ORIGINAL RESEARCH

Bagcilar Med Bull
DOI: 10.4274/BMB.galenos.2026.85866

Outflow Tract Versus Non-outflow Tract Origins in Premature Ventricular Complexes: Distinct Electrophysiological Phenotypes and Structural Consequences

Prematüre Ventriküler Komplekslerde Çıkış Yolu ve Çıkış Yolu Dışı Kökenler: Farklı Elektrofizyolojik Fenotipler ve Yapısal Sonuçlar

Yusuf Yılmaz[1], Adem Atıcı[1], Ayhan Küp[2], Fatma Betül Özcan[1], Erdem Çevik[3], Mustafa Yılmaz[4], Ali Uğur Soysal[5], Mehmet Tugay Yumuk[6], Sevil Tuğrul Yavuz[7], Medeni Karaduman[8], İshak Yılmaz[9], Mustafa Çalışkan[1]

[1]İstanbul Medeniyet University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Koşuyolu High Specialization Training and Research Hospital, Department of Cardiology, İstanbul, Turkey
[3]İstanbul University, İstanbul Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
[4]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Department of Cardiology, İstanbul, Turkey
[5]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
[6]Private Batman World Hospital, Clinic of Cardiology, Batman, Turkey
[7]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Department of Cardiology, İstanbul, Turkey
[8]Van Yüzüncü Yıl University Faculty of Medicine, Department of Cardiology, Van, Turkey
[9]Şanlıurfa Training and Research Hospital, Clinic of Cardiology, Şanlıurfa, Turkey

Abstract

Objective: Premature ventricular complexes (PVCs) from different anatomical sites exhibit distinct electrophysiological characteristics. While outflow tract (OT) origins are well-characterized, non-outflow tract (Non-OT) properties remain poorly defined.

Method: This retrospective study analyzed 1.644 patients with PVC burden ≥5% stratified by origin: right ventricular outflow tract [(RVOT); n=587], left ventricular outflow tract [(LVOT); n=628], RV origin other than OT (Non-RVOT; n=205), and LV origin other than OT (Non-LVOT; n=224). Electrocardiographic parameters, holter monitoring, autonomic markers, and echocardiographic findings were compared across groups.

Öz

Amaç: Farklı anatomik bölgelerden köken alan prematüre ventriküler kompleksler (PVK), birbirinden farklı elektrofizyolojik özellikler sergilemektedir. Çıkış yolu (OT) kökenli PVK literatürde iyi tanımlanmış olsa da çıkış yolu dışı (Non-OT) odakların özellikleri yeterince açıklanmamıştır.

Yöntem: Bu retrospektif çalışma, PVK yükü ≥%5 olan 1,644 hastayı orijinlerine göre dört gruba ayırarak incelemiştir: Sağ ventrikül çıkış yolu [(RVOT); n=587], sol ventrikül çıkış yolu [(LVOT); n=628], OT dışı sağ ventrikül (Non-RVOT; n=205) ve OT dışı sol ventrikül (Non-LVOT; n=224). Gruplar arasında elektrokardiyografik parametreler, holter monitorizasyon verileri, otonomik belirteçler ve ekokardiyografik bulgular karşılaştırılmıştır.

Address for Correspondence: Yusuf Yılmaz, İstanbul Medeniyet University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
E-mail: dr.ysufyilmaz@gmail.com **ORCID:** orcid.org/0000-0002-6676-2740
Received: 05.02.2026 **Accepted:** 06.06.2026 **Epub:** 22.06.2026

Cite this article as: Yılmaz Y, Atıcı A, Küp A, Özcan FB, Çevik E, Yılmaz M, et al. Outflow tract versus non-outflow tract origins in premature ventricular complexes: distinct electrophysiological phenotypes and structural consequences. Bagcilar Med Bull. [Epub Ahead of Print]

Abstract

Results: Non-OT tract origins demonstrated significantly greater electrical complexity with multifocal PVCs at twice the rate of OT sites (p<0.001). Coupling interval dispersion was markedly elevated in non-RVOT (103.1±89.2 ms) and non-LVOT (89.2±49.2 ms) compared to RVOT (54.6±45.9 ms) and LVOT (54.8±43.2 ms) (p<0.001). Despite lower PVC burden (~7.1% vs. ~12.4%), the non-LVOT group exhibited the most advanced left ventricular remodeling with significantly larger systolic and diastolic diameters (p<0.001). Non-LVOT demonstrated highest circadian variability (48.2%) with nocturnal symptom predominance (48.2%). The Interpolation rate was significantly higher in non-LVOT (34.8%) versus RVOT (p<0.001).

Conclusion: Anatomical origin may be a critical determinant of electrical complexity and structural vulnerability independent of PVC burden. Non-OT origins exhibit unique electrophysiological characteristics with enhanced left ventricular remodeling susceptibility, suggesting location-specific mechanisms drive disease progression.

Keywords: Anatomical origin, circadian variability, electrophysiology, left ventricular remodeling, premature ventricular complexes

Öz

Bulgular: Çıkış yolu dışı odakların, çıkış yolu odaklarına kıyasla iki kat daha yüksek oranda multifokal PVK sergileyerek belirgin şekilde daha yüksek bir elektriksel kompleksiteye sahip olduğu saptanmıştır (p<0,001). Coupling interval dispersiyonu, Non-RVOT (103,1±89,2 ms) ve Non-LVOT (89,2±49,2 ms) gruplarında; RVOT (54,6±45,9 ms) ve LVOT (54,8±43,2 ms) gruplarına göre anlamlı derecede yüksek bulunmuştur (p<0,001). Daha düşük PVK yüküne rağmen (~%7,1'e karşı ~%12,4), Non-LVOT grubu anlamlı düzeyde daha geniş sistolik ve diyastolik çaplar ile en ileri düzeyde sol ventrikül remodelingi (yeniden şekillenme) göstermiştir (p<0,001). Non-LVOT grubu %48,2 ile en yüksek sirkadiyen varyasyonu ve noktürnal semptom baskınlığını sergilemiştir. İnterpolasyon oranı, Non-LVOT grubunda (%34,8) RVOT grubuna göre anlamlı derecede yüksek saptanmıştır (p<0,001).

Sonuç: Anatomik köken, PVK yükünden bağımsız olarak elektriksel kompleksitenin ve yapısal duyarlılığın bir beliryecisi olabilir. OT dışı odaklar, artmış sol ventrikül remodeling yatkınlığı ile birlikte seyreden özgün elektrofizyolojik özellikler sergilemektedir; bu durum, hastalık progresyonunda lokasyona özgü mekanizmaların rol oynadığını düşündürmektedir.

Anahtar kelimeler: Anatomik köken, elektrofizyoloji, prematüre ventriküler kompleksler, sirkadiyen varyasyon, sol ventrikül remodelingi

Introduction

Premature ventricular complexes (PVCs) are among the most common ventricular arrhythmias, with a prevalence that increases with extended monitoring duration (1). While traditionally considered benign, cumulative evidence indicates that a high PVC burden is associated with an increased risk of left ventricular (LV) dysfunction, heart failure, and adverse cardiovascular outcomes (2,3). The primary pathophysiological mechanisms—triggered activity, automaticity, and reentry—each possesses distinct electrophysiological characteristics and clinical implications (4).

The anatomical origin of PVCs is a critical determinant of both clinical presentation and prognosis. In patients without structural heart disease, the right (RVOT) and left ventricular outflow tracts (LVOT) are the most frequent sites of idiopathic origin (5). However, PVCs may also arise from non-outflow tract (Non-OT) locations. Distinguishing between OT and Non-OT origins is essential for predicting their unique electrophysiological and clinical behaviors (4,5).

The autonomic nervous system (ANS) significantly modulates ventricular arrhythmogenesis through heart rate variability (HRV) and circadian fluctuations in autonomic tone (6). Disruptions in these patterns, such as reduced nocturnal parasympathetic activity or persistent sympathetic dominance during sleep, are associated with elevated cardiovascular risk (6). Furthermore, the coupling interval (CI)—the duration between a sinus beat and a ventricular ectopic beat—reflects both autonomic modulation and substrate characteristics (7). CI variability may indicate intrinsic electrophysiological differences within the ectopic focus, potentially contributing to arrhythmia formation (7).

Persistent PVCs induce cardiac remodeling, including LV dilatation, interstitial fibrosis, and myocardial inflammation (8). However, the impact of specific PVC origins on these structural consequences remains poorly defined. Recent evidence suggests that certain origins may uniquely affect ventricular geometry and function, independent of the arrhythmic burden. Additionally, while multifocal PVCs exhibit increased electrical heterogeneity, their prevalence and clinical significance across different anatomical sites require further elucidation (9).

Despite the recognized influence of OT origins, data regarding the electrophysiological, autonomic, and structural changes induced by Non-OT PVCs remain limited (10). Therefore, this study aimed to comprehensively compare electrophysiological characteristics, autonomic

parameters, and structural findings across four distinct groups: RVOT, LVOT, RV origin other than OT (Non-RVOT), and LV origin other than OT (Non-LVOT).

Materials and Methods

Study Design and Ethical Approval

This retrospective observational cohort study examined electrophysiological characteristics, holter monitoring parameters, ANS markers, and structural cardiac findings across four distinct PVC origin groups. Data were systematically collected from medical archives of patients who presented to cardiology outpatient clinics between 2020 and 2025. The study protocol was reviewed and approved by the Ethics Committee of University of Health Sciences Turkey, Göztepe Prof. Dr. Süleyman Yalçın City Hospital (date: 22.01.2026, decision no: 2026/0036), and all procedures were conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study enrollment.

Study Population and Data Collection

The initial cohort consisted of 4.640 patients who presented to cardiology outpatient clinics with electrocardiographically documented PVCs and underwent 24-hour ambulatory electrocardiographic monitoring. Comprehensive patient data, including demographic characteristics, clinical parameters, laboratory results, and diagnostic test findings, were systematically extracted from electronic medical records. Clinical parameters encompassed symptom duration, symptom characteristics (palpitations, dyspnea, chest pain, syncope), and temporal symptom patterns. Symptom timing was categorized as daytime (occurring between 06:00-22:00 hours), nighttime (occurring between 22:00-06:00 hours), or any-time (occurring throughout the day) based on documented patient reports in medical records. Data regarding hypertension, diabetes mellitus, dyslipidemia, and smoking history were extracted through a comprehensive review of the patients' electronic medical reports. Current medication use at the time of holter monitoring, including beta-adrenergic blockers and calcium channel blockers, was recorded. Structural cardiac pathology was systematically excluded through, transthoracic echocardiography, exercise stress testing, coronary computed tomography angiography, invasive coronary angiography, and/or cardiac magnetic resonance imaging as clinically indicated.

The following criteria were used to determine patient eligibility for the study: (1) age ≥18 years; (2) documented PVC burden ≥5% on 24-hour holter monitoring; (3) absence of structural heart disease as confirmed by comprehensive cardiac imaging; (4) preserved LV systolic function with ejection fraction ≥50% as determined by transthoracic echocardiography; and (5) absence of obstructive coronary artery disease as assessed by non-invasive or invasive coronary evaluation.

Exclusion criteria included: (1) Documented history of coronary artery disease or prior myocardial infarction; (2) inherited cardiac channelopathies or cardiomyopathies including Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, or long QT syndrome; (3) presence of atrial fibrillation or other supraventricular arrhythmias; (4) active myocarditis or pericarditis; (5) moderate-to-severe valvular heart disease; (6) use of class I or III antiarrhythmic medications at the time of enrollment; and (7) incomplete clinical, electrocardiographic, echocardiographic, or ambulatory monitoring data. Following rigorous application of these criteria, the final study cohort comprised 1.644 patients with complete datasets for all study parameters.

Electrocardiographic Analysis and PVC Origin Determination

Standard 12-lead electrocardiograms (ECG) were obtained during sinus rhythm and during PVC occurrence. PVC origin was determined using established electrocardiographic criteria based on QRS morphology, axis, and specific waveform characteristics according to a stepwise algorithmic approach. For differentiation between the RVOT and LVOT, the V2 transition ratio and R-wave morphology in lead I were utilized as primary determinants (e.g., a V2 transition ratio ≥0.60 indicated an LVOT origin). Non-OT origins were identified by the presence of atypical axes and specific bundle branch block morphologies—right bundle branch block for left ventricular origins and left bundle branch block for right ventricular origins—that did not fulfill the criteria for OT localization as described by Anderson et al. (11).

The patients were categorized into four distinct groups based on the identified PVC origin: RVOT, LVOT, Non-RVOT, and Non-LVOT. To ensure methodological rigor, 100 randomly selected ECG recordings were independently evaluated by two senior cardiologists blinded to the clinical data. The interobserver agreement for PVC origin classification was excellent (Cohen's kappa coefficient, κ=0.91), and the intraclass correlation coefficients for continuous ECG parameters ranged from 0.88 to 0.94. Electrocardiographic parameters measured during PVC occurrence included PVC-QRS duration, R-wave duration, peak QRS duration,

and QRS ratio (PVC-QRS duration divided by sinus QRS duration). Sinus rhythm electrocardiographic parameters including QRS duration, QT interval, and corrected QT interval (QTc) using Bazett's formula were also recorded. The PVC-sinus T interval, defined as the interval between the peak of the PVC T-wave and the peak of the subsequent sinus T-wave, was measured to assess post-ectopic recovery characteristics (11).

Holter Monitoring and Arrhythmia Analysis

All patients underwent 24-hour ambulatory electrocardiographic monitoring using standard three-channel holter recording systems. Holter recordings were analyzed by experienced cardiologists blinded to clinical data. PVC burden was calculated as the percentage of total ventricular beats that were PVCs over the 24-hour recording period.

CI parameters were comprehensively analyzed, including mean CI, CI dispersion (defined as the difference between maximum and minimum CIs), and CI variability (calculated as the standard deviation of CIs). Multifocal PVCs were defined as the presence of three or more distinct PVC morphologies on 12-lead electrocardiography. Interpolated PVCs were identified as PVCs occurring between two consecutive sinus beats without disrupting the underlying sinus rhythm. Complete mechanical compensation was defined as the presence of a full compensatory pause following the PVC.

Echocardiographic Evaluation

Transthoracic echocardiography was performed using commercially available ultrasound systems according to standardized protocols recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. LV dimensions including end-diastolic diameter and end-systolic diameter were measured in the parasternal long-axis view. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's biplane method. Left atrial diameter was measured in the parasternal long-axis view at end-systole. All measurements were performed by experienced sonographers blinded to clinical and electrocardiographic data, and values were averaged over three consecutive cardiac cycles (12).

ANS Assessment

ANS function was assessed through analysis of circadian variability in PVC occurrence and symptom patterns. Circadian variability was defined as the presence of significant diurnal variation in PVC frequency or symptom occurrence. Patients were classified based on predominant symptom timing: daytime symptoms (06:00-22:00 hours), nighttime symptoms (22:00-06:00 hours), or any-time symptoms (no clear circadian pattern). HRV parameters, including mean heart rate (HR) during daytime and nighttime periods, were analyzed to assess autonomic modulation.

Statistical Analysis

Statistical analyses were performed using SPSS software version 22.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on distribution normality as assessed by the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages. Comparisons among the four PVC origin groups were performed using One-Way Analysis of Variance for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, and chi-square test or Fisher's exact test for categorical variables. Post-hoc pairwise comparisons were conducted using Tukey's honestly significant difference test for normally distributed variables and Dunn's test with Bonferroni correction for non-normally distributed variables. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

Results

Baseline Characteristics and Demographic Profile

The study population comprised 1.644 patients, stratified into four distinct cohorts based on PVC origin: RVOT (n=587), LVOT (n=628), Non-RVOT (n=205), and Non-LVOT (n=224). Baseline characteristics including age and body mass index were comparable across all groups, showing no statistical variance. However, a significant difference was observed in gender distribution; the Non-LVOT group demonstrated a marked male dominance (63.4%), whereas the lowest proportion of males was recorded in the LVOT group (51.9%) (Table 1).

Symptomatic Presentation

Clinical presentation varied significantly regarding both the duration and prevalence of symptoms. The RVOT group exhibited the longest symptom duration (15.7±16.2 months), in contrast with the Non-RVOT group, which reported the shortest clinical history (10.8±14.5 months). Notably, although the Non-RVOT

Table 1. Baseline clinical and echocardiographic characteristics according to PVC origin

Variable	RVOT (n=587)	LVOT (n=628)	Non-RVOT (n=205)	Non-LVOT (n=224)	p-value
Age, years	48.7±13.7	50.5±15.0	49.4±13.5	50.4±16.0	0.158
Male sex, n (%)	344 (58.6)[a]	326 (51.9)[b]	114 (55.6)[ab]	142 (63.4)[c]	0.013
Hypertension, n (%)	165 (28.1)[a]	244 (38.9)[b]	69 (33.7)[ab]	66 (29.5)[a]	0.001
Diabetes mellitus, n (%)	86 (14.7)[a]	140 (22.3)[b]	40 (19.5)[ab]	48 (21.4)[ab]	0.006
Symptomatic patients, n (%)	512 (87.2)[a]	551 (87.7)[a]	193 (94.1)[b]	190 (84.8)[a]	0.004
Smoking, n (%)	218 (37.1)	194 (30.9)	66 (32.2)	84 (37.5)	0.080
Symptom duration, months	15.7±16.2[a]	14.0±15.2[ab]	10.8±14.5[b]	12.1±14.5[ab]	<0.001
BMI, kg/m²	26.2±3.5	26.8±4.2	26.5±4.5	26.2±4.1	0.220
LVEF, %	61.3±5.4[a]	61.2±6.7[a]	62.5±3.9[b]	60.1±5.2[c]	<0.001
LVDd, cm	4.7±0.4[a]	4.7±0.4[a]	4.6±0.3[a]	4.8±0.4[b]	<0.001
LVDs, cm	3.1±0.5[a]	3.1±0.5[a]	3.0±0.4[a]	3.2±0.5[b]	<0.001

RVOT: Right ventricular outflow tract, LVOT: Left ventricular outflow tract, Non-RVOT: Non-outflow tract right ventricular origin, Non-LVOT: Non-outflow tract left ventricular origin, BMI: Body mass index, LVDd: Left ventricular diastolic diameter, LVDs: Left ventricular systolic diameter, LVEF: Left ventricular ejection fraction, PVC: Premature ventricular complex. Values are mean ± standard deviation or n (%). One-Way ANOVA with Tukey post-hoc test was used for continuous variables; chi-square test for categorical variables. Superscript letters ([a, b, c]) indicate statistically significant pairwise differences (p<0.05). Variables without superscript letters showed no significant difference between groups (p≥0.05)

group had the shortest duration, it reached the highest proportion of symptomatic patients (94.1%), significantly exceeding the Non-LVOT cohort (84.8%) (Table 1).

Cardiovascular Risk Factors

The cardiovascular risk profile was more pronounced in patients with left-sided outflow tract (OT) origins. The prevalence of hypertension and diabetes mellitus was significantly higher in the LVOT group compared to the RVOT group (Table 1). In contrast, smoking status remained uniform across the four cohorts, with no significant variation detected.

Echocardiographic Findings

In accordance with the study's exclusion criteria, LVEF was preserved across all groups (≥50%). However, significant inter-group variation was still observed (Table 1, Figure 1). The Non-RVOT group exhibited the highest LVEF, while the lowest valueswere recorded in the Non-LVOT group. Post-hoc analysis confirmed that the Non-RVOT group differed significantly from both the LVOT and Non-LVOT cohorts.

LV dimensions also differed significantly across groups. Notably, both left ventricular systolic diameter (LVDs), and LVDd were significantly larger in the Non-LVOT group compared to all other cohorts (Table 1). Despite lower PVC burden, these findings point toward a more advanced pattern of LV remodeling in the Non-LVOT group, even while maintaining an LVEF above the exclusion threshold.

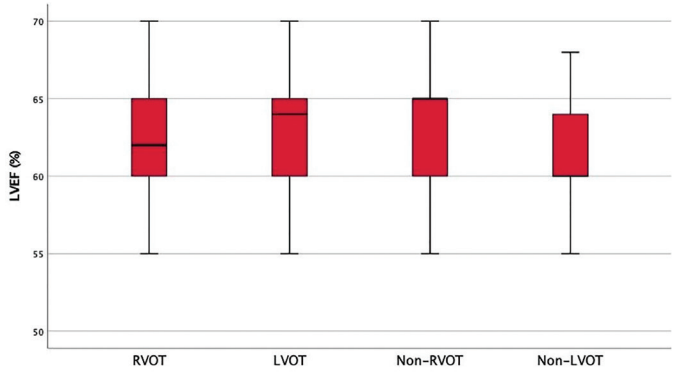

Figure 1. Comparison of LVEF across four PVC origin groups

Box plots displaying the distribution of left ventricular ejection fraction (LVEF, in percentage) across the four study groups. The box represents the interquartile range, the line within the box indicates the median value, and the whiskers extend to the minimum and maximum values. All four groups demonstrated preserved left ventricular systolic function with median LVEF values ranging from 60% to 62.5%. Despite the absence of overt systolic dysfunction, the Non-LVOT group showed a slightly lower median LVEF (60.1%) compared to other groups, and this difference was statistically significant (p<0.001). This finding suggests that left ventricular non-outflow tract PVCs may have subtle effects on global systolic function even in the absence of clinically evident cardiomyopathy

LVEF: Left ventricular ejection fraction, PVC: Premature ventricular complex, Non-LVOT: Non-outflow tract left ventricular origin, Non-RVOT: Non-outflow tract right ventricular origin

Electrocardiographic Parameters

Circadian Variability and Autonomic Modulation

Circadian variability and symptom distribution revealed a clear autonomic dichotomy among the groups (Table 2). The Non-LVOT group exhibited the most pronounced circadian variability (48.2%), markedly exceeding all other groups. Notably, this group was characterized by a pronounced nocturnal predominance, with nearly half of the patients (48.2%) reporting symptoms at night. In contrast, LVOT origins had a peak in daytime symptom prevalence (58.9%).

Arrhythmic Burden and HR Profiles

The PVC burden exhibited a significant difference between groups (Table 2, Figure 2). Both RVOT and LVOT groups demonstrated significantly higher PVC percentages (approx. 12.4-12.5%) compared to the Non-RVOT and Non-LVOT cohorts (approx. 6.8-7.1%). This contrast was equally evident in the 24-hour PVC counts, where OT origins averaged nearly double the arrhythmic volume of Non-OT origins (~12.800 vs. ~6.600 PVCs).

HR parameters also showed distinct patterns; while mean HR was slightly higher in the Non-OT groups, the LVOT group was characterized by significantly lower daytime mean HR (Table 2). Conversely, nighttime HR were consistently higher in the Non-OT cohorts compared to their OT counterparts.

PVC Morphology

Electrocardiographic analysis revealed distinct morphological patterns across the four groups (Table 3). PVC-QRS duration was significantly more prolonged in left-sided origins (LVOT and Non-LVOT) compared to right-sided origins (RVOT and Non-RVOT) (Figure 3). Similarly, PVC R-wave duration followed this trend, with significantly higher values recorded in the LVOT and Non-LVOT groups. The QRS ratio further distinguished these cohorts, reaching its peak in the LVOT group.

Regarding sinus rhythm, a divergent pattern emerged in sinus QRS duration between the cohorts. Repolarization indices showed that the QTc interval was significantly prolonged in both RVOT (429.5±31.1 ms) and LVOT (430.4±31.6 ms) groups compared to Non-OT cohorts (Table 3). The Non-

Table 2. Holter monitoring, PVC burden, and heart rate parameters

Variable	RVOT	LVOT	Non-RVOT	Non-LVOT	p-value
PVC burden (%)	12.4±10.3[a]	12.5±10.7[a]	6.8±7.4[b]	7.1±8.4[b]	<0.001
24-hour PVC count	12.830±10.672[a]	12.756±11.081[a]	6.534±6.998[b]	6.742±8.004[b]	<0.001
Mean heart rate, bpm	72.9±10.0[a]	71.8±10.6[a]	74.5±11.2[b]	74.4±9.0[b]	0.001
Daytime mean HR, bpm	80.5±11.5[a]	77.5±10.5[b]	80.0±12.7[ab]	81.5±10.9[a]	<0.001
Nighttime mean HR, bpm	62.3±10.3[a]	61.9±10.7[a]	65.3±11.0[b]	64.8±9.5[b]	<0.001
Circadian variability (%)	26.4[a]	32.1[a]	38.5[a]	48.2[b]	<0.001
Nocturnal symptoms (%)	12.6[a]	18.3[a]	28.8[a]	48.2[b]	<0.001
Daytime symptoms (%)	52.1[a]	58.9[b]	45.4[a]	28.6[c]	<0.001

RVOT: Right ventricular outflow tract, LVOT: Left ventricular outflow tract, Non-RVOT: Non-outflow tract right ventricular origin, Non-LVOT: Non-outflow tract left ventricular origin, bpm: Beats per minute, HR: Heart rate, PVC: Premature ventricular complex. Values are mean ± standard deviation or percentage. Superscript letters ([a, b, c]) denote statistically significant pairwise differences (p<0.05)

Table 3. Electrocardiographic parameters

Variable	RVOT	LVOT	Non-RVOT	Non-LVOT	p-value
PVC QRS duration, ms	154.7±24.5[a]	165.2±30.4[b]	157.4±28.3[ab]	163.1±31.9[b]	<0.001
PVC R-wave duration, ms	73.6±29.5[a]	88.4±34.0[b]	67.0±24.5[a]	91.6±29.2[b]	<0.001
PVC peak QRS duration, ms	75.4±22.0[a]	80.2±21.2[b]	61.8±25.1[c]	69.2±21.5[a]	<0.001
Sinus QRS duration, ms	84.3±13.2[a]	87.4±13.4[b]	87.6±13.5[b]	83.0±14.7[a]	<0.001
Sinus QT interval, ms	393.8±34.6[a]	387.9±36.1[b]	388.4±39.7[b]	383.7±37.0[b]	0.002
Sinus QTc interval, ms	429.5±31.1[a]	430.4±31.6[ab]	422.2±30.7[b]	418.3±33.2[b]	<0.001
QRS ratio	1.75±0.51[a]	1.91±0.57[b]	1.84±0.52[ab]	1.88±0.69[b]	<0.001

RVOT: Right ventricular outflow tract, LVOT: Left ventricular outflow tract, Non-RVOT: Non-outflow tract right ventricular origin, Non-LVOT: Non-outflow tract left ventricular origin, PVC: Premature ventricular complex. Data are mean ± standard deviation. Superscript letters ([a, b]) indicate statistically significant pairwise differences (p<0.05)

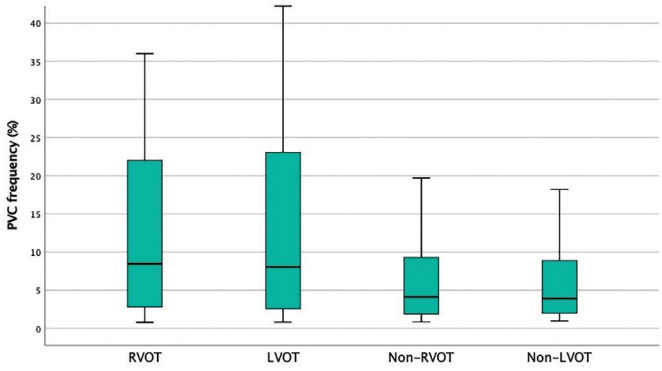

Figure 2. Comparison of PVC frequency across four PVC origin groups

Box plots illustrating the distribution of PVC frequency (expressed as percentage of total ventricular beats) across the four study groups. The box represents the interquartile range, the line within the box indicates the median value, and the whiskers extend to the minimum and maximum values. RVOT and LVOT groups demonstrated significantly higher PVC burden (median approximately 12-13%) compared to Non-RVOT and Non-LVOT groups (median approximately 5-7%, p<0.001). This approximately 2-fold difference in arrhythmic burden between outflow tract and non-outflow tract origins suggests distinct electrophysiological mechanisms, with outflow tract PVCs likely driven by triggered activity mechanisms that produce higher arrhythmic burden, while non-outflow tract PVCs may reflect automaticity-based mechanisms with lower overall frequency

PVC: Premature ventricular complex, Non-LVOT: Non-outflow tract left ventricular origin, Non-RVOT: Non-outflow tract right ventricular origin

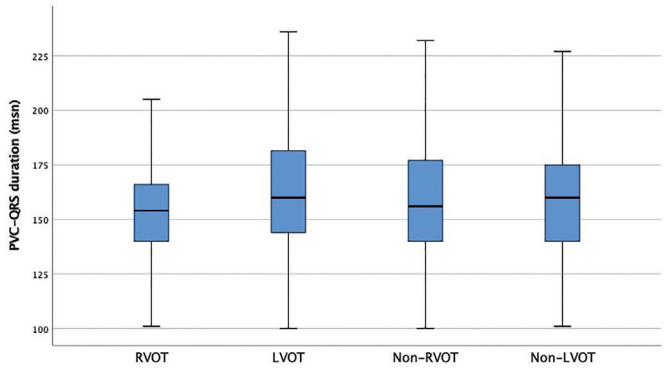

Figure 3. Comparison of premature ventricular complex (PVC)-QRS duration across four PVC origin groups

Box plots showing the distribution of PVC-QRS duration (in milliseconds) across the four study groups: right ventricular outflow tract (RVOT), left ventricular outflow tract (LVOT), non-RVOT right ventricular origin (Non-RVOT), and non-LVOT left ventricular origin (Non-LVOT). The box represents the interquartile range (25th to 75th percentile), the line within the box indicates the median value, and the whiskers extend to the minimum and maximum values. LVOT and Non-LVOT groups demonstrate significantly longer PVC-QRS durations compared to RVOT and Non-RVOT groups (p<0.001), suggesting differences in depolarization pathways and conduction velocities related to anatomical origin. The median PVC-QRS duration was approximately 155 ms in RVOT, 165 ms in LVOT, 157 ms in Non-RVOT, and 163 ms in Non-LVOT groups

RVOT group was characterized by the shortest PVC peak QRS duration, distinguishing it significantly from all other cohorts.

CI Analysis

CI parameters emerged as the most discriminative markers for distinguishing traditional OT origins from Non-OT ectopic sites. CI dispersion was markedly elevated in both Non-RVOT (103.1±89.2 ms) and Non-LVOT (89.2±49.2 ms) groups compared to their OT counterparts (p<0.001) (Table 4). Notably, the Non-RVOT group exhibited the highest degree of dispersion, representing approximately a 1.9-fold increase over the RVOT group (54.6±45.9 ms) and a 1.8-fold increase over the LVOT group (54.75±45.9 ms). Analysis of CI variability followed a consistent pattern, revealing significant electrophysiological heterogeneity among the groups (p<0.001). The Non-RVOT cohort demonstrated the most pronounced fluctuations (66.0±63.3), indicating a highly unstable firing pattern compared to all other groups (Table 4). While the RVOT (40.6±54.6) and LVOT (42.9±47.7) groups exhibited comparable and relatively stable variability profiles, the Non-LVOT group (50.8±35.9) occupied an intermediate position—showing a trend toward higher variability than the OT cohorts but remaining statistically similar to both OT and Non-RVOT groups due to its transitional characteristics (Table 4).

Electrical Complexity and Therapeutic Patterns

Non-OT origins were characterized by significantly greater electrical complexity (Table 4). Multifocal ventricular ectopic systoles were notably more prevalent in the Non-RVOT and Non-LVOT groups, doubling the rates observed in OT cohorts. Furthermore, the interpolation rate was significantly higher in the Non-LVOT group than in the RVOT group. Regarding pharmacological management, beta-blocker use peaked in the RVOT group, while calcium channel blockers were more frequently utilized in Non-OT cohorts.

Discussion

This comprehensive analysis of 1.644 patients reveals that PVC origin is a critical determinant of distinct

Table 4. Coupling interval, electrical complexity, and pharmacological treatment

Variable	RVOT	LVOT	Non-RVOT	Non-LVOT	p-value
A. Coupling interval					
CI dispersion, ms	54.6±45.9[a]	54.8±43.2[a]	103.1±89.2[b]	89.2±49.2[b]	<0.001
CI variability	40.6±54.6[a]	42.9±47.7[a]	66.0±63.3[b]	50.8±35.9[ab]	<0.001
PVC coupling interval, ms	511±82	520±88	512±83	507±78	0.138
B. Electrical complexity					
Multifocal PVC, n (%)	89 (15.2)[a]	112 (17.8)[a]	68 (33.2)[b]	94 (42.0)[b]	<0.001
Interpolated PVC, n (%)	124 (21.1)[a]	156 (24.8)[a]	62 (30.2)[ab]	78 (34.8)[b]	<0.001
Complete pause, n (%)	301 (51.4)	294 (46.8)	107 (52.2)	108 (48.2)	0.134
C. Pharmacological treatment					
β-blockers, n (%)	50 (8.5)[a]	40 (6.4)[a]	5 (2.4)[b]	16 (7.1)[a]	<0.001
CCB, n (%)	283 (48.2)[a]	267 (42.5)[a]	122 (59.5)[b]	136 (60.7)[b]	<0.001
No treatment, n (%)	184 (31.3)[a]	247 (39.3)[b]	52 (25.4)[a]	50 (22.3)[a]	<0.001

RVOT: Right ventricular outflow tract, LVOT: Left ventricular outflow tract, Non-RVOT: Non-outflow tract right ventricular origin, Non-LVOT: Non-outflow tract left ventricular origin, CCB: Calcium channel blocker, CI: Coupling interval, PVC: Premature ventricular complex. Continuous variables are mean ± standard deviation; categorical are n (%). Superscript letters ([a, b]) indicate significant pairwise differences (p<0.05)

electrophysiological and clinical phenotypes. Our findings demonstrate that anatomical location significantly influences autonomic modulation, structural cardiac consequences, and electrical complexity, providing a nuanced framework for understanding PVC pathophysiology.

Mechanistic Insights: CI and Arrhythmic Burden

A primary finding was the marked electrophysiological heterogeneity in the Non-RVOT group, characterized by a CI dispersion approximately 1.9-fold greater than the RVOT group and 1.8-fold greater than the LVOT group. The CI represents the temporal relationship between the preceding sinus beat and the ectopic complex, and variability in this parameter reflects beat-to-beat fluctuations in the timing of ectopic activity (7). While the stable and organized CIs in the OT origins are consistent with triggered activity mechanisms, where afterdepolarizations occur at relatively fixed intervals, the marked CI heterogeneity in the Non-RVOT group suggests a fundamentally different substrate. This potentially reflects an automaticity-based mechanism with parasystolic characteristics, wherein the focus fires independently of the underlying rhythm (13). Furthermore, the Non-RVOT group's shortest peak QRS duration suggests rapid initial depolarization, potentially indicating a more centrally located focus or specialized conduction access.

Regarding arrhythmic burden, OT origins (RVOT and LVOT) demonstrated approximately twofold higher PVC burdens compared to Non-OT sites. The high burden in these traditional regions is consistent with triggered activity mechanisms, which manifest as frequent, repetitive ectopic activity (7). Previous literature establishes that a PVC burden ≥5% is associated with increased risk of LV dysfunction and cardiomyopathy (CMP) development (14). The comparable high PVC burden in both OT groups may be explained by their shared embryological origin. During fetal development, the embryonic OT gives rise to both OTs, with the inferior portion forming the RVOT and the superior portion forming the LVOT (15). Despite their anatomical separation, this common developmental origin results in both regions retaining specialized myocardial characteristics including slower conduction velocity and enhanced automaticity, predisposing them to arrhythmias (15). Consistent with this shared electrophysiological substrate, Iwai et al. (16) showed that both RVOT and LVOT arrhythmias demonstrate similar clinical and electrophysiological mechanisms in their patient group. The significantly higher PVC burden in both OT groups compared to (Non-RVOT and Non-LVOT) supports the concept that the OT location itself, independent of ventricular laterality, may be the primary determinant of high arrhythmic burden.

The Non-LVOT Paradox: Autonomic Sensitivity and Structural Remodeling

Another important finding of this study is the dissociation between arrhythmic burden and structural remodeling observed in the Non-LVOT group. Despite a lower PVC burden (~7.1%), the Non-LVOT group exhibited the most advanced LV remodeling, reaching the largest systolic and diastolic diameters. This paradoxical finding indicates that anatomical location may be a more potent driver of

structural vulnerability than absolute PVC burden alone. The mechanism underlying these results may be related to the anatomical location of the focus causing greater left ventricular dyssynchrony (LVD) compared to right ventricular origins (15). LVD which is the temporal dispersion of regional myocardial contraction, emerges as a critical mechanism linking PVC location to structural remodeling. In support of this mechanism, a prospective swine model of paced ectopic beats showed that LV epicardial PVCs induced significantly greater LV remodeling compared to right ventricular apical PVCs, with final LVEF declining to 39.7% versus 48.6%, respectively (17). Notably, longer ectopic beat QRS duration and greater LVD were significantly associated with larger declines in LV systolic function, independent of PVC burden (17). This pathophysiological mechanism directly parallels our finding that Non-LVOT PVCs, despite lower absolute burden, produce more severe structural remodeling through location-dependent dyssynchrony.

Furthermore, our study revealed a marked nocturnal predominance of symptoms in the Non-LVOT group. This may be indicative of the dominance of location-dependent dyssynchrony over autonomic modulation. Although nocturnal parasympathetic predominance is generally associated with the suppression of ectopic activity, the inherent dyssynchrony of Non-OT foci may cause a resistance to autonomic suppression. In addition, nocturnal metabolic changes in cardiac myocytes may further exacerbate calcium dysregulation in regions of mechanical stress, while the anatomical characteristics of Non-OT myocardium may cause it to be less responsive to parasympathetic modulation compared to OT foci (17,18). As is known, the anatomical location is a determining factor in structural vulnerability through dyssynchrony but it may also confer electrophysiological susceptibility to nocturnal arrhythmogenesis.

Electrical Complexity and Electrocardiographic Morphology

Non-OT origin PVCs showed significantly greater electrical complexity, with multifocal origins doubling the rates observed in OT groups. This finding reflects the pathophysiological mechanism demonstrated by Yokokawa et al. (19) wherein broader QRS complexes characteristic of Non-OT origins create greater dyssynchrony and a more heterogeneous electrophysiological substrate prone to multiple ectopic foci. The same study showed that QRS prolongation independently increases the risk of PVC induced CMP, which indirectly promotes the multifocal substrate development (19). This mechanism is supported by a study in which increased QRS duration was shown to be an independent risk factor for CMP, and these results in turn generate new substrates which may be play a role for new origins for PVCs (20).

In addition, the significantly higher interpolation rate in the Non-LVOT group reflects location-specific conduction properties that permit ectopic impulses to conduct through the His-Purkinje system without disrupting sinus rhythm. In contrast, the prolonged QTc interval in the LVOT group suggests site-specific autonomic influences on repolarization kinetics (21). These findings collectively demonstrate that anatomical location is a critical determinant of electrical properties and substrate complexity, with important implications for clinical management and therapeutic outcomes.

Medication Response and Therapeutic Implications

The differential medication usage patterns across the four groups may reflect the underlying electrophysiological mechanisms and clinical characteristics. In our cohort, beta-blocker utilization peaked in the RVOT group, while calcium channel blockers were more frequently prescribed for Non-OT origins. It is important to acknowledge that this usage could represent a confounding factor, potentially influencing HR and CI parameters. However, These patterns may also suggest that clinicians may have observed the differential responsiveness of different PVC origins to various antiarrhythmic agents.

Recent studies examining treatment response predictors have demonstrated that age, LVEF, PVC QRS duration, CI variability, and the presence of multiple PVC morphologies are significant factors affecting treatment response to different antiarrhythmic agents (22). Advanced age and reduced LVEF were associated with better response to beta-blocker treatment, in contrast calcium channel blocker responders showed narrower QRS complexes. Beta-blocker responders demonstrated increased CI variability, suggesting a potential link to automaticity mechanisms, and had higher frequency of multiple PVC morphologies (22). These findings support the hypothesis that PVC origin and electrophysiological characteristics should guide therapeutic selection.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective design is susceptible to selection bias and relies on the accuracy of previously recorded data. Second, the classification of PVC origin was based on surface ECG criteria, which, despite

established algorithms, may not be as precise as invasive electrophysiological mapping although our interobserver agreement was high. Third, while we assessed autonomic function via circadian rhythms and HR, a more detailed analysis using time- or frequency-domain HRV indices was not performed. The absence of these data limits a more in-depth understanding of autonomic modulation. Fourth, while we observed significant structural differences, more extensive multivariable modeling adjusting for all potential confounders simultaneously was not performed; thus, the independent predictive value of anatomical origin requires further validation. Finally, the use of beta-blockers or calcium channel blockers by a portion of the study population is another limitation, as these agents could act as a potential confounding factor by influencing HR and CI parameters.

Conclusion

This study demonstrates that PVC origin significantly influences electrophysiological characteristics, autonomic modulation patterns, and structural cardiac consequences. Traditional OT origins (RVOT and LVOT) exhibit high arrhythmic burden with organized CIs, suggesting triggered activity mechanisms, while Non-RVOT and Non-LVOT demonstrate markedly elevated CI heterogeneity and enhanced autonomic sensitivity despite lower arrhythmic burden. Most notably, the Non-LVOT group exhibits the most advanced LV remodeling despite lower PVC burden, suggesting that anatomical origin and autonomic sensitivity may be equally important determinants of structural vulnerability as arrhythmic burden itself.

These findings have important implications for clinical risk stratification and therapeutic decision-making. The dissociation between arrhythmic burden and structural remodeling in Non-LVOT origins suggests that current risk stratification models based primarily on PVC burden may underestimate the structural vulnerability of patients with LV Non-OT origins. Future research incorporating, treatment response data, and long-term follow-up will be essential to establish origin-specific therapeutic strategies and clarify the natural history of structural remodeling in different PVC origin groups.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Ethics Committee of University of Health Sciences Turkey, Göztepe Prof. Dr. Süleyman Yalçın City Hospital (date: 22.01.2026, decision no: 2026/0036), and all procedures were conducted in strict accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants prior to study enrollment.

Footnotes

Authorship Contributions

Concept: Y.Y., F.B.Ö., E.Ç., M.Y., A.U.S., S.T.Y., İ.Y., Design: Y.Y., A.A., A.K., F.B.Ö., A.U.S., S.T.Y., M.K., Ö.Ç., Data Collection or Processing: Y.Y., A.A., M.Y., M.T.Y., M.K., M.Ç., Analysis or Interpretation: A.A., A.K., M.Y., A.U.S., S.T.Y., İ.Y., M.Ç., Literature Search: Y.Y, A.K., F.B.Ö., E.Ç., M.T.Y., M.K., Writing: Y.Y., M.Y., İ.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Sobotka PA, Mayer JH, Bauernfeind RA, Kanakis C Jr, Rosen KM. Arrhythmias documented by 24-hour continuous ambulatory electrocardiographic monitoring in young women without apparent heart disease. Am Heart J. 1981;101(6):753-759.
2. Lee GK, Klarich KW, Grogan M, Cha YM. Premature ventricular contraction-induced cardiomyopathy: a treatable condition. Circ Arrhythm Electrophysiol. 2012;5(1):229-236.
3. Tran CT, Calkins H. Premature ventricular contraction-induced cardiomyopathy: an emerging entity. Expert Rev Cardiovasc Ther. 2016;14(11):1227-1234.
4. Hoogendijk MG, Géczy T, Yap SC, Szili-Torok T. Pathophysiological mechanisms of premature ventricular complexes. Front Physiol. 2020;11:406.
5. Suba S, Pelter MM. Clinical significance of premature ventricular contraction among adult patients: protocol for a scoping review. Syst Rev. 2019;8(1):254.
6. He W, Lu Z, Bao M, Yu L, He B, Zhang Y, et al. Autonomic involvement in idiopathic premature ventricular contractions. Clin Res Cardiol. 2013;102(5):361-370.
7. de Vries LJ, Martirosyan M, van Domburg RT, Wijchers SA, Géczy T, Szili-Torok T. Coupling interval variability of premature ventricular contractions in patients with different underlying pathology: an insight into the arrhythmia mechanism. J Interv Card Electrophysiol. 2018;51(1):25-33.
8. Huizar JF, Kaszala K, Potfay J, Minisi AJ, Lesnefsky EJ, Abbate A, et al. Left ventricular systolic dysfunction induced by ventricular ectopy: a novel model for premature ventricular contraction-induced cardiomyopathy. Circ Arrhythm Electrophysiol. 2011;4(4):543-549.
9. Lin CY, Chang SL, Lin YJ, Lo LW, Chung FP, Chen YY, et al. Long-term outcome of multiform premature ventricular complexes in structurally normal heart. Int J Cardiol. 2015;180:80-85.
10. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients

with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997-4126.

11. Anderson RD, Kumar S, Parameswaran R, Wong G, Voskoboinik A, Sugumar H, et al. Differentiating right- and left-sided outflow tract ventricular arrhythmias: classical ECG signatures and prediction algorithms. Circ Arrhythm Electrophysiol. 2019;12(6):e007392.
12. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18(12):1301-1310.
13. Qin F, Zhao Y, Bai F, Ma Y, Sun C, Liu N, et al. Coupling interval variability: a new diagnostic method for distinguishing left from right ventricular outflow tract origin in idiopathic outflow tract premature ventricular contractions patients with precordial R/S transition at lead V3. Int J Cardiol. 2018;269:126-132.
14. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-ınduced cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(18):2328-2344.
15. Rivaud MR, Blok M, Jongbloed MRM, Boukens BJ. How cardiac embryology translates into clinical arrhythmias. J Cardiovasc Dev Dis. 2021;8(6):70.
16. Iwai S, Cantillon DJ, Kim RJ, Markowitz SM, Mittal S, Stein KM, et al. Right and left ventricular outflow tract tachycardias: evidence for a common electrophysiologic mechanism. J Cardiovasc Electrophysiol. 2006;17(10):1052-1058.
17. Walters TE, Rahmutula D, Szilagyi J, Alhede C, Sievers R, Fang Q, et al. Left ventricular dyssynchrony predicts the cardiomyopathy associated with premature ventricular contractions. J Am Coll Cardiol. 2018;72(23 Pt A):2870-2882.
18. Wagner S, Maier LS, Bers DM. Role of sodium and calcium dysregulation in tachyarrhythmias in sudden cardiac death. Circ Res. 2015;116(12):1956-1970.
19. Yokokawa M, Kim HM, Good E, Crawford T, Chugh A, Pelosi F Jr, et al. Impact of QRS duration of frequent premature ventricular complexes on the development of cardiomyopathy. Heart Rhythm. 2012;9(9):1460-1464.
20. Ma Q, Zou B, Shi Y, He Q, Zhang M, Feng C. Speckle tracking technology and investigation of risk factors for premature ventricular contraction-induced cardiomyopathy. Front Cardiovasc Med. 2025;12:1675906.
21. Marcus GM. Evaluation and management of premature ventricular complexes. Circulation. 2020;141(17):1404-1418.
22. Atici A, Sahin I, Doğan Ö, Barman HA, Kup A, Celik M, et al. Can the efficacy of a medical treatment be predicted based on the type of idiopathic premature ventricular contraction? J Electrocardiol. 2024;86:153782.