



Association of frequent premature ventricular complex >10% and stroke-like symptoms without a prior diagnosis of stroke or transient ischemic attack

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ABSTRACT

Introduction: Premature ventricular complex (PVCs) detected from long-term ECG recordings have been associated with an increased risk of ischemic stroke. However, there was limited data about the association between high PVCs burdens (>10%) and stroke-like symptoms without a prior diagnosis of stroke or transient ischemic attack in the long-term follow up.

Methods: The Kosin University 24-hours holter monitoring, echocardiography, electrocardiogram (ECG) database were reviewed from 2013 to 2015 to identify patients with frequent PVCs (>10%). We compared the long-term clinical outcomes between the patients with frequent PVCs (>10%) and control group without PVC.

Results: Among 572 patients who underwent 24-hours holter monitoring, finally, 373 consecutive patients (mean age; 59.5 ± 15.8 years, 45.2% male) were enrolled. Among them, 203 (54.4%) patients had high PVCs burdens (>10%). There was no difference of the baseline characteristics. In the long term follow-up, PVCs burden was not associated with PVCs-related symptoms ($P = 0.210$). In univariate analysis, female, non-sustained ventricular tachycardia (VT), sinus QRS duration, PVC coupling interval (CI), post-PVC CI, and late precordial R-wave transition of PVCs were associated with PVCs-related symptoms. In multivariate analysis, non-sustained VT ($P = 0.022$) and late precordial R-wave transition of PVCs ($P = 0.044$) were independent risk factors for PVCs-related stroke-like symptoms with frequent idiopathic PVCs > 10%.

Conclusion: High PVCs burdens (>10%) were associated with and stroke-like symptoms without a prior diagnosis of stroke or transient ischemic attack in the long-term follow up, suggesting more intensive medical therapy with close clinical follow-up will be required.

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1. Introduction

Stroke is the leading cause of disability and the third leading cause of death in the World. Etiologies of ischemic stroke are well-documented but remain undetermined in 15% to 40% of patients. Numerous risk factors have been identified as targets of preventive strategies [1,2].

Premature ventricular complex (PVCs) are mostly asymptomatic irregular heart rhythms commonly seen on electrocardiograms (ECGs) of the middle-aged and elderly [3,4].

PVCs have been examined as predictors of cardiovascular morbidity and mortality, especially with pre-existing heart disease. The presence

of PVCs was associated with a 2-fold increase in the rate of fatal coronary heart disease [5]. Frequent PVCs are associated with impaired ventricular relaxation and have the potential to remodel the heart. In addition to their additive arrhythmogenic potential, such adverse remodeling may increase the risk of atrial fibrillation (AF), potentially increasing the risk of clot formation and embolization. In contrast to the established association of AF with incident stroke, the relationship of ventricular rhythm abnormalities with stroke has not been much study [6,7]. In a recent report from the Atherosclerosis Risk in Communities (ARIC) study, the presence of PVCs on 2-minute ECG rhythm strips was associated with a higher risk of ischemic stroke, suggesting that incidentally detected PVCs, typically dismissed as benign findings, may be a risk marker for future stroke [8].

However, there was limited data about the association between high PVCs burdens (>10%) and stroke-like symptoms without a prior diagnosis of stroke or transient ischemic attack (TIA) in the long-term follow up. The aim of this study was to evaluate the association of frequent PVCs > 10% and stroke-like symptoms without a prior diagnosis of stroke or TIA.

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2. Methods

2.1. Study populations

We retrospectively reviewed the medical records of 572 patients who underwent 24 h holter monitoring at Kosin university gospel hospital from January 2013 to November 2015.

Inclusion criteria included patients with/without PVCs. Patients with a history of PVC documented by a standard electrocardiogram (ECG) or Holter-ECG were enrolled.

Exclusion criteria included a history of cardiomyopathy, or valvular or congenital heart disease; hepatic or renal disease (known chronic liver disease or aspartate aminotransferase [AST] >3 times than normal range, more advanced CKD or stage 3); an acute cardiovascular or cerebrovascular event within the preceding 3 months [Brain magnetic resonance imaging were done in all patients and all patients were consulted with neurologist for selection of the patients with stroke-like symptoms]; any major trauma or surgery within the preceding 3 months; hyperthyroidism; uncontrolled hypertension; malignancy; connective tissue disease; or any acute or chronic inflammatory disease; ischemic heart disease.

Finally, 373 consecutive patients (mean age; 59.5 ± 15.8 years, 45.2% male) at Kosin university gospel hospital from January 2013 to November 2015 were enrolled. And all patients were monitored to evaluate stroke-like symptoms, thromboembolic events, arrhythmic events, re-hospitalization and death during follow-up according to the frequent PVCs > 10%. Symptom evaluation was determined by reviewing the cardiology records, created by cardiologist. If the patient felt painless weakness, sudden numbness or a dead feeling on one side of the body, sudden painless loss of vision, and sudden loss of ability to understand what people were saying related PVCs observed on an ECG, this was defined as stroke-like symptoms [9,10]. The baseline characteristics of the patients are presented in Table 1.

2.2. Data collection

After ECG and chest X-ray, cardiovascular status was evaluated for each patient using echocardiography, an exercise test, 24-h Holter recordings, and blood laboratory data from the initial visit, as determined by the attending physicians. From the database, the following information was collected: (1) patient data, including sex, age, height, and weight; (2) cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure 90 mm Hg on admission) and diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin $\geq 6.5\%$); (3) cardiovascular disease status, including structural heart disease, congestive heart failure, or a history of a disabling cerebral infarction or TIA; and (4) use of medication. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.3. Definitions of premature ventricular complex, arrhythmia and electrocardiographic measurement

Participants were requested to fast and to refrain from smoking and consuming caffeinated beverages before the examination. Electrocardiographic data processing, monitoring, and quality control have been described elsewhere. Rhythm strips were classified 3 times by independent trained coders for total supraventricular, ventricular complexes, and ventricular runs, bigeminy, trigeminy, and multiform complexes. Coding for PVCs was done before this study's hypothesis was formulated and before stroke-like symptomatic outcomes were ascertained. Adjudication of disagreements was performed by the ECG center principal investigator or coding supervisor. PVCs and heart rate were determined from the rhythm strip.

Table 1

Baseline demographics, medications, ECG and echocardiographic findings according to frequent idiopathic premature ventricular complex >10%.

Variables	Control group (n = 170)	PVC > 10% group (n = 203)	P-value
Age (years)	57.6 \pm 16.4	61.0 \pm 15.2	0.042
Gender (Male, %)	80 (47.3)	88 (43.3)	0.465
DM (%)	34 (20.0)	34 (17.5)	0.591
HTN (%)	52 (30.6)	55 (28.4)	0.647
CAD (%)	21 (12.4)	22 (11.3)	0.871
PCI (%)	8 (4.7)	16 (8.2)	0.207
CABG (%)	1 (0.6)	0 (0)	0.467
Medication			
Anti-arrhythmics (%)			
Amiodarone (%)	0 (0)	15 (7.7)	<0.001
Propafenone (%)	0 (0)	2 (1.0)	0.501
Digoxin (%)	8 (4.8)	10 (5.2)	0.484
Beta-blocker (%)	14 (8.2)	104 (53.6)	<0.001
CCB (%)	34 (20)	42 (21.6)	0.989
ARB & ACEi (%)	28 (16.4)	33 (17.0)	0.896
Statins (%)	64 (37.6)	80 (39.4)	0.464
Aspirin (%)	43 (25.3)	50 (24.6)	0.268
Clopidogrel	20 (12.0)	26 (13.4)	0.118
VKA	19 (11.2)	19 (9.8)	0.732
Laboratory findings			
WBC (10^3 /uL)	7.8 \pm 3.0	7.4 \pm 2.7	0.598
Creatinine (mg/dL)	1.3 \pm 0.9	1.2 \pm 0.6	0.436
TSH (mg/dL)	2.8 \pm 1.7	2.7 \pm 1.6	0.898
fT4	1.2 \pm 0.5	1.2 \pm 0.4	0.683
Pro-BNP	1281.1 \pm 231.5	1469.5 \pm 876.4	0.700
Echo parameters			
LVEF (%)	59.1 \pm 11.9	62.9 \pm 13.5	0.006
LVIDs (mm)	31.2 \pm 9.4	34.5 \pm 7.9	0.001
LVIDd (mm)	46.8 \pm 8.0	50.6 \pm 6.6	<0.001
IVSD (mm)	12.1 \pm 3.7	10.8 \pm 2.7	<0.001
LVPWD (mm)	10.4 \pm 2.2	9.9 \pm 2.2	0.030
LAVi (mL/m ²)	22.1 \pm 17.9	24.8 \pm 12.1	0.193
E velocity (cm/s)	0.7 \pm 0.2	0.8 \pm 0.3	0.266
A velocity (cm/s)	0.7 \pm 0.2	0.7 \pm 0.2	0.111
E'	0.1 \pm 0.03	0.1 \pm 0.04	0.427
E/E'	11.4 \pm 6.6	11.9 \pm 7.0	0.511

Values are mean \pm SD (range). PVC indicates premature ventricular complex; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; PCI, percutaneous coronary intervention, CABG, coronary artery bypass graft surgery; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin converting enzyme inhibitor; VKA, vitamin K antagonist; WBC indicates white blood cell count; fT4, free thyroxine 4; proBNP, pro-B type N-terminal peptide; LVEF, left ventricular ejection fraction; LVIDs, left ventricular systolic diameter; LVIDd, left ventricular diastolic diameter; IVSD, interventricular septal diameter; LAVi, left atrial volume index; E, the peak mitral flow velocity of the early rapid filling wave; A, peak velocity of the late filling wave due to atrial contraction; E', early diastolic mitral annulus velocity; A', late diastolic mitral annulus velocity.

The presence of any PVCs was classified by the frequency of their occurrence on 24 hours Holter monitoring. Mean 2.8 times/person of 24 hours Holter monitoring were done during the follow-up.

Several other ECG parameters were measured including 1) Baseline sinus cycle length (ms), from the R peak of one sinus beat to the R peak of the next sinus beat; 2) PVC QRS width (ms), from the onset of the PVC to the terminal S wave; 3) PVC coupling interval (CI, ms), from the onset of the R wave of the previous sinus beat to the onset of the PVC; 4) PVC CI ratio (%), PVC CI/sinus cycle length \times 100%; 5) Post-PVC CI, from the onset of the PVC to initiation of the next sinus beat; 6) Post-PVC CI ratio (%), post-PVC CI/sinus cycle length \times 100%; 7) PVC amplitude (mV), highest amplitude of the PVC in the precordial leads [11]. The Muse® Cardiology Information System (GE Healthcare, Piscataway, NJ, USA) was used to measure the width and amplitude of the PVCs, as well as CI and cycle length of both the PVCs and sinus beats. To assess intra-observer variation, parameters were measured for five consecutive normal sinus rhythms and PVC beats.

In our study, paroxysmal AF was defined as sinus rhythm on ECG and previous diagnosis of paroxysmal AF by referring physicians. Patients whose AF was estimated to continue for ≥ 7 days after the initial visit were considered to have persistent AF originally. Asymptomatic AF

was defined as AF documented on 12 lead ECG during a visit, in the absence of any new symptoms such as palpitations, tachycardia, fatigue, malaise, shortness of breath on exertion, dyspnea, chest pain, syncope, or pre-syncope related to AF or other illnesses. During the follow-up period, the onset of persistent AF was defined as the first time in which all ECGs indicated AF after ≥ 3 consecutive ECGs at intervals of ≥ 1 week after the initial examination [12].

2.4. Characteristic analysis of PVCs associated with stroke-like symptoms on the 24 hours Holter monitoring

A receiver operating characteristics curve for the number of PVCs on the 24 hours Holter monitoring revealed that a cutoff of PVC burden with $>10.5\%$ best separated patients with and without stroke-like symptoms in our study. The area under curve (AUC) was 0.627 (95% CI 0.557–0.697; $P = 0.001$) and the sensitivity was 90.2%, and the specificity was 94.4%.

2.5. Transthoracic echocardiography

All enrolled subjects underwent 2-dimensional transthoracic echocardiography (TTE). All examinations were performed using a commercially available Vivid 9™ (GE Medical System, Vingmed, Horten, Norway) ultrasound system. All recorded echocardiograms were measured and interpreted with clinical information blinded using a computerized off-line analysis station (Echopac™ 6.3.4; GE Medical System).

All measurements were derived from 3 consecutive cardiac cycles and averaged. The left ventricular (LV) dimensions, wall thicknesses and left atrial dimensions (LAD) were determined in the parasternal long-axis view with the M-mode cursor positioned just beyond the mitral leaflet tips perpendicular to the long axis of the ventricle according to the recommendations of the American Society of Echocardiography [13]. The LV ejection fraction (LVEF) was obtained via the modified biplane Simpson method from the apical 4- and 2-chamber views. LV dysfunction was defined as LVEF $< 55\%$ in our study [14].

2.6. Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and the research protocol was approved by the ethics committee of Kosin university gospel hospital [15]. All patients provided written informed consent.

2.7. Statistical analysis

All continuous variables are expressed as either mean \pm standard deviation (SD) or median (25th, 75th interquartile range), depending on the distribution. For continuous data, statistical differences were evaluated using Student's *t*-test or the Mann-Whitney *U* test, depending on the data distribution. Categorical variables are presented as frequencies (percent) and were analyzed using the chi-squared test. To determine whether any of the variables were independently related to stroke-like symptom and new-onset LV dysfunction according to PVCs burden, a multivariate analysis of variables with a P -value < 0.05 in the univariate analysis was performed using linear logistic regression analysis. All correlations were calculated using Spearman's rank correlation test. All statistical analyses were conducted using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $P < 0.05$ (two-sided).

3. Results

The baseline demographics for both groups are listed in Table 1. Among 373 patients who underwent 24-h Holter monitoring, 203 (54.4%) patients had high PVCs burdens ($>10\%$). Baseline characteristics

Table 2

Clinical outcomes according to according to frequent idiopathic premature ventricular complex $>10\%$.

Variables	Control group (n = 170)	VPC $> 10\%$ group (n = 203)	<i>P</i> -value
Follow-up duration (months)	40.7 \pm 24.6	42.3 \pm 18.8	0.349
Re-admission (%)	90 (52.9)	115 (59.6)	0.205
Total Death (%)	0 (0)	9 (5.3)	0.004
Cardiac death (%)	0 (0)	2 (0.9)	
Total thromboembolic events (%)	7 (4.1)	8 (4.0)	1.000
CVA (new onset, %)	7 (4.1)	8 (4.0)	
Peripheral thromboembolism (%)	0 (0)	0 (0)	
Bleeding complications (%)	10 (5.9)	5 (2.5)	0.115
Arrhythmic Events (%)	8 (4.7)	58 (28.9)	<0.001
AF or ATach	8 (4.7)	12 (5.6)	
VT or VF	0 (0)	48 (23.3)	

Values are mean \pm SD (range). PVC indicates premature ventricular complex; CVA, cerebrovascular accidents; AF, atrial fibrillation; ATach, atrial tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation.

were not statistically different between the PVC $> 10\%$ group and the non- PVC group, except for age ($P < 0.042$).

For the history of medications, there was no difference between the PVC $> 10\%$ group and the non- PVC group, except for amiodarone ($P < 0.001$), and Beta-blocker ($P < 0.001$), that were used more often in the PVC $> 10\%$ group than in the non-VPC group.

In baseline laboratory findings, there was no difference between the PVC $> 10\%$ group and the non- PVC group. And there was no difference of the echocardiographic findings between the PVC $> 10\%$ group and the non- PVC group, except for LVEF, LVIDs, LVIDd, IVSD, and LVPWD (Table 1).

All patients were also monitored to evaluate arrhythmic events including AF, atrial tachycardia, atrial premature complex (APC), VT, and VPCs, re-hospitalization and death during follow-up. In our study, arrhythmic events was higher in patients with PVC $> 10\%$ compared to those without PVCs ($P < 0.001$; Table 2).

Age, hypertension, PVC $> 10\%$, LV hypertrophy, E/E' velocity, mitral regurgitation grade, and NT-proBNP level were associated with stroke-like symptoms without a prior diagnosis of stroke or TIA in univariate analysis. In multivariate analysis, PVC $> 10\%$ and E/E' velocity were independent risk factors for stroke-like symptoms without a prior diagnosis of stroke or TIA in our study (Table 3).

In subgroup analysis in patients with PVC $> 10\%$, female, non-sustained ventricular tachycardia (VT), sinus QRS duration, PVC coupling interval (CI), post- PVC CI, and late precordial R-wave transition of PVCs were associated with stroke-like symptoms without a prior diagnosis of stroke or TIA in univariate analysis. In multivariate analysis, non-sustained VT ($P = 0.022$) and late precordial R-wave transition of PVCs ($P = 0.044$) were independent risk factors for stroke-like symptoms without a prior diagnosis of stroke or TIA in our study

Table 3

Univariate and multivariate Cox analyses for stroke-like symptoms without a prior diagnosis of stroke or transient ischemic attack at 4-year follow-up.

Variable. N (%)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Age	1.007 (0.991–1.023)	0.404		
Atrial fibrillation	1.260 (0.449–3.533)	0.661		
Hypertension	1.485 (0.879–2.508)	0.140		
PVC $> 10\%$	2.122 (1.020–4.413)	0.044	3.421 (1.092–10.726)	0.035
LVH	1.608 (0.964–2.680)	0.069		
E/E'	1.035 (0.998–1.073)	0.066	1.068 (1.001–1.140)	0.048
MR grade	1.598 (1.090–2.342)	0.016		
NT-proBNP	1.002 (1.001–1.015)	0.049		

OR indicates odd ratio; CI, confidence interval; PVC, premature ventricular complex; LVH, left ventricular hypertrophy; E/E', the peak mitral flow velocity of the early rapid filling wave/early diastolic mitral annulus velocity; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B type natriuretic peptide.

Table 4

Univariate and multivariate Cox analyses for PVCs-related stroke-like symptoms (A) and new-onset LV dysfunction (B) in patients with frequent idiopathic premature ventricular complex >10% at 4-year follow-up.

(A)	Univariate analysis		Multivariate analysis	
Variable N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
Female (gender)	1.750 (1.001–3.174)	0.049		
Non-sustained VT	2.265 (1.099–4.670)	0.027	2.501 (1.141–5.485)	0.022
Sinus QRS duration (ms)	0.985 (0.970–0.999)	0.050		
PVC CI (ms)	0.036 (0.002–0.834)	0.038		
Post- PVC CI (ms)	0.382 (0.148–0.987)	0.047		
After V3 transition of Precordial R-wave	1.937 (1.032–3.638)	0.040	1.992 (1.017–3.914)	0.044

(B)	Univariate analysis		Multivariate analysis	
Variable N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.963 (0.924–0.994)	0.045		
Before V3 transition of precordial R-wave	3.900 (1.136–13.387)	0.031		
CI ratio	0.927 (0.871–0.987)	0.018	0.902 (0.815–0.999)	0.037
LAD	0.906 (0.834–0.986)	0.022		
LVEF	1.083 (1.022–1.146)	0.006	1.326 (0.999–1.760)	0.049
LVEDV	0.980 (0.962–0.998)	0.030		
LVESV	0.967 (0.941–0.994)	0.016		

OR indicates odds ratio; CI, confidence interval; VT, ventricular tachycardia; PVC CI, PVC coupling interval - from the onset of the R wave of the previous sinus beat to the onset of the PVC; Post- PVC CI, from the onset of the PVC to initiation of the next sinus beat.

OR indicates odds ratio; CI, confidence interval; VT, ventricular tachycardia; PVC CI, PVC coupling interval - from the onset of the R wave of the previous sinus beat to the onset of the PVC; Post- PVC CI, from the onset of the PVC to initiation of the next sinus beat.

OR indicates odds ratio; CI, confidence interval; CI, coupling interval; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume, LVESV, left ventricular end systolic volume.

[Table 4(A)]. And PVCs burden was not associated with new-onset LV dysfunction ($P = 0.17$) in patients with PVC > 10%. In univariate analysis, younger age, smaller chamber size including LV and left atrium, higher LVEF at baseline, short coupling interval (CI, CI/sinus cycle length) ratio, and early precordial R-wave transition of PVCs were significantly associated with new-onset LV dysfunction. In multivariate analysis, shorter CI ratio ($P = 0.037$) and higher LVEF at baseline ($P = 0.05$) were independent risk factors for new-onset LV dysfunction in patients with frequent idiopathic PVCs > 10% [Table 4(B)].

Kaplan-Meier curves show that the event free survival from stroke-like symptoms without prior diagnosis of stroke or TIA ($P = 0.007$; Fig. 1, supplement material) are lower in patients with PVC > 10% compared with those without PVC > 10% at 4 year follow-up.

4. Discussion

4.1. Major findings

In our study, we showed that high PVCs burdens (>10%) were associated with stroke-like symptoms without a prior diagnosis of stroke or TIA in the long-term follow up, suggesting more intensive medical therapy to control PVCs burden with close clinical follow-up will be required.

4.2. PVC burden, stroke-like symptoms and new onset LV dysfunction

Previous study reported that PVCs are associated with incident stroke and the presence of PVCs on routine screening ECG was associated with higher risk of ischemic stroke. Furthermore, this relationship is statistically significant and stronger in the subgroup without traditional risk factors for stroke such as diabetes or hypertension [5]. Our results considering stroke-like symptom without a prior diagnosis of stroke or TIA point toward a stronger association of high PVCs burdens (>10%) rather than with thrombotic stroke (potentially caused by atherosclerosis in the cerebral circulation).

Frequent PVCs have been associated with a LV diastolic dysfunction and have the potential for cardiac remodeling, enhancing thromboembolism. And given the stronger association of PVCs with embolic than with thrombotic stroke observed, it is plausible that PVCs are associated

with increased risk of AF. However, that study did not specifically examine the relationship between PVCs and pure ischemic stroke [16]. In our study, we excluded the patients with ischemic strokes and we tried to find the relationship between PVCs > 10% and stroke-like symptoms without a prior diagnosis of stroke or TIA. And there was no difference of the incidence of atrial arrhythmia including AF, APC and atrial tachycardia in both groups. And increased LA size reflecting cardiac remodeling has been shown to be a strong predictor of AF [17,18]. However, there was no difference of LA size at baseline and long-term follow-up in our study.

Previous study reported that heart rate declined, PVCs and APCs increased per 5-year increase in age [19]. In our study, PVC > 10% group are also older than those without PVC > 10% ($P = 0.042$). However, there was no significant association between age and stroke-like symptoms without a prior diagnosis of stroke or TIA statistically in multivariate Cox analysis (Table 3).

Hemodynamic differences are related to the origin site of PVCs. If a PVC occurs in the LV, it may have greater hemodynamic significance than a PVC originating in the right ventricle (RV). RV PVCs are conducted to the LV later than LV PVCs, thereby allowing more time for ventricular filling than LV PVCs [11]. In our study, consistently with previous study, before V3-transition of precordial R-wave, suggestive of LV originated PVCs was significantly associated with LV dysfunction and after V3-transition of precordial R-wave, suggestive of RV originated PVCs was significantly associated with PVCs-related stroke-like symptoms without a prior diagnosis of stroke or TIA rather than LV dysfunction.

There are no prior reports of any positive longitudinal relationship between PVC > 10% and stroke-like symptoms without a prior diagnosis of stroke or TIA. This is the first study to evaluate the association of frequent PVC > 10% and stroke-like symptoms without a prior diagnosis of stroke or TIA.

It is of interest that although, PVCs burden was not associated with new-onset LV dysfunction ($P = 0.17$) in patients with PVC > 10%, high PVCs burdens (>10%) were associated with stroke-like symptoms without a prior diagnosis of stroke or TIA in the long-term follow up (Fig. 1; supplement material). In subgroup analysis in patients with PVC > 10%, various factors were associated with stroke-like symptoms, including female, non-sustained VT, sinus QRS duration, PVC coupling interval

(CI), post- PVC CI, and late precordial R-wave transition of PVCs in univariate analysis. However, in multivariate analysis, non-sustained VT ($P = 0.022$) and late precordial R-wave transition of PVCs ($P = 0.044$) were independent risk factors for stroke-like symptoms with frequent idiopathic PVC > 10% in our study at 4-year clinical follow-up, suggestive of sustainable PVCs and RV origin are supposed to be associated with stroke-like symptoms in Table 4(A).

We hypothesized that ventricular ectopic beats may also be a risk factor for stroke-like symptoms on the basis of the following facts. First of all, PVCs may impair atrioventricular synchrony and PVCs can be associated with transient lower blood pressure which may deteriorate the cerebrovascular microcirculation both locally and systemically. During the arterial blood pressure monitoring, we can see the transient lowering blood pressure when ventricular ectopic beats occurs, which was consistent with previous study [20–22]. However, further prospective studies are needed to determine if a true causal mechanism exists between frequent PVCs and stroke-like symptoms, as well as to access whether the mechanisms is dependent on a specific subtype of VPCs.

4.3. Study limitations

First, this study was a single-center, retrospective study derived from a real world practice with inherent limitations. Hence the results of our study should be considered as hypothesis generating, and future prospective studies are warranted to confirm our results. Second, it may be useful to analyze spontaneous PVC-CI using a 24-hour Holter recording. The CI may be affected by the situation, including the place, time, and medication. The PVC-CI was measured using a 24-hour Holter recording as much as possible and the majority of the CI-dispersion using a 24-hour Holter recording were almost the same in this study. However, we could not measure all patients using a Holter recording and we needed to investigate PVC morphology and the accuracy CI. Therefore, it was difficult to compare PVC morphology and measure the accuracy CI using a 24-hour Holter recording. Third, patients with potentially reversible causes were excluded from the study. Therefore, the results of this study cannot be transferred to other patient populations with first detected PVC. Fourth, the patients with PVCs could not be monitored continuously. Therefore, there was limitation to generate the direct correlation of PVCs burden with clinical outcomes. However, 2.8 times per patients of 24 hours Holter monitoring were done during the long-term follow-up. And if the patient had PVCs-related symptom, 24 hours Holter monitoring was done in those patients. And this study has presents a new vision for PVCs focusing on the neurologic effects beyond arrhythmia. Fifth, there could be any chances that stroke like symptoms are confused with the anti-arrhythmic agent associated symptoms. Therefore, we enrolled all patients before treatment of anti-arrhythmics.

5. Conclusion

High PVCs burdens (>10%) were associated with and stroke-like symptoms without a prior diagnosis of stroke or TIA in the long-term follow up, suggesting more intensive medical therapy with close clinical follow-up will be required.

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Conflicts of interest

No other conflicts of interest.

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