Effect of circadian variability in frequency of premature ventricular complexes on left ventricular function

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BACKGROUND Frequent idiopathic premature ventricular complexes (PVCs) can result in a reversible form of cardiomyopathy.

OBJECTIVE The purpose of this study was to assess the impact of variability in PVC frequency throughout the day on PVC-induced cardiomyopathy.

METHODS The subjects of this study were 107 consecutive patients (58 men [54%]; mean age 49.7 ± 15.0 years; left ventricular ejection fraction 50.4% ± 11.4%) referred for ablation of frequent PVCs. All patients underwent 24-hour Holter monitoring before the ablation procedure. The circadian variation in PVC burden was determined and correlated with the presence or absence of cardiomyopathy.

RESULTS A total of 43 patients (40%) had cardiomyopathy. Patients with cardiomyopathy had an ejection fraction of 38.4% ± 6.9%, a higher PVC burden (28.5% ± 11.5% vs 19.5% ± 10.5%; $P = .0001$), less variability in circadian PVC distribution (coefficient of variation hourly: 31.5% ± 21% vs 59.8% ± 32.4%; $P = .0001$), and more frequent interpolated PVCs (20 patients [47%] vs 15 patients [23%]; $P = 0.022$), and were more frequently asymptomatic than patients without cardiomyopathy (56% vs 19%; $P = .0001$). In multivariate analysis, consistency in PVC burden throughout the day was an independent predictor of PVC-induced cardiomyopathy (odds ratio 16.3; 95% confidence interval 1.7–155.3; p = 0.015).

CONCLUSION In patients with frequent PVCs, consistency in hourly PVC frequency throughout the day is an independent predictor of PVC-induced cardiomyopathy.

KEYWORDS PVC; Cardiomyopathy; PVC-induced cardiomyopathy; Circadian variation; Variability; Predictor of cardiomyopathy; Ablation; Premature ventricular complexes

ABBREVIATIONS **CoV** = coefficient of variation; **LV** = left ventricular; **PVC** = premature ventricular complex

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Introduction

Frequent premature ventricular complexes (PVCs) can cause a reversible cardiomyopathy.[1–4] Several factors have been associated with PVC-induced cardiomyopathy: PVC burden,[5] presence of interpolated PVCs,[6] presence or absence of symptoms,[7] QRS duration of PVCs,[8] and epicardial PVC origin.[8] The circadian variation in PVCs in patients with frequent PVCs has not been analyzed in detail. The purpose of this study was to assess the impact of circadian PVC variability on PVC-induced cardiomyopathy.

Methods

Patients characteristics

The subjects (Table 1) of this retrospective study were 107 consecutive patients (58 men [54%]; mean age 49.7 ± 15.0 years; left ventricular [LV] ejection fraction 50.4% ± 11.4%) with frequent PVCs referred for catheter ablation between November 2005 and September 2011. LV dysfunction with an ejection fraction of <50% was present in 43 patients (40%). The patient's symptoms included palpitations in 68 patients (64%), lightheadedness in 14 patients (13%), syncope in 3 patients (3%), while 36 patients (34%) were asymptomatic.

The patients had failed to respond to a mean of 0.8 ± 0.3 antiarrhythmic medications including β-blockers and calcium channel blockers. The presence of structural heart disease was ruled out by echocardiography, cardiac magnetic resonance imaging, cardiac catheterization, and/or stress testing. All patients underwent echocardiography and 95 patients cardiac magnetic resonance imaging.

Assessment of LV function

Echocardiography was performed before the ablation procedure using Simpson's formula. For assessment of the LV ejection fraction, the second of 2 consecutive sinus beats was used to avoid postextrasystolic potentiation. An LV ejection fraction of <50% was considered abnormal. Echocardiography with a quantitative assessment of the LV function was

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Table 1 Characteristics of patients with and without cardiomyopathy

Characteristic	Patients with cardiomyopathy	Patients without cardiomyopathy	*P*
No. of patients	43	64	
Age (y)	48.5 ± 15.9	47.1 ± 12.9	.24
Sex: male	32 (74)	26 (41)	.001
Ejection fraction (%)	38.3 ± 5.3	58.4 ± 4.3	.0001
Duration of palpitation (mo)*	133.5 ± 123.2	52.4 ± 68.8	.008
PVC burden (%)	28.5 ± 11.5	19.5 ± 10.5	.0001
Monomorphic PVC	12 (28)	35 (55)	.006
Interpolation	20 (47)	15 (23)	.022
Asymptomatic patients	24 (56)	12 (19)	.0001
QRS duration of PVCs (ms)	157.2 ± 12.8	149.7 ± 12.4	.0001
CoV hourly (%)	31.5 ± 21	59.8 ± 32	.0001
Interquartile CoV (%)	24 ± 18	47 ± 30	.0001
Interquartile CoV <31%	35 (81)	22 (34)	.0001
Heart rate (beats/min)	75.3 ± 8.5	76.3 ± 11.6	.81
β-Blockers	30 (70)	47 (73)	.68
Calcium channel blocker	7 (16.3)	21 (33)	.056
Digoxin	1 (2.3)	2 (3.1)	.84
AA	9 (21)	17 (27)	.51
ACE inhibitor/ARB	22 (51)	14 (22)	.002

Values are presented as mean ± SD or as n (%).

AA = antiarrhythmic therapy including amiodarone; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CoV = coefficient of variation; PVC = premature ventricular complex.

*Duration in symptomatic patients.

repeated 3–6 months postablation. A patient was considered to have PVC-induced cardiomyopathy if the abnormal ejection fraction either normalized or increased at least 15% from the initial value. The interobserver agreement between 2 readers was a κ value of 0.80 ($P = .0001$).

Holter monitoring

Twenty-four-hour Holter monitoring was performed before the ablation procedure. Holter monitoring was used to determine the PVC burden and the distribution of the PVCs over a 24-hour period. The coefficient of variation (CoV) was used to describe the variation in PVCs in Holter monitoring. The CoV was defined as a ratio between the standard deviation and the mean. It is a measure of the dispersion of a frequency distribution, that is, the distribution of the PVC burden. The PVC distribution in 24-hour Holter monitoring was assessed as a measure of the intraindividual variability in the PVC burden between quartiles of the day (hours: 0000–0600, 0600–1200, 1200–1800, and 1800–0000) and also hourly. The distribution of the PVCs over the quartiles of the 24-hour recording time was assessed in each patient. Furthermore, the PVC burden per quartile was compared between patients. Holter monitoring was repeated 3–4 months postablation, and a PVC burden of ≤80% of the initial burden was defined as a successful ablation procedure.

Electrophysiological procedure and ablation

The protocol was approved by the institutional review committee. After informed consent was obtained, several multipolar catheters were placed in the right ventricle, the right atrium, and the His bundle position. Activation mapping was performed for frequent PVCs and pace mapping for infrequent PVCs. For right-sided procedures, 3000 units of heparin were initially administered as a bolus followed by 1000 units every hour. For left-sided procedures, a 5000-unit bolus was administered after arterial access was obtained and the heparin dosage was then titrated to maintain an activated clotting time of ≥250 seconds.

A 3.5-mm open-irrigated-tip catheter (ThermoCool NaviStar, Biosense Webster Inc, Diamond Bar, CA) was used for mapping and ablation. Radiofrequency energy was applied at a power of 30–35 W and a maximal temperature of 45°C.

Follow-up

Patients were seen in 3 and 12–48 months postablation. An echocardiogram was repeated 3–6 months postablation if the baseline ejection fraction had been abnormal. All antiarrhythmic medications were discontinued if ablation was effective. β-Blockers and heart failure medications were continued initially and were discontinued if and when LV function and dimensions normalized. No new medications were added after an effective ablation procedure.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Discrete variables were compared using the Fisher exact test or χ^2 test, as appropriate, and continuous variables were compared using the 2-sample *t* test. Repeated measures were compared using the Wilcoxon rank sum test. Levene's test was used to test the homogeneity of variance between groups. A correlation coefficient was calculated to assess the relationship between PVC burden variance and symptom duration. Parameters that were associated with a *P* value of <.1 were used in the logistic regression analysis with LV dysfunction as a dependent variable to assess whether they were independently associated with LV dysfunction. Results were reported as odds ratios with 95% confidence intervals. All data were analyzed by using SPSS statistical software version 20.0 (SPSS Inc, Chicago, IL). A *P* value of <.05 was considered statistically significant.

Results

Baseline characteristics

In univariate analysis (Table 2), male sex, high PVC burden, presence of interpolation, asymptomatic status, longer QRS duration of PVC and symptom duration, presence of pleomorphic PVCs, and low hourly and low interquartile variation in the PVC burden were associated with cardiomyopathy (Tables 1 and 2). The sites of origin of PVCs were similar between patients with and without cardiomyopathy. The PVC burden in patients without symptoms was higher

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