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Long-term outcome of multiform premature ventricular complexes in structurally normal heart

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ABSTRACT

Background: Multiform premature ventricular complexes (PVCs) are common electrocardiographic abnormalities in patients with structurally normal hearts. However, the prognostic value of these complexes remains unclear. This study aimed to clarify the role of PVC polymorphism in predicting adverse outcomes.
Methods and result: We examined the database for 24-hour electrocardiography monitoring between January 1, 2002 and December 31, 2004. We analyzed 3351 individuals with apparently normal hearts. Kaplan–Meier curves and multivariate Cox proportional hazards models were employed to estimate the effect of multiform PVC and uniform PVC on the number of incident adverse events. Average follow-up time was 10 ± 1 years. Patients with multiform PVC were older and had a higher prevalence of comorbidities. In multivariate analysis, patients with multiform PVC had an increased incidence of mortality (hazard ratio [HR]: 1.642, 95% confidence interval [CI]: 1.327–2.031), hospitalization (HR: 1.196, 95% CI: 1.059–1.350), cardiovascular hospitalization (HR: 1.289, 95% CI: 1.030–1.613), new-onset heart failure (HF; HR: 1.456, 95% CI: 1.062–1.997), transient ischemic accident (HR: 1.411, 95% CI 1.063–1.873), and new-onset atrial fibrillation (AF; HR: 1.546, 95% CI: 1.058–2.258) compared to the group without PVC. Patients with multiform PVC had a higher rate of mortality (HR: 1.231, 95% CI: 1.033–1.468) and all cause-hospitalization (HR: 1.147, 95% CI: 1.025–1.283) compared with patients with uniform PVC.
Conclusion: The presence of multiform PVC was associated with a higher incidence of mortality, hospitalization, transient ischemic attack, new-onset AF, and new-onset HF independent of other clinical risk factors.

1. Introduction

Premature ventricular complex (PVC) is an early depolarization of the ventricular myocardium and is a common finding on electrocardiography (ECG) in patients with or without structural heart diseases [1–3]. Frequent PVC has been defined as more than one beat of PVC during a 2-minute ECG recording or more than 30 beats of PVC over a 1-hour recording (720/day) [4]. Increased PVC burden has been associated with sudden cardiac death, cardiovascular (CV) events, cardiomyopathy, and ischemic stroke [4–6]. A previous study suggested that multiform PVC might be associated with adverse events (i.e., CV events or new/worsening heart failure [HF]) and underlying cardiac disease [7]. However, the prognostic value of the PVC pattern (uniform or multiform) has not been extensively investigated. To the best of our knowledge, no clinical studies to date have investigated the relationship between PVC morphology and clinical outcome in patients with structurally normal hearts. We hypothesized that multiform PVC can predict adverse outcomes in patients with apparently normal hearts and less PVC burdens (PVC < 720/day) [4,8]. The aim of this study was to evaluate the prognostic significance of PVC polymorphism revealed by continuous ambulatory ECG monitoring in patients with apparently normal hearts.

2. Methods

2.1. Study population

This retrospective, observational study was based on the "Registry of 24-hour ECG monitoring at Taipei Veterans General Hospital" database. Taipei Veterans General Hospital is a large integrated healthcare delivery system providing comprehensive medical services to more than three million populations in Taiwan. The study group included 5903

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Table 1
Study population characteristics.

	No PVC	Uniform	Multiform	P value
	n = 1111	n = 1074	n = 1166	
Age (year)	50.7 ± 20.1	58.7 ± 19.3	65.7 ± 16.9	<0.001
Sex (male)	518 (46.6)	592 (55.1)	800 (68.6)	<0.001
Diabetes mellitus	62 (5.6)	80 (7.4)	110 (9.4)	0.002
Hypertension	240 (21.6)	335 (31.2)	443 (38.0)	<0.001
Hyperlipidemia	61 (5.5)	80 (7.4)	68 (5.8)	0.130
Chronic kidney disease	3 (0.3)	15 (1.4)	16 (1.4)	0.01
Cirrhosis	5 (0.5)	9 (0.8)	9 (0.8)	0.497
Atrial fibrillation	74 (6.7)	78 (6.7)	79 (6.8)	0.967
Chronic lung disease	22 (2.0)	28 (2.6)	33 (2.8)	0.404
Anti-arrhythmic[a]	5 (0.5)	2 (0.2)	6 (0.5)	0.244
Anti-hypertension	146 (12.2)	176 (16.4)	242 (20.8)	0.003
Beta-blocker	44 (3.9)	46 (4.3)	52 (4.5)	0.213
Calcium channel blocker	92 (8.2)	101 (9.4)	124 (10.6)	0.105
ACEI/ARB	31 (2.7)	36 (3.4)	46 (3.9)	0.287
Diuretics	46 (4.4)	48 (4.5)	74 (6.3)	0.153
Alpha-blocker	8 (0.7)	8 (0.7)	10 (0.9)	0.502
Statin	57 (5.1)	77 (7.2)	66 (5.7)	0.114

Values are number of events (%) unless otherwise indicated. PVC indicates premature ventricular complex.
[a] Class I or class III antiarrhythmic drugs.

consecutive patients with age more than 18 years old who received 24-hour ECG monitoring by physicians' clinical decision between January 1, 2002 and December 31, 2004 in Taipei Veterans General Hospital. Patients were referred for Holter monitoring for the following indications: palpitations, syncope, suspected arrhythmia, and clinical follow-up depended on physician's decision. Collected variables, including past medical history, risk factors, comorbidities, and medications, were obtained from one or more primary or secondary hospital discharge diagnoses, outpatient visits, emergency visits, and the Collaboration Center of Health Information Application (CCHIA), Ministry of Health and Welfare in Taiwan. The International Classification of Diseases, Ninth Revision (ICD9) codes were ascertained for the underlying diseases before 24-hour ECG monitoring. The diagnoses were recorded twice in outpatient department records, or at least once in in-patient records. Participants with prevalent sustained or non-sustained ventricular tachycardia (defined as reported history of tachycardia on baseline 12-lead ECG or on baseline Holter monitoring), permanent pacemaker (confirmed as a reported history of permanent pacemaker at their first study encounter on baseline 12-lead ECG or on baseline Holter monitoring), HF (confirmed by physician report, discharge summary, and echocardiography report), previous myocardial infarction (confirmed by physician report or review of medical chart), history of ablation, and valvular heart disease (confirmed by physician report or review of medical chart) were excluded. Patients with frequent PVC, more than 720 beats per day [4,8], were excluded. The final sample included 3351 patients with apparently normal hearts. Medical history was collected from all patients, and physical examinations were performed. Baseline CV comorbid conditions were confirmed by participant history and physical examination, physician report, and medical record review. Our previous studies have provided the validation of the above said methodology [9,10].

2.2. Follow-up and event ascertainment

Follow-up visits of all participants were scheduled depending on the clinical course or after a new event in this study. Patients with regular medication were scheduled regular follow-up with 1 to 3 month interval. After the document of each new event, patients were followed every two weeks for one month and then one to three month interval. Patients without regular medication were scheduled follow-up every one year or after new events depending on physician's decision. The follow-up data was retrieved from Taipei Veterans General Hospital and Taiwan National Health Insurance Research Database (NHIRD). The Taiwan's National Health Insurance (NHI) program enrolled 23 million people, which covered 99% of the country's population. The insurance claim database can be used for studies of natural diseases, and clinical research in real-world clinical settings. In this cohort dataset, the patients' original identification numbers had been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the NHI database and could be followed up continuously. The primary endpoints of this study were all-cause mortality, hospitalization for CV-related conditions (CV hospitalization), all-cause hospitalization, new-onset atrial fibrillation (AF), ischemic stroke, transient ischemic attack (TIA), and new-onset HF. Potential incident events, the number of inpatients, and all deaths were investigated in detail based on initial identification through *International Classification of Diseases* diagnostic codes or mention of an endpoint on the hospital face sheet, previous discharge summary, outpatient clinic report and the database of the CCHIA which had been validated previously [10–12]. Hospitalization was defined as an overnight stay in a hospital ward, excluding the visits in the Emergency Department. New-onset HF and new-onset AF were confirmed by physician reports, documented echocardiography reports, electrocardiographic reports, and medical record review during regular clinical visits or mention of an endpoint on the hospital face sheet and discharge summary. Ischemic stroke was confirmed by brain images. The follow-up period was from the registry start date to February 28, 2013.

2.3. PVC and morphology assessment

All subjects underwent 24-hour ambulatory Holter monitoring (Medilog FD4, Oxford Instruments, sampling rate 2048 Hz). Simultaneous three-channel 24 h Holter recorded by a digitized Holter analyzer (Medilog FD4, Oxford Instruments) and analyzed by Medilog Excel-3 (Medilog Cardiology information system V2.3, Oxford Instruments) identified ventricular premature beats. QRS morphology was automatically performed by a digitized Holter analyzer and obtained after review and manual editing by two experienced technicians. Two physicians again manually reviewed the whole automatic interpretation of recording of all arrhythmic episodes and all unknown strips. One licensed electrophysiologist (Cardiologist) confirmed the report. There was no strict recording start time, and the recording stops after 24 hour recording. Patients who didn't complete a full 24-hour monitoring period or had detachment of electrodes during 24-hour monitoring were excluded as poor-quality ECG monitoring. Patients with PVCs of a single morphology (uniform) during 24-hour Holter monitoring comprised the uniform PVC group, while the multiform PVC group included patients with PVCs of at least two morphologies (i.e., initial and mean axes of the QRS complex and the T-wave differed between two PVCs in one channel of the recording, which was confirmed by an experienced electrophysiologist) during 24-hour Holter monitoring.

2.4. Risk factors

Data were collected on the basis of demographic characteristics (i.e., age and sex) from the medical records of patients. Target comorbidities, such as diabetes mellitus, hypertension, chronic kidney disease, and liver disease were determined using the *International Classification of Diseases*, *Ninth Revision* codes obtained from medical charts at the time of examination. Baseline AF was based on baseline 12-lead ECG or on baseline Holter monitoring. Medical history of anti-arrhythmia (class I and III anti-arrhythmic drugs) and anti-hypertension medication (including beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, diuretics, and alpha-blockers) was determined by medical chart review. All target comorbidities were validated by physical examination, physician report, medical record review, and CCHIA.

2.5. Statistical analysis

All analyses were performed using SPSS statistical software, version 20.0. Baseline patient characteristics were reported as means ± standard deviations for continuous variables and as percentages for categorical variables. Baseline characteristics between the three groups (Group 1, patients without PVC; Group 2, patients with uniform PVC; and Group 3, patients with multiform PVC) were compared using one-way analysis of variance for continuous variables. The chi-square test with Yates' correction was used to analyze the categorical variables. Kaplan–Meier survival curves were used to analyze survival data (i.e., time to adverse event). The log-rank test was used to compare survival curves. A Cox proportional hazards model was used to determine multivariate predictors of time to adverse event. The full model included all the variables that were considered statistically significant ($P < 0.05$) in the baseline characteristics.

The relative risk for a given endpoint associated with PVC morphology was estimated by calculating the hazard ratio (HR) using a Cox regression hazards model. This model was run with all parameters that had a P-value < 0.05 in their baseline data (i.e., age, sex, hypertension, diabetes mellitus, and anti-hypertensive medication). Comparisons between the groups for cause of death were performed using the chi-square test for categorical variables. HRs for polymorphisms in different subgroups of patients with individual risk factors are shown in a Forest plot.

3. Results

3.1. Baseline characteristics, PVC morphology and long-term outcomes

All 3351 patients in this study with mean of PVC 49 beats/day were followed up for 10 ± 1 years. Patients were referred for Holter monitoring for following indications: palpitations, syncope, suspected arrhythmia or clinical follow-up depending upon on physician's decision. The baseline characteristics of the patients are presented in Table 1. Patients with uniform PVC were generally older with a higher prevalence of males, diabetes mellitus, hypertension, chronic kidney disease, and anti-hypertensive medications in comparison with patients without PVC. Furthermore, patients with multiform PVC were older with a higher prevalence of males, diabetes mellitus, hypertension, chronic kidney disease, and anti-hypertensive medications in comparison with patients with uniform PVC. There was no significant difference in prevalence of hyperlipidemia, cirrhosis, atrial fibrillation and pulmonary diseases in these three groups. The prescription of anti-arrhythmic agents and statin usage also did not differ in these three groups. During