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Original Article

Effect of burden and origin sites of premature ventricular contractions on left ventricular function by 7-day Holter monitor

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Abstract

Recent studies have shown that premature ventricular contractions (PVCs) could enlarge the heart, but its risk factors are incompletely understood as a single 24-hour recording cannot reflect the true PVC burden due to day-to-day variability. Our purpose was to investigate the effect of burden and origin sites on left ventricular (LV) function in patients with PVCs by 7-day Holter electrocardiography (ECG). From May 2012 to August 2013, 112 consecutive patients with PVCs were recruited from the authors' affiliated hospital. All patients received 2-dimensional transthoracic echocardiography, 12-lead routing ECG and 7-days Holter ECG. Serum *N*-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured. A total of 102 participants with PVCs were included in the final analysis. Origin of PVCs from the tricuspid annulus had the highest burden and NT-proBNP level. LV papillary muscle had a higher LV ejection fraction (EF) level and a lower LV end-systolic dimension (ESD) than other PVC foci ($P<0.05$). The high burden group had a higher LV end-diastolic dimension (EDD) and LVESD but lower LVEF than the other two groups ($P<0.05$). Female, older age, physical work, and history of PVCs had a significantly positive correlation with symptoms. Male, older age, physical work, and high burden were positive predictors of enlarged LVEDD, LVESD and higher serum NT-proBNP level, but lower LVEF. Seven-day dynamic ECG Holter monitor showed the true PVC burden on patients with PVCs. PVCs with a lower burden or origin from the LV papillary muscle and the fascicle were relatively benign, while PVCs with a higher burden or origin from the tricuspid annulus may lead to cardiac dysfunction.

Keywords: premature ventricular contractions, burden, origin sites, left ventricular function

Introduction

Premature ventricular contractions (PVCs) are commonly encountered in daily clinical practice. Incidence of PVCs is related to the detection methods and study population. PVCs are common with an estimated prevalence of 1%-4% in the general population[11], and have been detected in 1% of subjects by standard

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12-lead electrocardiography (ECG) and in 40%-75% of subjects by Holter ECG monitoring for 24-48 hours[2].

In normal subjects, PVCs are usually associated with no clinical symptoms, but in some people they may cause incapacitating symptoms such as pectoralgia, palpitations, syncope and heart failure[3]. Traditionally, subjects with PVCs have a benign prognosis in non-structural heart disease[1,4]. However, recent studies have found that PVCs lead to heart enlargement and even reversible cardiomyopathy[5-15].

It is still unknown why most patients with frequent PVCs have a benign course, while up to 1/3 of them develop cardiomyopathy. One possible explanation is that evaluation of PVC burden using 24-hour Holter monitoring may be inadequate and may misrepresent the true PVC burden of patients[16-17]. PVCs arise from various locations in the ventricle, but the effects of origin site of PVCs on cardiac structure and function are still controversial[18-20]. This study evaluated if burden and origin sites of PVCs are associated with left ventricular (LV) function by 7 consecutive days ECG monitoring, and analyzed influencing factors of burden and the symptoms of PVC patients, so as to provide a more comprehensive basis for the treatment of PVC patients and improve their quality of life.

Patients and methods

Patients

From May 2012 to August 2013, 112 consecutive patients with PVCs were recruited from the authors' affiliated hospital. All participants had at least one documented episode of PVCs by 12-lead surface ECG or 24-48 hour Holter ECG recording, and had not taken any anti-arrhythmic drugs for at least 5 half-lives. All patients provided informed consent and the study was approved by the local institutional board at the authors' affiliated institution.

Exclusion criteria for patients were listed as follows: (a) structural heart disease; (b) liver or kidney dysfunction combined with other serious diseases, and life expectancy was less than 1 year; (c) PVCs caused by reversible causes (infection, electrolyte imbalance, and drugs, etc.); (d) unwillingness to sign informed consent.

Data acquisition

After medical history inquiry and recording, physical examination was performed to exclude related disease. Serum *N*-terminal pro-brain natriuretic peptide (NT-proBNP) levels were determined, and 2-dimensional transthoracic echocardiography, 12-lead routine ECG and 7-day-Holter ECG were performed in all patients. Some patients with a higher burden of PVCs underwent cardiac electrophysiological examination or coronary angiography. Serum NT-proBNP level was analyzed as instructed by the manufacturer by electrochemiluminescence analyzer Roche Elecsys 2010 using a Roche NT-proBNP electrochemiluminescent immunoassay kit (Roche Diagnostics, Rotkreuz, Switzerland). Measurement range of NT-proBNP was 5-35000 pg/mL. Normal values in male were 0-85 pg/mL (≤44 years), 0-121 pg/mL (45-54 years), 0-210 pg/mL (55-64 years), 0-376 pg/mL (65-74 years) and 0-486 pg/mL (≥75 years). Normal values in female were 0-130 pg/mL (≤44 years), 0-249 pg/mL (45-54 years), 0-287 pg/mL (55-64 years), 0-301 pg/mL (65-74 years) and 0-738 pg/mL (≥75 years).

Cardio Trak CT Series Holter recorder from Hangzhou Medical Equipment Co., Ltd. was used to record holographic 3-channel ECG for 7 days. Holter results were separatly analyzed by 2 cardiologists who were blinded to the ECG results.

Two–dimensional echocardiography

Two-dimensional (2D) ECG was obtained in each case using an ultrasound machine (Vivid7, GE Medical Systems, Milwaukee, WI, USA) with an M4S probe. Patients were examined in the left lateral decubitus position, and images were acquired at end expiration to minimize global cardiac movement. LV end-diastolic and end-systolic diameters (EDD and ESD) were measured by 2D method from the parasternal long-axis view. They were recorded from 3 consecutive cycles in M mode using methods adopted by the American Society of Echocardiography. LV end-diastolic volume (EDV) and LV end-systolic volumes (ESV) were measured using Simpson biplane method, and LV ejection fraction (EF) was calculated as (EDV-ESV)/EDV.

Site of origin of PVCs

PVC burden refers to the ratio of the number of PVCs divided by the total heart rate. Origin of PVCs was diagnosed by 12-lead ECG or electrophysiological examination. The site of origin of PVCs was analyzed by 2 clinical electrophysiologists who were blinded to the results. Mapped site of PVC ablation during the electrophysiologic study of 32 patients that underwent radiofrequency ablation was verified with ECG estimation. The criteria that used to define the site of origin of PVCs based on their ECG features were listed as follows[21-23]: (1) Right ventricular outflow tract (RVOT): left bundle branch block (LBBB) morphology with an inferior axis, tall R waves in the inferior leads in

II, III, aVF and negative (QS) complexes in aVR and aVL, and an all-negative QRS or a small "r" wave in lead V1. (2) LV outflow tract (LVOT): right bundle branch block (RBBB) morphology, tall R waves in the inferior leads in II, III, aVF and negative (QS) complexes in I and aVL. (3) Mitral annulus: RBBB morphology similar to type A pre-excitation syndrome wave, tall R waves in lead V1, early precordial transition to lead V2, and lead V6 form is RS or type Rs. (4) The tricuspid annulus: LBBB morphology similar to type B pre-excitation syndrome wave. (5) The LV papillary muscle: RBBB morphology with a small q wave preceding R wave in lead V1, left anterior or posterior fascicular block which is not typical. (6) Fascicular: typical RBBB (rsR') morphology with the superior (the left posterior fascicle) or inferior (the left anterior fascicle) axis. (7) The other sites: PVCs originated from LV free wall has a RBBB morphology with negative in aVL and lead I. PVCs originated from RV free wall has a LBBB morphology with a non-inferior axis. PVCs originated from Great cardiac vein has a LBBB morphology similar to RVOT origin but with a more prominent "r" wave amplitude and duration in lead V1, in addition to a predominantly positive QRS complex in lead I, and more prominent "R" wave in lead V6[21-23].

Questionnaire

In our study, self-made general data questionnaire was applied to the recruited PVC patients (The questionnaire is available online as Supplementary Table 1). According to previous studies[3,5,7-9,16-19,24], a structured general data questionnaire was designed specifically for PVC patients based on face-to-face interview to PVC patients by taking the advice by experts and panel discussions. The questionnaire included age, gender, education level, marital status, occupation, symptoms, and history of PVCs, smoking state, alcohol intake, caffeinated beverages, and symptoms.

Each participant was interviewed by the investigator in a standardized manner before they took 7-consecutive-day echocardiography monitoring. If the participant was illiterate, the investigator would explain the questions to the patient and his/her relative, and helped the participant to complete the questionnaire. If the participant wanted to fill it by themselves, they could finish it according to directions on the questionnaire. If the data was not filled out completely, we will contact the patients again for additional information.

Statistical analysis

Data were double-entered into Epidata 3.1 and analyzed by SPSS18.0. Continuous variables were expressed as mean ± SD. Frequencies, percentages, means, and standard deviations were used to describe demographic and characteristics of the general data of PVC patients. Continuous variables were compared using one-way ANOVA (normal distributions) or Wilcoxon's rank sum test (for non-normal distributions). Equal variances assumed were assessed with the LSD test. Equal variances not assumed were assessed with Tamhane's T2 test. Categorical variables were compared using Fisher's exact test or χ^2-test. Correlations between variables were tested using the Spearman or Pearson test. Linear regression analysis was performed using backward elimination to determine significant variables for predicting LV function. All statistical tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Characteristics and burden of the participants

In total, questionnaires were distributed to 112 patients, and 102 were effective samples (response rate was 91.07%). Seven cases were excluded because they removed the Holter recorders before the completion of monitoring periods. The remaining two questionnaires were excluded because the patients could not endure onset of severe symptoms and then took anti-arrhythmic drugs. One questionnaire was excluded because the patient was only 5 years old**.** The mean age of 102 effective participants was 44.11±15.16 (range 18-72) years, the mean duration of PVCs was 4.76±6.28 (0.1-30) years, and the mean heart rate was 75.38±8.53 (56-104) beats/minute. Thwenty-seven patients had primary hypertension, 9 patients had diabetes mellitus, and 17 patients had hypercholesterolemia.

Characteristics and burden of the participants are shown in ***Table 1***. The mean burden of 102 patients was 14.47%±11.88% (0.02-49.21)%. The patients were divided into the low burden group (<10%; $n=42$), the medium burden group (10%-20%; $n=31$), and the high burden group (>20%; $n=29$). No significant differences were found in age, gender, education level, marital status, occupation, history of PVCs, smoking, alcohol intake, caffeinated beverages, history of hypertension, diabetes mellitus, or hypercholesterolemia among the 3 burden groups. ***Table 2*** demonstrates the number and percentage of symptoms in 102 patients with PVCs. Eight (7.84%) patients had no symptoms, 16 (15.69%) patients had 1 symptom, 16 (15.69%) patients had 2 symptoms, 25 (24.51%) patients had 3 symptoms, 20 (19.61%) patients had 4 symptoms, 5 (4.85%)

Table 1 **Characteristics and burden of 102 PVC patients**

Characteristics	Groups	*n* (%)	Burden
Gender	Male	48 (47.1)	14.36±12.18 (0.02-49.21)
	Female	54 (52.9)	14.57±11.73 (0.02-48.08)
Age (years)	≤44	47 (46.1)	17.69±11.91 (0.05-49.21)
	45-54	26 (25.5)	11.87±11.70 (0.02-48.08)
	55-64	23 (22.5)	12.11±11.55 (0.02-38.31)
	≥65	6 (5.9)	12.51±10.94 (2.30-31.58)
Education level	Illiterate	6 (5.9)	19.79±16.68 (8.85-49.21)
	Primary/Junior high school	25 (24.5)	12.85±13.98 (0.02-48.08)
	Senior high school	31 (30.4)	15.71±11.01 (0.06-47.28)
	College or higher	40 (39.2)	13.72±10.42 (0.02-37.78)
Marital status	Unmarried	21 (20.6)	16.49±10.83 (0.04-47.28)
	Married	78 (76.5)	14.13±12.22 (0.01-49.21)
	Divorced/Widowed	3 (2.9)	9.14±10.93 (2.31-21.75)
Occupation	Full mental work	38 (37.3)	13.48±10.11 (0.04-47.28)
	Major mental work	30 (29.4)	15.37±12.52 (0.02-38.31)
	Major physical work	27 (26.4)	16.07±14.52 (0.02-49.21)
	Full physical work	7 (6.9)	9.79±5.32 (0.26-18.21)
History of PVCs	<1	34 (33.3)	10.29±11.47 (0.02-49.21)
	1-3	26 (25.5)	19.70±11.85 (2.30-48.08)
	>3	42 ((41.2)	14.61±11.15 (0.26-47.28)
Smoking	Never/Seldom	80 (78.4)	14.10±11.31 (0.02-48.08)
	Sometimes/Always	16 (15.7)	12.21±11.59 (0.28-31.58)
	Quit	6 (5.9)	25.40±16.31 (6.55-49.21)
Alcohol intake	Never/Seldom	75 (73.5)	15.27±11.56 (0.02-48.08)
	Sometimes/Always	19 (18.6)	9.37±9.30 (0.26-31.58)
	Quit	8 (7.9)	19.04±17.31 (2.80-49.21)
Caffeinated beverages	Never	49 (48.0)	13.42±12.54 (0.02-48.08)
	Seldom	42 (41.2)	15.64±11.60 (0.02-49.21)
	Sometimes	6 (5.9)	16.43±10.54 (6.34-36.05)
	Always	5 (4.9)	12.64±11.03 (2.51-31.47)

PVCs: premature ventricular contractions

patients had 5 symptoms, 7 (6.86%) patients had 6 symptoms, and 5 (4.90%) patients had 7 symptoms. Palpitations, fatigue and shortness of breath were the most common symptoms in patients with PVCs.

Distribution of origin sites of PVCs

The origin of PVCs in 47 patients (46.1%) was from the RVOT, in 23 patients (22.6%) from the LVOT, in 5 patients (4.9%) from the mitral annulus, in 8 patients

Table 2 **Symptoms of 102 PVC patients**

Symptoms	Low burden group (%) (*n*=42)	Moderate burden group (%) (*n*=31)	High burden group (%) (*n*=29)	Total cases (%) (*n*=102)
Dizziness	17(42.50)	9(22.50)	14(35.00)	40(39.22)
Amaurosis	7(41.18)	5(29.41)	5(29.41)	17(16.66)
Syncope	2(16.66)	5(41.67)	5(41.67)	12(11.76)
Palpitations	35(43.75)	21(26.25)	24(30.00)	80(78.43)
Shortness of breath	21(38.89)	18(33.33)	15(27.78)	54(52.94)
Pectoralgia	14(37.84)	10(27.03)	13(35.13)	37(36.27)
Fatigue	27(42.19)	19(29.69)	18(28.12)	64(62.75)

PVCs: premature ventricular contractions

(7.8%) from the tricuspid annulus, in 5 patients (4.9%) from the LV papillary muscle, in 9 patients (8.8%) from the fascicle, and in the remaining 5 patients (4.9%) from the other parts (the pulmonary artery, the LV free wall and the epicardium). No significant differences were found in age, gender, and other variables among the 7 origin sites. The burden in different origin sites of 102 patients with PVCs is shown in ***Fig. 1***. PVCs originated from the tricuspid annulus had the highest burden than those from other sites. PVCs originated from the LV papillary muscle and the fascicle had the lowest burden than those from other sites.

LV function

The median serum NT-proBNP content was 110.50 ng/L(25%-75%CI 45.00～108.00 ng/L). Ninety-one (89.2%) PVC patients had normal NT-proBNP content, and 11 (10.8%) patients had higher NT-proBNP levels. NT-proBNP levels in different groups are shown in ***Table 3***. Patients with PVCs originated from RVOT showed lower NT-proBNP levels than those from LVOT. Patients with PVCs originated from the mitral annulus, the LV papillary muscle and the fascicle had normal NT-proBNP level. We also found that patients with PVCs originated from the tricuspid annulus had the highest NT-proBNP level compared other different origin. The mean burdens of patients with normal NT-proBNP content and those with higher NT-proBNP levels were 12.90±10.50 (0.02-48.08)% and 27.44±15.04 (2.73-49.21)%, respectively.

The mean value of LVEDD was 49.81±4.25 (42-60) mm; the mean value of LVESD was 32.69±3.72 (26-44) mm in male, the mean value of LVEDD was 47.80±4.06 (41-59) mm; the mean value of LVESD was 31.43±3.09 (25-39) mm in female, and the mean value of LVEF was 33-73 (63.14±5.21) mm. ***Table 4*** shows the effect of different origin sites on LVEDD, LVESD and LVEF of the 102 patients with PVCs. PVCs originated from the LV papillary muscle had a higher LVEF level and a lower LVESD than those from other PVC foci ($P<0.05$). ***Table 5*** shows the effect of different burdens on LVEDD, LVESD and LVEF of the 102 patients with PVCs. The high burden group had a larger LVEDD and LVESD and lower LVEF than the other 2 groups ($P<0.05$).

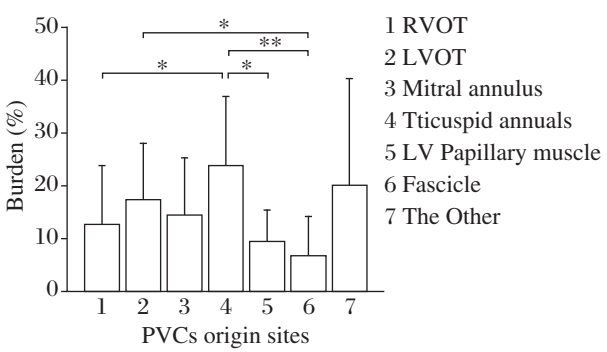

Fig. 1 **The burden in different origin sites of 102 PVCs patients.** The y axis indicates the burden of premature ventricular contractions (PVCs). There was a statistically significant difference of burden among the tricuspid annulus with the right ventricular out tract (RVOT), the left ventricular (LV) papillary muscle, and the fascicle groups. There was a significant difference of burden between the fascicle and left ventricular out tract (LVOT group). * indicate $P<0.05$, ** indicate $P<0.01$. Error bars, mean±SD.

Table 3 **Different origin sites/burden groups effect on NT–proBNP level of 102 PVCs patients**

Origin sites/burden groups	Normal NT-proBNP level, *n*(%)	Higher NT-proBNP level, *n*(%)
RVOT	43(91.5)	4(8.5)
LVOT	20(86.9)	3(13.1)
Mitral annulus	5(100.0)	0(0)
Tricuspid annulus	6(75.0)	2(25.0)
LV Papillary muscle	5(100.0)	0(0)
Fascicle	9(100.0)	0(0)
The other	3(60.0)	2(40.0)
Low burden	40(95.2)	2(4.8)
Medium burden	29(93.5)	2(6.5)
High burden	22(75.9)	7(24.1)

NT-proBNP: N-terminal fragment of brain natriuretic peptide; PVCs: premature ventricular contractions; RVOT: right ventricular out tract; LVOT: left ventricular out tract; LV: left ventricular.

Determinants of symptoms and LV function of patients with PVCs

Spearman correlations of characteristics, burden, origin sites and LV function parameters with symptoms are shown in ***Table 6***. Age had significantly positive correlation with palpitations ($P=0.017$) and fatigue ($P=0.025$). Significant positive correlation was found between physical work and shortness of breath ($P=0.018$). Female, physical work, and LVEF had significantly positive correlation with dizziness ($P=0.018$; $P=0.012$; $P=0.025$). Significantly positive correlation was found between female gender and amaurosis ($P=0.033$). Female and physical work were significantly positively correlated with syncope ($P=0.025$; $P=0.032$). By calculating all types of symptoms of each patient as their own total symptoms, we found that symptoms had a significantly positive correlation with female gender ($P=0.013$), older age ($P=0.036$), physical work ($P=0.019$) and history of PVCs ($P=0.021$).

Table 4 **Different origin sites and LVEDD, LVESD and LVEF**

Origin sites	LVEDD(mm)		LVESD(mm)		LVEF(%)
	Male	Female	Male	Female	
RVOT	49.37±4.17	47.74±3.73	32.58±3.50*	31.29±2.52	63.28±3.69*
LVOT	49.38±2.67	49.20±4.53	32.50±1.93*	32.33±4.03	62.96±7.30*
Mitral annulus	51.50±1.91	41	34.50±2.08*†	32	60.52±9.18*
Tricuspid annulus	50.80±5.16	47.00±2.00	33.80±3.63*	32.33±2.08	61.64±1.85*
LV Papillary muscle	45.67±0.58	47.00±7.07	27.67±2.08	30.33±4.24	68.22±4.26
Fascicle	48.00±4.18	45.25±3.775	30.60±2.96	28.75±3.30	65.00±4.29
The other	55.25±5.50	50	32.69±3.72*	32	63.18±5.21*

*$P<0.05$ *vs.* LV papillary muscle group; †$P<0.05$ *vs.* Fascicle group; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEF: left ventricular ejection fraction; PVCs: premature ventricular contractions; RVOT: right ventricular out tract; LVOT: left ventricular out tract; LV: left ventricular. There was only one female PVCs patient originated from mitral annulus and the other sites, respectively.

In backward regression analysis, the dependent variables were NT-proBNP, LVEDD, LVESD and LVEF, respectively, and the independent variables were the characteristics of participants, including age, gender, education level, occupation, history of PVCs, smoking status, alcohol intake, caffeinated beverages, burden and origin sites. ***Table 7*** shows that higher burden was a predictor of higher level of NT-proBNP. Male and higher burden were predictors of larger LVEDD. Male, physical work, and higher burden were predictors of larger LVESD. Older age and higher burden were predictors of lower LVEF.

Discussion

Premature ventricular contractions (PVCs) commonly occur in the general population. They typically carry a good prognosis without structural heart disease. However, recent studies found that PVCs have been implicated in the development of LV dysfunction and cardiomyopathy[8,17,19], but the risk factors and pathogenic mechanisms are incompletely understood. Generally, PVC burden should be assessed by continuous Holter monitoring for at least 24 hours. Thus, a single 24-hour recording may not reflect the true PVC burden and its detection rate was only (40-75)% due to day-to-day variability[2], a strong suspicion that frequent PVCs may lead to LV dysfunction may warrant extended Holter recordings of 48 to 72 hours or several 24-hour Holter recordings[17]. This study was the first to use 7-day dynamic ECG Holter monitoring on patients with PVCs. The burden of all patients in this study were the mean data of 7 consecutive days.

In our study, 102 consecutive patients with PVCs with no other identified causes of cardiomyopathy underwent 7-day Holter monitoring. We found that the majority of patients had clinical symptoms,. Approximately three quarters of the patients reported palpitations, 62.75% patients felt fatigue, and about half of the patients had symptoms of shortness of breath. The high incidence of symptoms in our study may be associated with the source of patients who were all outpatients seeking medical care. Interestingly, we found that patients with PVCs in the high burden group had more severe symptoms of syncope than those in the low burden group. However, patients with PVCs in the low burden group had more mild symptoms of fatigue, palpitations and shortness of breath than those in the high burden group. It is probably due to patients with high burden PVCs had poorer cardiac function than those patients with low burden PVCs[21,25]. Therefore, patients with high burden PVCs had more severe symptoms than patients with low burden PVCs. Moreover, patients with high burden PVCs had less mildly symptomatic due to tolerance of poor cardiac function. Patients with low burden PVCs are more

Table 5 **Different burdens and LVEDD, LVESD and LVEF**

Burden groups	LVEDD(mm)		LVESD(mm)		LVEF(%)
	Male	Female	Male	Female	
Low burden	49.95±4.47	47.00±4.44*	31.79±3.64*	30.65±2.92*	63.90±4.99*
Medium burden	49.21±3.40	46.76±3.23*	31.57±2.92*	31.00±3.28*	64.46±3.69*
High burden	51.47±4.49	50.36±3.38	34.87±3.73	33.21±2.58	60.78±6.18

*$P<0.05$ *vs.* high burden group; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEF: left ventricular ejection fraction; PVCs: premature ventricular contractions

Table 6 **Correlations of characteristics, burden, origin sites and left ventricular function parameters with symptoms**

Items	Palpitations	Shortness of breath	Pectoralgia	Fatigue	Dizziness	Amaurosis	Syncope	Total symptoms
Gender	-0.017	0.095	0.017	0.198	0.234*	0.211*	0.222*	0.244*
Age	0.236*	0.112	0.100	0.222*	0.134	0.037	0.038	0.208*
Education level	-0.060	-0.198	-0.046	-0.128	-0.176	-0.070	-0.109	-0.145
Occupation	0.041	0.235*	0.084	0.130	0.249*	0.152	0.212*	0.233*
History of PVCs	0.084	0.104	0.134	0.161	0.169	0.087	-0.022	0.228*
Smoking	0.071	0.077	-0.049	-0.160	-0.160	-0.180	-0.184	-0.144
Alcohol intake	0.058	0.016	0.163	-0.125	-0.179	-0.122	-0.132	-0.072
Caffeinated beverages	0.057	-0.063	-0.052	-0.135	-0.103	-0.116	-0.196	-0.145
Burden	-0.020	-0.015	-0.072	-0.032	0.062	0.043	0.193	0.104
Origin sites	-0.102	-0.107	-0.055	-0.049	0.109	-0.005	-0.078	-0.050
NT-proBNP	0.105	-0.115	-0.131	0.072	0.044	0.014	0.069	0.002
LVEDD	0.036	0.013	-0.085	-0.066	-0.009	-0.135	0.022	0.044
LVESD	0.017	0.063	-0.135	-0.149	-0.019	-0.125	-0.011	-0.079
LVEF	0.006	-0.053	-0.026	-0.002	-0.223*	0.102	0.026	0.002

*: Correlation is significant at the 0.05 level (2-tailed); **: Correlation is significant at the 0.01 level (2-tailed); PVCs: premature ventricular contractions; NT-proBNP: N-terminal fragment of brain natriuretic peptide; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEF: left ventricular ejection fraction

sensitive to those with mild symptoms such as palpitations and fatigue and shortness of breath.

PVCs in most structural heart diseases are originated from the left ventricle, whereas PVCs in most patients without structural heart disease are originated from the right ventricle. Farzaneh *et al.* have demonstrated that, in patients without structural heart disease, 80% PVCs were originated from the right ventricule, while the remaining 20% were originated from the LV[26]. For those PVCs originated from the right ventricle, most of them are originated from RVOT, which is similar to our finding. RVOT was the most common origin site (46.1%). LVOT was the second most common origin site (22.6%). Our study also revealed that the PVCs

Table 7 **The regression analysis coefficients of predictors of NT–proBNP, LVEDD, LVESD and LVEF level in 102 PVCs patients**

	Model	Unstandardized coefficients B	Standardized coefficients bata	t	P
NT–proBNP	Constant	0.963	-	21.253	0.000
	Burden	0.013	0.381	4.122	0.000
LVEDD	Constant	50.102	-	37.637	0.000
	Burden	0.122	0.341	3.726	0.000
	Male	-2.042	-0.241	-2.632	0.010
LVESD	Constant	30.393	-	24.210	0.000
	Burden	0.096	0.324	3.525	0.000
	Male	-1.536	-0.463	-2.897	0.015
	Physical work	0.698	0.179	1.951	0.048
LVEF	Constant	68.028	-	37.284	0.000
	Burden	-0.106	-0.242	-2..449	0.016
	Age	-0.075	-0.218	-2.204	0.030

PVCs: premature ventricular contractions; NT-proBNP: N-terminal fragment of Brain natriuretic peptide, LVEDD: left ventricular end-diastolic dimension, LVESD:left ventricular end-systolic dimension, LVEF: left ventricular ejection fraction. For NT-proBNP, R=0.381, R^2=0.145, F=16.995, P=0.000; For LVEDD, R=0.415, R^2=0.172, F=10.318, P=0.000; For LVESD, R=0.489, R^2=0.240, F=6.977, P=0.000; For R=0.286, R^2=0.082, F=4..417, P=0.015.

originated from the tricuspid annulus had the largest burden, and the PVCs originated from the fascicle and the LV papillary muscle had the lowest burden (both less than 20%) than other sites. This is unique and different from the previous findings[21], which did not find any association between PVC burden and origin sites. This may be attributed to that a single 24-hour recording may not reflect the true PVC burden. In our study, we carried out 7-day Holter recording for all patients.

BNP or NT-proBNP is an important indicator for LV dysfunction and early diagnosis of heart failure[27]. BNP and NT-proBNP are cardiovascular biomarkers that are released from cardiomyocytes in response to increases in ventricular wall stress[28]. Wall stress in a chamber is directly related to the diameter of the chamber and the transmural pressure and inversely related to the thickness of the wall[29]. Recent evidence suggested that BNP can be used as a biomarker for non-heart failure mechanisms, preclinical diseases, and other pathologic states of myocardial disease[30-31]. In this study, we demonstrated that the NT-proBNP level of PVC patients originated from RVOT was lower than that from LVOT. This is supported by our findings and previous studies. Tada *et al.* reported that high BNP concentration was found more often in I-VT/PVCs originated from the LV than those from the right ventricle[32]. This is similar to our finding, but we also found that patients with PVCs originated from the tricuspid annulus had the highest rate of higher NT-proBNP level. To our knowledge, this is the unique finding that patients with PVCs originated from the tricuspid annulus had the highest burden and NT-proBNP level than those from other foci. Our study also revealed that all patients with PVCs originated from the fascicle and the LV papillary muscle had a normal NT-proBNP level. Patients with PVCs originated from the LV papillary muscle and the fascicle had higher LVEF but lower LVESD than those from other foci. This is not unique and is very similar to previous findings[21]. Freddy *et al.* found a minority of patients with left-anterior or left-posterior fascicular PVCs had higher LVEF as compared to those with PVCs from other foci[21].

With the "bio-psycho-social" medical model, health-related quality of life is increasingly used as a comprehensive index system to evaluate the efficacy endpoint, disease outcome and treatment outcomes. Although PVCs are not directly life-threatening, its onset of clinical symptoms (such pectoralgia, palpitations, syncope, and etc.) seriously affect the quality of life in these patients, severe cases can lead to arrhythmogenic cardiomyopathy, even increase risk of sudden death. The symptoms seriously affected patients with PVCs in mental and psychological aspects. Our study revealed that female, older age, physical work, history of PVCs and NT-proBNP levels had significantly positive correlation with symptoms of PVC patients. Though males usually have a larger LVEDD and LVESD, there is a trend that female patients with PVCs have reported more symptoms than male patients. It may be due to the social role function which males played made their threshold increases of complained physical discomfort, the discomfort of PVCs can be tolerated generally. Physiological differences made female patients more sensitive to physical stimulus, and the discomfort symptoms increased the psychological pressure. Studies have shown that when the symptoms disappeared, the quality of life in patients with PVCs were increased, and the improvement was more obvious in female than in male[33-34]. Regression analysis also revealed that physical work was predictors of larger LVESD. PVCs patients whose work involves physical labor suffered more symptoms than mental worker. This may be attributed to the fact that physical workers are engaged in more physical activities than mental workers, which could induce the PVCs episodes. This interpretation is supported by previous studies[35-37]. Older age was a predictor of lower LVEF, and that is why they had much more symptoms than young people. Patients with longer history of PVCs and higher NT-proBNP levels generally have more symptoms than those with shorter history of PVCs and lower NT-proBNP levels because of poor LV function[27-28]. The other finding from our study was that higher burden was a predictor of higher level of NT-porBNP, larger LVEDD, larger LVESD, and lower LVEF, which is very similar to the finding of previous studies[32,38].

The study limitations are listed as follows: the sample size of the patient population was relatively small and the data was collected from only one academic hospital of one geographical location. Although in our recruited patients, there were 32 cases who underwent radiofrequency ablation, further follow-up is needed to find out if there is a difference among different origin sites and burden groups. Moreover, we did not assess the variety of PVCs in this study. Furthermore, the quality of life was not evaluated in patients with PVCs. Further studies are necessary to address these limitations.

In conclusion, our results demonstrated that PVCs with lower burden or their origin from LV papillary muscle and fascicle were benign, while PVCs with higher burden or their origin from tricuspid annulus may lead to cardiac dysfunction. Healthcare education should therefore be given to those PVC patients who are older in age, female, physical worker, with long history of PVCs and high serum NT-proBNP levels so as to release the pressure caused by symptoms. Older in age, male, physical work

and high burden patients should be followed up in case of decrease in LV function.

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