. The final mapped site of successful VES ablation during the electrophysiology study, utilizing 3D activation maps and fluoroscopy images, was validated by comparing the ECG-estimated site of origin with the final mapped site of successful VES ablation.

Results

The mean age of the patients was 59.8 ± 17.0 years (range: 21–87) (Table 1). The mean ejection fraction (EF) percent-

Table 1. Electrocardiographic characteristics of the patients

	EF <%50 (n=18)	EF >%50 (n=16)	Total	p
Age (years)	63.6±15.1	55.6±18.5	59.8±17.0	0.224
Diastolic diameter (cm)	5.3±0.5	4.7±0.5	4.9±0.6	0.004
VES burden (%)	32.3 (1.8–49.8)	16.7 (9.9–34.7)	23.4 (1.8–49.8)	0.0001
Compensatory pause (ms)	1051.5±175.7	938.0±186.3	998.1±187.1	0.088
Coupling interval (ms)	525.9±55.7	481.6±42.0	505.1±53.9	0.018
QRS interval (ms)	189.9±31.3	132.8±13.3	163.0±37.7	0.0001
Min heart rate (bpm)	51.5±8.2	47.7±4.4	49.7±6.9	0.198
Max heart rate (bpm)	113.2±21.5	125.7±22.3	119.1±22.5	0.198
Mean heart rate (bpm)	73.2±14.3	78.7±7.9	75.8±11.9	0.281

EF: Ejection fraction; VES: Ventricular extrasystole; QRS: Represents the depolarization of ventricles; Min: Minimum; Max: Maksimum, bpm: beats per minute

Table 2. Demographic and VES origin characteristics of the patients

	EF <%50 (n=18)		EF >%50 (n=16)		p
	n	%	n	%	
Gender					
Female	6	33.3	7	43.8	0.300
Male	12	66.7	9	56.3	
HT					
No	7	38.9	10	62.5	0.303
Yes	11	61.1	6	37.5	
DM					
No	11	61.1	14	87.5	0.125
Yes	7	38.9	2	12.5	
CAD					
No	10	55.6	15	93.8	0.019
Yes	8	44.4	1	6.3	
VES output location					
RVOT	0	0.0	13	82.3	<0.001
LVOT	1	5.6	0	0.0	
Mitral Annulus	8	44.4	1	6.3	
LCC	4	22.2	1	6.3	
Summit	3	16.7	1	6.3	
Parahisian	2	11.1	0	0.0	

HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; RVOT: Right ventricule outflow tract; LVOT: Left ventricule outflow tract; LCC: Left coronary cuspis

age of the patients was 49.5±11.3 (range: 25–67). Patients with EF <50% (n=18) had significantly higher diastolic diameter, VES burden, CI, and QRS duration than patients with EF >50% (n=16) (Table 1). A comparison between groups was made regarding hypertension, diabetes mellitus, and coronary artery disease, and summarized in Table 2. In addition, VES output location was similarly compared between groups and summarized in Table 2 as well (Table 2). A positive correlation was found between VES burden and QRS duration in the group with EF <50% (r=0.664; p=0.002). VES originated from the mitral annulus (MA) in those who developed VES-CMP (p<0.001), whereas VES originating from the RV outflow tract (RVOT) was significant in the group who did not develop CMP (p<0.001) (Table 2). CI values according to EF value are presented in Table 3.

Table 3. Coupling interval values according to EF value

	Mean±SD	Median (min-max)	p
EF <50	420.5±64.1	407 (326–523)	0.001
EF >50	498.7±48.8	508 (365–566)	

SD: Standard deviation

Discussion

Idiopathic ventricular arrhythmias, particularly those involving VES and non-sustained VT, are often asymptomatic and are consequently frequently detected incidentally during routine examinations. In the absence of structural heart disease, ventricular premature beats are generally regarded as benign. In our study, individuals with LVEF <50% were categorized as having VES-related CMP. In most patients without structural heart disease who undergo ablation due to VES or VT, the origin is the RVOT.[9] Symptomatic VESs commonly originate from the RVOT and less frequently from the left ventricular outflow tract, aortic root, or MA. Particularly, VESs originating from the RVOT typically have an excellent benign prognosis.[9] In the patient population we followed with VES-CMP, the most common origin of VES was originating from the MA. In symptomatic VES patients, beta blockers and calcium channel blockers are typically prescribed. Calcium channel blockers cannot be used especially in the group with regurgitation. As in other regions of origin, drug therapy was not very successful in suppressing VES in our patient cohort. In the results of our study, in addition to VES burden being important in the development of CMP, other risk factors include male gender, patients being asymptomatic (due to delayed diagnosis), VES QRS duration (>150 ms), MA origin (i.e., left ventricular origin, due to its contribution to dyssynchrony), and/or long coupling time.[7,10] In VES CMPs, the cardiac effect of VESs is ectopic and early, heart rate irregularity, and post-extrasystolic potentiation, LV dyssynchrony, atrioventricular dyssynchrony, and increased heart rate.[11] In patients (n=10) who had symptomatic heart failure despite medical treatment and in whom we performed ablation with a prediagnosis of VES-CMP, normalization of LVEF was observed in seven of them (EF >50%) at the 4th-month follow-up. Although the ECG and electrophysiological features of these patients, as well as the

follow-up of the remaining three patients, continue, the absence of improvement in the left ventricular systolic function despite successful ablation may be related to another underlying non-ischemic cause of CMP or channelopathies.[12]

The study also revealed that a shorter VES CI was a predisposing factor for VES-CMP. The hemodynamic effects vary based on the CI between the preceding sinus beat and the VES. A shorter CI may lead to more significant hemodynamic consequences. VES occurring after a short CI may reduce stroke volume according to the Frank-Starling law if there is insufficient time for left ventricular (LV) filling. Conversely, when VES occurs after a long CI, there is more time for ventricular filling. However, there is a growing need for studies to determine how long it takes for LVEF to improve after ablation or the extent of retrospective improvement in patients with VES-CMP. In addition, there is a need for additional criteria for early diagnosis and intervention beyond the predictors mentioned. The approach of our clinic to VESs and the necessity of closely monitoring patients with criteria considered at high risk for developing VES-CMP are highlighted.

Study Limitations

Limitations should be considered when interpreting the study. Firstly, it is a retrospective study, which entails inherent limitations associated with this methodology. Patients in our study underwent ablation for symptomatic VESs from a highly selected group, and some patients may have other unidentified CMPs unrelated to VESs, which we cannot exclude. In addition, (LVEF assessment may be misinterpreted in patients with dense VES burden, potentially leading to a relatively high LVEF after VES ablation. Moreover, improvements in LVEF after VES ablation in patients with reduced LVEF compared to baseline should be interpreted considering the expected regression toward the mean. Factors such as VES burden/frequency associated with LV dysfunction, long duration of VES, origin site, and multiformity also pose limitations. Furthermore, it is not possible to exclude reverse causality, suggesting that features such as VESs may be a consequence rather than a cause of CMP in this study.

Conclusion

Frequent VESs may contribute to (LV systolic dysfunction based on certain characteristics. VESs originating from the MA, higher burden, longer CIs, and wider QRS complexes are more strongly associated with the development of CMP, potentially leading to marked LV dyssynchrony. Ablation of VESs, particularly in individuals with CMP without other recognized causes, appears to result in an improvement in LVEF. The identification of VESs in both patients with and without alternative causes of CMP in this study sheds light on targeting them for potential improvement in LV function through ablation. However, large population studies are required to definitively assess the causal relationship between VESs and CMP, as well as the long-term effects of VES burden and its characteristics on subsequent ventricular function.

Disclosures

Ethics Committee Approval: The study was approved by the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (no: 2023/06-06, date: 12/04/2023).

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