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RESEARCH ARTICLE

Clinical Characteristics and Features of Idiopathic Premature Ventricular Contractions with an Enlarged Left Atrium in Patients Without Structural Heart Diseases

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Abstract

Background and aims: Idiopathic premature ventricular contractions (PVCs) may cause subtle changes in left atrium (LA) structure and function. Here, we investigated whether serum sodium, body mass index (BMI), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and other characteristics might be associated with LA in these patients.
Methods: A total of 268 consecutive patients diagnosed with idiopathic PVCs were retrospectively analyzed. We assessed associations of enlarged LA and with the clinical features obtained from 24-hour Holter monitoring, electrocardiography and serum data in patients with PVCs.
Results: Patients with an enlarged LA (n = 101), compared with a normal LA (n = 167), had significantly lower serum sodium (140.9 ± 3.0 mmol/L vs 141.7 ± 2.8 mmol/L; P = 0.022), higher BMI (24.5 ± 2.7 kg/m^2 vs 21.7 ± 2.5 kg/m^2; P < 0.001), higher NT-proBNP [99.3 (193.6) pg/mL vs 77.8 (68.8) pg/mL; P < 0.001] and lower average heart rates (73.0 ± 8.0 bpm vs 75.3 ± 7.6 bpm; P = 0.019). No significant differences were observed in P-wave dispersion, QRS duration, PVC coupling interval, pleomorphism, circadian rhythm, non-sustained ventricular tachycardia, serum potassium, serum magnesium, hypersensitive C-reactive protein, low-density lipoprotein cholesterol, symptoms and PVC duration.
Conclusions: Beyond the burden of PVCs, attributes such as serum sodium, BMI, NT-proBNP and average heart beats may potentially correlate with LA enlargement in individuals with idiopathic PVCs.

Keywords: premature ventricular contractions; left atrium; serum sodium; body mass index; N-terminal pro-B-type natriuretic peptide

Introduction

Premature ventricular contractions (PVCs) have traditionally been considered benign in patients without structural heart disease [1, 2]. Nevertheless, a growing body of evidence suggests that PVCs may be a plausible cause of cardiomyopathy, left ventricle (LV) systolic dysfunction and elevated risk of sudden cardiac death [3–6], although the mechanisms underlying these associations remain unclear. Recently, several studies focusing on the influence of PVCs on left atrium (LA) remodeling [7, 8] have indicated that the abnormal hemodynamic effects of PVCs on LV systolic function may result in subtle

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damage to, and significant enlargement of, the LA [7]. However, few data are available regarding the clinical factors contributing to LA enlargement in patients with PVCs. In this study, we aimed to investigate the clinical characteristics of individuals with idiopathic PVCs and an enlarged LA.

Methods

Study Population

A total of 268 patients diagnosed with idiopathic PVCs at the Second Affiliated Hospital of Chongqing Medical University between March 2009 and November 2016 were included in this retrospective study, on the basis of review of individual medical records and serum data. Informed consent was obtained from all study participants. The exclusion criteria comprised echocardiographic evidence of structural heart disease, presence of hypertension, moderate or severe valvular regurgitation, coronary artery disease, atrial arrhythmia, sick sinus syndrome, other complex ventricular arrhythmias, diabetes, abnormal liver enzymes, anemia, hyperthyroidism, severe electrolyte disturbances and life expectancy less than 1 year.

Clinical Characteristics

Clinical characteristics were collected, encompassing demographic factors such as age and sex, as well as physiological parameters including systolic blood pressure (SBP); diastolic blood pressure (DBP); average heart rate; BMI; duration of PVCs; and symptoms such as palpitation, dizziness, chest pain and syncope. Additionally, serum data including serum sodium, serum potassium, serum magnesium, hypersensitive C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and low-density lipoprotein cholesterol (LDL-C) were gathered.

24-Hour Holter Monitoring

The following information was extracted from ambulatory 24-hour Holter recordings and 12-lead electrocardiograms: 1) basic summary of Holter information: PVC burden (number of PVCs divided by the number of total beats during 24 hours), PVC frequency, number of total beats in 24 hours number of episodes of non-sustained ventricular tachycardia (VT); 2) PVC characteristics: pleomorphism, coupling interval, circadian rhythm, retrograde P waves, QRS width and P-wave dispersion.

Transthoracic Echocardiography

All patients underwent transthoracic echocardiography with a commercially available ultrasound machine and were evaluated by impartial readers (trained, registered cardiac sonographers). The left atrial diameter (LAD) was measured in parasternal long-axis views, whereas the LV end-diastolic/end-systolic volumes and the LV ejection fraction were measured in apical four-chamber view. Moreover, the right atrial maximum anteroposterior diameter, right ventricular end-diastolic volume, fractional shortening, and peak E and A wave velocities were evaluated according to the American Society of Echocardiography guidelines [9].

On the basis of LAD measurements, patients were classified into two categories: those with an enlarged LA (LAD ≥34 mm) and those with a normal LA (LAD <34 mm).

Statistical Analysis

All statistical analyses were performed in SPSS 19.0 software (SPSS Inc.). Continuous variables are presented as mean ± standard deviation, and were compared with Student's t-test (normal distributions). For continuous variables not showing a normal distribution, range and median values are reported, and Mann-Whitney's U-test was used for analysis. Normality was assessed with the Shapiro-Wilk test. Categorical variables were compared with the $\chi 2$-test. Logistic regression was used to explore factors associated with elevated risk of enlarged LA in patients with idiopathic PVCs. Interferential variables were excluded through multivariate analysis. Pearson's bivariate correlation analysis was used to determine the correlations between variables. Additionally, a receiver operating characteristic (ROC) curve was constructed to determine a cutoff value for the PVC burden associated with enlarged LAD. The cutoff value was determined on the basis of the optimal combination of sensitivity and

specificity. A two-sided $P < 0.05$ was considered to indicate statistical significance.

Results

Clinical Characteristics

This study included 268 patients (90 men and 178 women) with a mean age of 48.1 ± 15.8 years. A summary of patients' clinical characteristics is presented in Table 1. A total of 101 (38%) patients had an enlarged LA, whereas 167 (62%) patients had a normal LA.

Patients with enlarged LA, compared with normal LA, were significantly older (52.2 ± 13.1 years old vs 45.7 ± 16.8 years old, $P < 0.001$), and had higher BMI (24.5 ± 2.7 kg/m^2 vs 21.7 ± 2.5 kg/m^2, $P < 0.001$) and SBP (124.4 ± 11.2 mmHg vs 121.2 ± 9.6 mmHg, $P = 0.013$), but lower average heart rates (73.0 ± 8.0 bpm vs 75.3 ± 7.6 bpm, $P = 0.019$). However, no significant differences were observed between groups in terms of sex, DBP, appearance of clinical symptoms and duration of PVCs.

Serum data indicated that the enlarged LA group, compared with the normal LA group, had significantly lower serum sodium (140.9 ± 3.0 mmol/L vs 141.7 ± 2.8 mmol/L, $P = 0.022$) and serum calcium (2.20 ± 0.24 mmol/L vs 2.26 ± 0.22 mmol/L, $P = 0.027$), and higher NT-proBNP [9.56–4017.0 (99.3) pg/mL vs 5.0–798.0 (77. 8) pg/mL, $P < 0.001$]. Furthermore, patients with an enlarged LA were more likely to have higher hypersensitive C-reactive protein [60 (59) vs 127 (76), $P = 0.004$]. However, the levels of serum potassium, serum magnesium and LDL-C did not show significant differences between groups.

PVC Characteristics

The characteristics of the patients' PVCs, determined through 24-hour Holter monitoring (and routine 12-lead electrocardiography), are listed in Tables 2 and 3. Patients with enlarged LA, compared with those with normal LA, had a greater PVC burden (17.6 ± 14.0% vs 14.2 ± 13.0, $P = 0.004$) and fewer total beats in a 24-hour period (100414.6 ± 13732.8 vs 105131.8 ± 13951.9, $P = 0.007$), whereas the PVC frequency did not show significant differences between groups. Patients with more than 20,000 PVCs per 24 hours (or a PVC burden >20%), showed an incrementally greater prevalence of enlarged LA than those with a lower burden of PVCs (Table 3). Significant differences between groups were also observed in P-wave dispersion

Table 1 Clinical Characteristics of Enrolled Patients.

Clinical characteristics	Normal LA (n = 167)	Enlarged LA (n = 101)	P value
Male, n (%)	57 (34)	33 (33)	0.806
Age (years)	45.7 ± 16.8	52.2 ± 13.1	<0.001
BMI (kg/m^2)	21.7 ± 2.5	24.5 ± 2.7	<0.001
SBP (mmHg)	121.2 ± 9.6	124.4 ± 11.2	0.013
DBP (mmHg)	74.3 ± 6.3	74.4 ± 7.4	0.911
Average heart rate (bpm)	75.3 ± 7.5	73.0 ± 8.0	0.019
Serum potassium (mmol/L)	3.91 ± 0.30	3.95 ± 0.32	0.288
Serum magnesium (mmol/L)	0.86 ± 0.12	0.85 ± 0.10	0.423
Serum sodium (mmol/L)	141.70 ± 2.82	140.86 ± 3.06	0.022
Serum calcium (mmol/L)	2.26 ± 0.22	2.20 ± 0.24	0.027
Hypersensitive C-reactive protein, n (normal) (%)	127 (76)	60 (59)	0.004
NT-proBNP/(pg/mL) (range[median])	5.0–798.0 (77. 8)	9.56–4017.0 (99.3)	<0.001*
LDL-C (mg/dL)	2.6 ± 0.8	2.7 ± 0.7	0.165
Duration of PVCs (months) (range[median])	0.03–480 (12)	0.03–480 (12)	0.166*
Symptoms, n (no symptoms) (%)	43 (26)	24 (24)	0.716

*Mann-Whitney's U-test; BMI, body mass index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal natriuretic peptide; SBP, systolic blood pressure.

Table 2 Electrocardiographic Characteristics of Enrolled Patients.

	Normal LA (n = 167)	Enlarged LA (n = 101)	P value
PVC frequency	15277.7 ± 15388.3	18095.7 ± 14911.9	0.143
Number of total beats in 24 hours	105131.8 ± 13951.9	100414.6 ± 13732.8	0.007
PVC burden (%)	14.2 ± 13.0	17.6 ± 14.0	0.048
Pleomorphism, n (%)	24 (14)	16(16)	0.743
Coupling interval (ms) (range[median])	320–720 (440)	320–800 (440)	0.801*
Circadian rhythm (daytime dominantly/ nighttime dominantly/divided equally), n (%)	89/64/14 (53/38/9)	47/41/13 (47/40/13)	0.385
Retrograde P waves, n (%)	41(25)	17 (17)	0.137
QRS width (ms) (range[median])	120–220 (160)	120–220 (160)	0.810*
P-wave dispersion (ms) (range[median])	27–80 (40)	20–80 (40)	<0.001*
Non-sustained VT (range[median])	0–22072 (0)	0–832 (23)	<0.001*

*Mann-Whitney's U-test; PVCs, premature ventricular contractions; VT, ventricular tachycardia.

Table 3 PVC Burden and LAD.

	LAD >34 mm	
	N	%
PVC frequency/24 hours		
<10,000 (n = 118)	42	36.2
10–20,000 (n = 67)	21	31.3
>20,000 (n = 83)	38	45.8
PVC burden (%PVC/all beats)		
<10% (n = 121)	41	33.9
10–20% (n = 62)	18	29.0
>20% (n = 85)	42	49.4

LAD, left atrial maximum anteroposterior diameter; PVCs, premature ventricular contractions.

[20–80 (40) ms vs 27–80 (40) ms, P < 0.001], and patients with enlarged LA were more likely than those with normal LA to have episodes of non-sustained VT in a 24-hour period [0–832 (0) vs 0–22072 (0), P < 0.001]. Pleomorphism, retrograde P waves, coupling interval, circadian rhythm and QRS width did not significantly differ between the enlarged LA group and the normal LA group.

PVC Burden and LAD: Subgroup Analysis

To assess the possible correlation between LAD and PVC burden, we conducted a subgroup analysis within the study population (Figure 1, Tables 2 and 3). Remarkably, a statistically significant linear correlation, although weak, was identified between PVC burden and LAD in patients with idiopathic

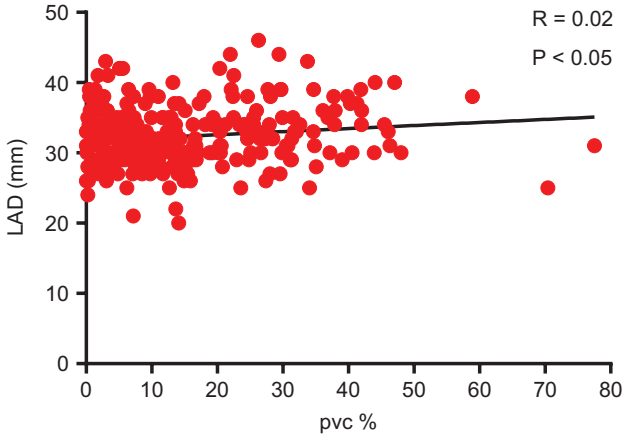

Figure 1 Linear Correlation Between LAD and PVC Burden. LAD, left atrial diameter; PVCs, premature ventricular contractions.

PVCs (Figure 1, R = 0.02, P < 0.05). Furthermore, after accounting for confounding factors such as age, BMI, SBP and other relevant characteristics (Table 4), we determined that PVC burden was an independent predictor of LAD (P = 0.003).

ROC analysis indicated that a PVC burden cut-off value of 17% had 72% specificity and 48% sensitivity [area under the curve (AUC) = 0.57] (Figure 2, Table 4) in predicting enlarged LA. Use of this cutoff value correctly identified 48 of 101 patients (48%) with idiopathic PVCs with enlarged LA.

Multivariate Analysis

The results of binary logistic regression analysis of the variables with P-values <0.05 in a comparison

Table 4 Cutoff Data for PVC Burden, on the Basis of ROC Curves Indicating Combined Sensitivity and Specificity.

PVC burden (%)	Sensitivity (%)	Specificity (%)
2	90	11
4	80	22
7	70	31
10	60	47
15	50	68
17	48	72
21	40	77
25	30	81
30	20	88
39	10	96

PVCs, premature ventricular contractions.

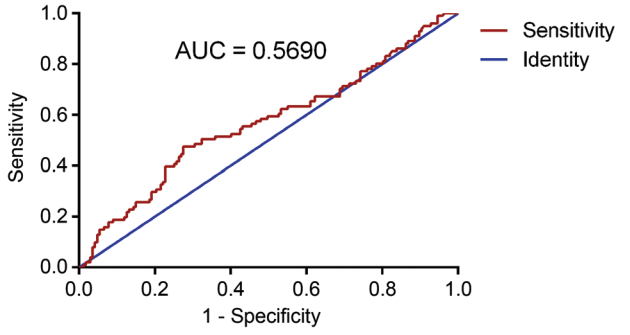

Figure 2 Receiver Operating Characteristic Curve Indicating Sensitivity and Specificity for Predicting Idiopathic PVC Induced Enlarged LA According to PVC Burden. PVCs, premature ventricular contractions; LA, left atrium.

between the enlarged LA group and normal LA group are presented in Table 5. After adjustment for variables found to be statistically significant in the univariate analysis, serum sodium (P = 0.006), BMI (P < 0.001), total number of beats in 24 hours (P = 0.006), average heart rate (P = 0.047) and NT-proBNP (P = 0.008) were independently associated with enlarged LA, whereas the other parameters, including age, SBP, P-wave dispersion, non-sustained VT, retrograde P waves, serum calcium and hypersensitive C-reactive protein, were not. No significant correlation was found between age and LA enlargement, potentially because the study population included only individuals with idiopathic premature ventricular contractions.

Discussion

Main Findings

In our study involving 268 consecutive patients diagnosed with idiopathic PVCs, we identified several independent predictors of PVC-induced LA enlargement. Notably, diminished serum sodium levels emerged as a significant predictor. Additionally, factors such as BMI, NT-proBNP levels, PVC burden, decreased mean heart rate, and low numbers of total beats in a 24-hour period were also found to be independently associated with LA enlargement. Importantly, whereas a weak linear correlation was observed between PVC burden and LA size, PVC burden was independently

Table 5 Multivariate Analysis of Characteristics Associated with the Presence of Enlarged LAD.

Independent variables	Odds ratio	95%CI	P Value
Age	1.006	0.979–1.035	0.652
BMI	1.704	1.458–1.992	<0.001
SBP	1.011	0.977–1.048	0.522
Average heart rate	0.951	0.904–0.999	0.047
Number of total beats in 24 hours	1.000	1.000–1.000	0.006
PVC burden	1.046	1.015–1.077	0.003
P-wave dispersion	1.005	0.979–1.032	0.699
Non-sustained VT	0.999	0.998–1.001	0.545
Serum sodium	0.835	0.734–0.950	0.006
Serum calcium	0.585	0.132–2.592	0.481
Hypersensitive C-reactive protein	1.601	0.768–3.338	0.209
NT-proBNP	1.004	1.001–1.006	0.008

BMI, body mass index; CI, confidence interval; LAD, left atrial diameter; NT-proBNP, N-terminal natriuretic peptide; SBP, systolic blood pressure; VT, ventricular tachycardia.

associated with LA enlargement in patients with idiopathic PVCs. Furthermore, a PVC burden exceeding 17% was significantly associated with greater risk of LA enlargement. To our knowledge, this study provides the first documented evidence demonstrating a significant association between lower serum sodium levels and PVC-induced enlargement of the LA.

Serum Sodium and LA

A remarkable discovery in this study was the correlation between serum sodium and PVC-induced LA enlargement. Mico von Rotz et al. have found an association between sodium levels and an elevated PVC count [10]; however, the underlying mechanism remains elusive. Several hypotheses have been suggested to explain this intriguing observation. Notably, the activation of both the sympathetic nervous system and the renin angiotensinogen system share common mechanisms in the pathological processes of both PVC and hyponatremia. Prior studies have shown that hyponatremia reflects elevated activation of renin-angiotensin-aldosterone and the sympathetic nervous system [11, 12] PVCs may induce abnormal cardiac hemodynamics and elevate myocardial oxygen consumption [13], thereby triggering sympathetic tone, activating the renin-angiotensin-aldosterone system, increasing renal blood flow, and promoting sodium and water re-absorption [14]. This cascade of events can also increase secretion of arginin vasopressin from the atrium and ultimately stimulate hyponatremia [15–17]. Furthermore, during extrasystole, the atrium has been hypothesized to contract while the atrioventricular valves are closed, thereby increasing LA pressure and consequently atrial wall stress. This elevated pressure stimulates the secretion of atrial natriuretic peptide, which subsequently contributes to a further decrease in serum sodium levels. On the basis of these considerations, lower serum sodium levels have been postulated to be independently associated with PVC-induced LA enlargement.

PVC Burden and LA

Our findings revealed an independent association between PVC burden and LA. A high PVC burden has been well established to be associated with elevated risk of developing cardiomyopathy [18, 19]. Additionally, PVCs may induce LA enlargement [8], although the underlying mechanism remains unknown. Our results indicated that a high-PVC burden is an independent predictor of PVC-induced LA enlargement. Several hypotheses based on these findings may proposed. First, PVCs may lead to inefficient atrial contractions. During extrasystole, the atrium contracts while the atrioventricular valves are closed [8], thus increasing LA volume and subsequently atrial wall stress. Furthermore, during ventricular diastole, the LA is exposed to the pressure of the LV, thus resulting in increased LA pressure to maintain adequate LV filling [20]. Subsequently, chamber dilatation and stretching of the atrial myocardium result [21, 22]. Simultaneously, PVCs cause electrical and mechanical desynchrony resulting in chamber dilatation and diminished ventricular function [13], thus ultimately inducing LA enlargement. Moreover, patients with PVCs have been shown to exhibit elevated adrenergic and neurohormonal activity, thereby triggering remodeling in the atria [15, 23]. Furthermore, in this study, we demonstrated that a PVC burden cutoff of 17% was associated with the presence of enlarged LA but did not identify every affected patient.

Clinical Characteristics and LA

This study also revealed a significant association between BMI and LA enlargement. Specifically, patients with enlarged LA had a higher BMI than those with normal LA size. Previous research has demonstrated that high BMI is associated with diastolic dysfunction in individuals with normal LV ejection fraction [24]. Additionally, LA enlargement is strongly correlated with higher BMI or adiposity [10, 25, 26], although the underlying mechanism remains unclear. One possible explanation for this association might be the increased cardiac workload required to supply a higher cardiac output and increase oxygen consumption in individuals with higher BMI, because of their larger body surface [26–28].

Furthermore, this study demonstrated elevated concentrations of NT-proBNP in patients with enlarged LA. BNP and NT-proBNP are well-established cardiovascular biomarkers reflecting myocardial wall tension in response to increases in ventricular wall stress [29, 30]. Idiopathic PVCs can induce unexpected and abrupt changes in LV wall tension, thereby exerting mechanical stress on the myocardium [31]. As discussed earlier, the

LA plays a crucial role in maintaining LV filling and subsequently LV stroke volume in idiopathic PVCs. On the basis of these observations, we hypothesize that high NT-proBNP concentrations might indirectly correlate with enlarged LA in idiopathic PVCs.

Study Limitations

This study has several limitations. First, because of time constraints, we conducted a retrospective analysis, thus potentially introducing inherent biases. Furthermore, the inclusion of patients who underwent blood tests and echocardiography might have led to selection bias. Second, the evaluation of PVC characteristics was based solely on a single 24-hour Holter recording. Importantly, this recording might not have accurately captured the true PVC burden, because the frequency of PVCs can fluctuate throughout the day, even within the same patient.

Conclusions

According to the findings of this research, an association exists between decreased serum sodium levels, increased PVC burden, decreased mean heart rate, higher BMI and elevated NT-proBNP with the enlargement of the LA among individuals without structural heart diseases. Moreover, our findings may implicate a PVC burden exceeding 17% in the development of PVC-induced LA enlargement. Nevertheless, this study was unable to establish a causal relationship between these aforementioned factors and LA enlargement; therefore, further investigation in this area is necessary.

Data Availability Statement

Clinical data are available through the corresponding author.

Ethics Statement

Ethical approval was obtained from the Second Affiliated Hospital of Chongqing Medical University.

Author Contributions

Xue Kuang and Zengzhang Liu conceived the study. Xue Kuang, Jinhang Che and Caiyin Zheng acquired the data. Xue Kuang and Yuxiang Long analyzed the data. Xue Kuang reviewed the literature and prepared the first draft of the manuscript. Zengzhang Liu critically reviewed and edited the manuscript, and approved the final version. All authors have read and approved the final manuscript.

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Conflicts of Interest

The authors have no conflicts of interest.

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