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Electrophysiology

Impact of Premature Ventricular Complex (PVC) Burden on the Left Ventricle in the Structurally Normal Heart: Hemodynamic Alterations of Idiopathic PVC on Echocardiography

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Background: Premature ventricular complex (PVC) without structural heart disease is mostly viewed as a benign arrhythmia. However, the high burden of PVC causes cardiomyopathy due to intraventricular dyssynchrony. The effects of ectopic contraction on left ventricular (LV) hemodynamics in the structurally normal heart are unclear.
Objectives: To examine the effect of PVC burden on LV dimension, LV systolic function, and intraventricular blood flow, and to determine whether ectopic ventricular contraction affects LV hemodynamics.
Methods: Patients aged ≥ 18 years with PVC ≥ 5% on Holter recording were enrolled and divided into groups G1 (5-10%), G2 (10-20%), and G3 (≥ 20%). We excluded patients with structural heart diseases, pacemakers, and LV systolic dysfunction [LV ejection fraction (LVEF) < 50%]. Clinical characteristics and routine transthoracic echocardiography parameters were compared.
Results: The end-systolic LV internal dimension increased according to the PVC burden from G1 to G3 (p = 0.001). LVEF was inversely associated with PVC burden from G1 to G3 (p = 0.002). The same pattern was seen for LV outflow tract (LVOT) maximal velocity (p = 0.005) and maximal pressure gradient (PG) (p = 0.005), LVOT velocity time integral (VTI) (p = 0.03) and LV stroke volume index (LVSI) (p = 0.008).
Conclusions: Systolic function and LV end-systolic dimension were inversely associated with PVC burden. Decreased LVOT flow velocity and PG were related to increased PVC burden. LVOT VTI and LVSI were smaller when the PVC burden exceeded 20%. These negative hemodynamic manifestations of idiopathic PVC were considerable even in structure normal hearts, hence the early elimination of PVC is strongly advised.

Key Words: Hemodynamics • Idiopathic PVC • Premature ventricular complex

INTRODUCTION

Premature ventricular complex (PVC) is not uncommon, and PVC with structural heart disease is often considered a precursor to ventricular tachycardia.[1,2] How-

Abbreviations	
2D	Two-dimensional
LV	Left ventricular
LVEF	LV ejection fraction
LVIDd	End-diastolic LV internal dimension
LVIDs	End-systolic LV internal dimension
LVOT	LV outflow tract
LVSI	LV stroke volume index
MV	Mitral valve
PG	Pressure gradient
PVC	Premature ventricular complex
TTE	Transthoracic echocardiography
VTI	Velocity time integral

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ever, when PVC occurs in patients with structurally normal hearts, this so-called idiopathic PVC is mostly considered benign.[3,4] Recently, a study showed that a high PVC burden is likely to cause heart failure, especially when PVC ≥ 5%.[5] Evidence has also shown that PVC may elevate left ventricular (LV) filling pressure.[6] The explanation for these pathologies may be related to interventricular dyssynchrony,[7,8] which disturbs LV hemodynamics. Some researchers have even proposed that electrical ablation of the PVC origin may help to normalize LV function.[9] However, it is unclear how idiopathic PVC affects LV hemodynamics. This study aimed to investigate the association between PVC burden and LV hemodynamics by using routine echocardiographic parameters in patients with idiopathic PVC to identify those at risk of heart failure.

METHODS

Study design

This was a retrospective, cross-sectional, and descriptive study performed on patients already undergoing 24-hour Holter monitoring and transthoracic echocardiography; the Institutional Review Board of China Medical University Hospital approved this study protocol.

Patient selection

Holter records from January 2019-December 2020 (N = 9985) were screened. The inclusion criteria were age ≥ 18 years, and PVC > 5%. A total of 581 patients were included initially, and their 24-hour Holter recordings, echocardiographic reports and medical chart were reviewed. Of these patients, 245 were excluded due to the following reasons: pacemaker implantation (to avoid Holter misreading) (N = 7), lack of echo data (N = 125), structural heart disease (N = 35) including ischemic cardiomyopathy (with history of prior myocardial infarction, unstable angina, triple-vessel disease, post bypass surgery or percutaneous coronary intervention; N = 24), hypertrophic cardiomyopathy (N = 3), valvular heart disease (≥ moderate regurgitation or stenosis or post valvular surgery, N = 5), congenital heart disease (corrected or non-corrected, N = 1), group 1 pulmonary artery hypertension (N = 2), and idiopathic systolic dysfunction [LV ejection fraction (LVEF) < 50% without any identified cause on a comprehensive evaluation; N = 78].

Finally, 336 patients with a structurally normal heart and systolic function (so-called idiopathic PVC) were enrolled (Figure 1). According to the percentage of PVC (total PVC/total heart rate) on 24-hour Holter monitoring, the enrolled patients were divided into groups G1 (5-10%), G2 (10-20%), and G3 (≥ 20%). Most of the patients were in G1 (N = 148), the mean PVC burden in G1 was 7457 ± 1731 PVCs per day (Figure 1).

Two-dimensional transthoracic echocardiography

Echocardiographic studies were performed using a Vivid E9 cardiac ultrasound system (General Electric, Milwaukee, WI, USA). Two-dimensional (2D) transthoracic echocardiography (TTE) was routinely performed within 3 months when Holter monitoring showed a high PVC burden. LV dimensions were measured using the M-mode method of parasternal long-axis imaging according to the American Society of Echocardiography standards. LVEF was calculated using the Teichholz method. If the image quality was not suitable, Simpson's method was used.

Valvular regurgitation was quantified using color

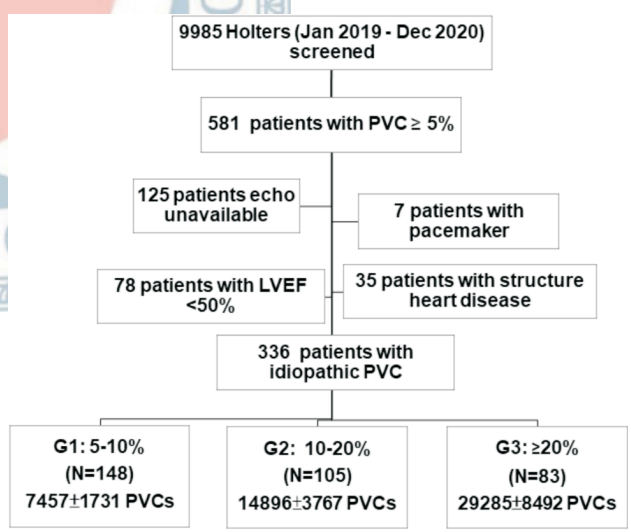

Figure 1. *Patient selection and grouping. Reports of Holter from Jan 2019 to Dec 2020 were screened (N = 9985). Patients age ≥ 18 year and premature ventricular complex (PVC) ≥ 5% were selected (N = 581). Patients were excluded for echo unavailable (N = 125), pacemaker implantation (N = 7), structure heart disease (N = 35) (see text) and left ventricular systolic dysfunction (N = 78). Finally, a total of 336 patients with idiopathic PVC were studied. According to PVC burden, enrolled patients were divided into groups G1 (PVC = 5-10%), G2 (10-20%) and G3 (≥ 20%). LVEF, left ventricular ejection fraction.*

Doppler and Doppler imaging. Doppler was used to calculate LV outflow tract (LVOT) velocity, mitral valve (MV) inflow, and tricuspid valve systolic pressure gradient (PG). LV diastolic function was determined by mitral inflow and mitral annular velocity by tissue Doppler imaging.

All measurements were obtained on sinus rhythm; PVC was avoided carefully when performing routine 2D TTE acquisition. In patients with atrial fibrillation, five measurements were obtained and averaged.

Statistical analysis

Categorical variables are expressed as the number and percentage of patients. Differences in categorical variables were examined using Pearson's chi-square test. All continuous variables are reported as median (interquartile range). A nonparametric statistical method (Kruskal-Wallis test) was used to compare groups. Multivariable logistic regression analysis was used to compare clinical outcomes. All tests of significance were two sided, and $p \leq 0.05$ was considered statistically significant. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of the idiopathic patients. The mean age of the patients was 61 (49-71) years, and 54.5% (183/336) were male. In addition, 11.8% (12/336) had atrial fibrillation, 11.6% (36/336) had diabetes, and 16.1% (50/336) had hypertension. There were no significant differences between the groups in baseline characteristics including age, sex, body height, body weight, and blood pressure.

Routine transthoracic echocardiography

The echocardiography characteristics are shown in Table 2. The median end-diastolic LV internal dimension (LVIDd) of the 336 patients was 50.2 (46.8-54.6) mm, and no significant difference was observed between groups in LVIDd. In addition, the median end-systolic LV internal dimension (LVIDs) was 32.0 (28.9-35.4) mm. Kruskal-Wallis test of LVIDs and PVC burden showed a significant difference between the groups ($p = 0.001$), and bivariate regression showed that LVIDs was positively associated with PVC% ($r^2 = 0.035$; $p = 0.0006$). The median LVEF was 58.7% (54.3-62.9%) in the whole cohort, and it was significantly different from G1-G3 ($p = 0.0011$). Bivariate regression showed that LVEF was negatively associated with PVC burden ($r^2 = 0.057$; $p < 0.0001$). LVOT maximum velocity was significantly different between groups ($p = 0.005$), and bivariate analysis showed that LVOT max velocity was negatively associated with PVC burden ($r^2 = 0.021$; $p = 0.0101$). The LVOT max PG was significantly different between the groups ($p = 0.005$), and bivariate regression also showed a negative association between these two variables ($r^2 = 0.017$; $p = 0.0195$).

The LVOT mean velocity was significantly different between the groups ($p = 0.0032$), and bivariate regression showed a negative correlation with PVC burden (r^2

Table 1. Baseline characteristics

Characteristics	Group 1 (N = 148)	Group 2 (N = 105)	Group 3 (N = 83)	Total (N = 336)	p value
Age*	62 (49-71)	59 (48-72)	63 (48-73)	61 (49-71)	0.89
Sex, N (%)					0.08
Male	72 (21.43)	58 (17.26)	53 (63.9)	183 (54.5)	
Body height (cm)*	161 (155-168)	162 (157-170)	161 (158-170)	162 (156-168)	0.19
Body weight (kg)*	63 (55.5-72)	63 (56-76)	67 (57.7-75)	63 (56-74)	0.32
SBP (mmHg)*	130 (119-143)	135 (120-151)	133 (123-145)	133 (120-145)	0.19
DBP (mmHg)*	76 (67-81)	77 (69-87)	77 (69-84)	77 (68-84)	0.28
Comorbidities, N (%)					
Diabetes	21 (6.77)	9 (2.90)	6 (7.89)	36 (11.6)	0.17
Hypertension	25 (8.06)	15 (4.84)	10 (13.2)	50 (16.1)	0.59
Atrial fibrillation	3 (0.89)	2 (0.60)	5 (14.7)	12 (11.8)	0.22

DBP, diastolic blood pressure; SBP, systolic blood pressure.

* Kruskal-Wallis test.

Table 2. Echocardiographic parameters

Characteristics	Group 1 (N = 148)	Group 2 (N = 105)	Group 3 (N = 83)	Total (N = 336)	p value*
AO diam	30.2 (27.1-33.3)	31.0 (27.5-34.1)	30.7 (27.8-34.0)	30.6 (27.4-33.7)	0.76
LA diam	35.9 (32.0-41.0)	36.4 (32.8-42.4)	37.1 (32.7-41.9)	36.5 (32.5-42.0)	0.55
IVSd	7.38 (6.57-8.50)	7.31 (6.23-8.46)	7.29 (6.52-8.18)	7.29 (6.45-8.41)	0.78
IVSs	10.8 (9.28-12.6)	10.3 (9.36-11.5)	11.1 (9.36-12.4)	10.8 (9.34-12.3)	0.27
LVIDd (LVEDD)	49.6 (46.2-53.1)	51.1 (47.1-56.1)	50.8 (48.2-54.9)	50.2 (46.8-54.6)	0.08
LVIDs (LVESD)	31.2 (27.9-34.7)	32.9 (29.1-36.3)	33.7 (30.2-36.3)	32.0 (28.9-35.4)	0.001†
LVPWd	7.54 (6.64-8.73)	7.48 (6.60-8.55)	7.48 (6.67-8.61)	7.50 (6.64-8.68)	0.92
EF (M-mode)	60.1 (55.3-65.3)	58.2 (54.4-62.7)	56.4 (53.2-61.2)	58.7 (54.3-62.9)	0.002†
LVd mass (ASE)	121.3 (97.6-151.2)	130.0 (99.5-164.1)	131.2 (105.4-155.0)	123.9 (98.7-154.8)	0.41
LVd mass Ind (ASE)	73.2 (61.0-87.0)	73.7 (61.2-95.5)	76.3 (62.6-86.9)	73.6 (61.3-88.8)	0.69
LAVI	27.5 (22.8-35.0)	27.6 (22.8-34.0)	27.8 (22.4-35.0)	27.7 (22.7-34.8)	0.96
LVOT Max Vel	0.96 (0.86-1.11)	0.98 (0.85-1.08)	0.91 (0.76-1.02)	0.95 (0.84-1.08)	0.005†
LVOT Max PG	3.69 (2.96-5.02)	3.84 (2.89-4.67)	3.31 (2.31-4.16)	3.61 (2.82-4.67)	0.005†
LVOT mean Vel	0.66 (0.55-0.73)	0.65 (0.57-0.72)	0.60 (0.53-0.67)	0.63 (0.55-0.71)	0.0032†
LVOT mean PG	1.97 (1.47-2.46)	2.03 (1.57-2.38)	1.70 (1.29-2.07)	1.83 (1.43-2.35)	0.0034†
LVOT VTI	20.0 (17.7-23.3)	20.0 (17.8-22.7)	19.2 (15.7-77.6)	19.8 (17.3-22.7)	0.03#
LVSV (Dopp)	69.5 (58.7-82.1)	70.4 (62.2-79.4)	63.3 (53.4-77.6)	68.4 (58.4-79.8)	0.048#
LVSI (Dopp)	42.2 (35.2-48.6)	41.6 (36.2-48.1)	37.6 (31.8-44.7)	41.1 (34.7-47.9)	0.008†
LVCO (Dopp)	4.76 (4.00-5.78)	5.00 (4.03-6.18)	4.59 (3.52-5.49)	4.79 (3.91-5.74)	0.08
LVCI (Dopp)	2.87 (2.39-3.38)	2.86 (2.43-3.64)	2.67 (2.04-3.11)	2.83 (2.36-3.39)	0.05
MV E Vel	0.71 (0.58-0.84)	0.70 (0.58-0.84)	0.73 (0.52-0.82)	0.71 (0.57-0.84)	0.60
MV A Vel	0.77 (0.63-0.90)	0.75 (0.63-0.92)	0.78 (0.63-0.90)	0.76 (0.63-0.90)	0.91
MV Dec T	205.9 (167.9-248.3)	191 (164.3-239)	207.8 (172.4-236.7)	203.1 (167.7-240.7)	0.27
MV E/A ratio	0.85 (0.68-1.23)	0.87 (0.69-1.22)	0.87 (0.66-1.20)	0.86 (0.68-1.22)	0.97
S′ (sep)	6.90 (5.80-7.93)	6.98 (6.06-8.32)	6.36 (5.23-8.08)	6.83 (5.73-8.06)	0.55
E′ (sep)	7.01 (5.06-8.73)	6.40 (4.98-8.42)	6.50 (4.43-8.59)	6.59 (4.98-8.62)	0.55
A′ (sep)	8.68 (7.24-10.2)	8.99 (7.72-10.2)	8.79 (6.78-10.0)	8.83 (7.34-10.2)	0.45
E/E′ Avg	9.70 (7.60-12.0)	9.60 (7.80-13.0)	9.95 (6.90-12.4)	9.80 (7.40-12.4)	0.88
TR Max Vel	2.25 (1.98-2.43)	2.25 (1.98-2.50)	2.17 (1.88-2.46)	2.24 (1.96-2.45)	0.59
TR Max PG	20.3 (15.1-23.6)	20.3 (15.7-25.0)	18.8 (14.1-24.2)	20.1 (15.2-24.0)	0.47
RVSP	28.2 (23.7-33.6)	29.7 (25.1-34.2)	28.8 (24.1-34.2)	28.9 (24.4-33.6)	0.47
WMSI	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.53

AO, aortic; ASE, American Society of Echocardiography; Diam, diameter; Dec T, deceleration time, Dopp, Doppler; E/E′ avg, E/E′ average; EF, ejection fraction; IVSd, inter-ventricular septum in diastole; IVSs, inter-ventricular septum in systole; LA, left atrium; LAVI, left atrial volume index; LCSI, left ventricular stroke index; LV, left ventricular; LVCI, left ventricular cardiac index; LVCO, left ventricular cardiac outcome; LVd, left ventricular end diastolic; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVIDd, left ventricular Internal dimension in diastole; LVIDs, left ventricular Internal dimension end-systole; LVOT, left ventricular outflow tract; LVPWd, left ventricular posterior wall width in diastole; LVSV, left ventricular stroke volume; Max, maximal; MV, mitral valve; PG, pressure gradient; RVSP, right ventricular systolic pressure; Sep, septum; TR, tricuspid regurgitation; Vel, velocity; VTI, velocity time integral; WMSI, wall motion score index.

* Kruskal-Wallis test.

# $p < 0.05$ is significant. † $p < 0.01$ is highly significant.

= 0.020; p = 0.0115). Moreover, the LVOT mean PG between groups also showed a significant difference (p = 0.0034), and bivariate regression also showed a negative association with PVC burden (r^2 = 0.0166; p = 0.0209). There was a significant difference in LVOT velocity time integral (VTI) between the groups (p = 0.03), and bivariate analysis showed a negative correlation between LVOT VTI and PVC burden (r^2 = 0.022; p = 0.0085). In addition, differences were observed in LV stroke volume (p = 0.048) and LV stroke volume index (LVSI) between

groups (p = 0.008), and bivariate analysis showed a negative correlation between LVSI and PVC burden (r^2 = 0.026; p = 0.0043).

No significant differences were observed in LV cardiac output and LV cardiac index, MV E velocity and A velocity, E/A ratio on LV inflow, annulus septal S′, E′, A′ velocity, or E/E′ ratio.

Clinical outcomes at 1 year of observation

There were no differences between groups in clinical outcomes upon cardiovascular hospitalization and cardiovascular mortality during 1 year of observation. Eighty-two patients (24.4%, 82/336) had another TTE in the following year. There was no association between PVC burden and new-onset LV systolic dysfunction (LVEF < 50%) (p = 0.80) (Table 3). However, many confounders need to be adjusted, and further prospective and longitudinal studies are needed.

DISCUSSION

Literature review

PVC is a common arrhythmia; however, the fundamental cause remains unknown.[10] Patients with PVC suffer from chest tightness, dyspnea, fatigue, and other symptoms of heart failure. The risk factors for frequent PVC include age, height, hypertension, smoking, sedentary lifestyle and a history of heart disease.[10,11] However, our data did not show a significant difference between the groups with regards to these risk factors.

When PVC is associated with structural heart disease, clinicians should always be alert because there is an extremely high risk of ventricular tachycardia and sudden death.[1,10,12,13] When a PVC is detected in association with a structurally normal heart (primary or idiopathic PVC), it is often diagnosed as a benign arrhythmia[4] and only followed up at an outpatient clinic[14,15] even if the burden of the PVC has been identified as potentially reaching the point of heart failure (PVC ≥ 5%).[5] However, many animal studies have provided electrophysiological evidence that ectopic ventricular rhythms can lead to heart failure.[16-22] PVC is produced by catheter pacing and then subjected to conventional ultrasound, or comparisons of before and after treatment with an electrocautery catheter can be used to illustrate the benefits of treating PVC. At present, most of the research on PVC has focused on catheter ablation,[23-26] and large-scale research on PVC has mostly been community-based observational studies.[27-29] Some previous studies have provided evidence that a higher PVC frequency is associated with a higher incidence of congestive heart failure and mortality,[27,30,31] while others have suggested that risk factors such as hypertension, smoking, and underlying structural heart diseases are associated with PVC frequency.[28,29] However, no study to date has directly discussed the effect of idiopathic PVC.

Table 3. One year clinical outcome

Characteristics	Group 1 (N = 148)	Group 2 (N = 105)	Group 3 (N = 83)	Total (N = 336)	p value*
CV hospitalization	14 (9.46)	11 (10.5)	4 (4.83)	29 (8.71)	0.3404
Univariable	Ref.	1.10 (0.48, 2.52)	0.47 (0.15, 1.49)		
Multivariable‡	Ref.	0.69 (0.13, 3.63)	0.48 (0.07, 3.50)		
All cause hospitalization	16 (11.0)	13 (12.4)	5 (6.02)	34 (10.21)	0.3273
Univariable	Ref.	1.14 (0.52, 2.48)	0.52 (0.18, 1.47)		
Multivariable‡	Ref.	0.92 (0.22, 3.85)	0.46 (0.09, 2.54)		
LV systolic dysfunction (N/total) (%)	2/30 (6.67)	2/26 (7.69)	3/26 (11.5)	7/82 (8.54)	0.80
Univariable	Ref.	1.17 (0.15, 8.92)	1.83 (0.28, 11.9)		
Multivariable‡	Ref.	0.02 (0.001, 999)	999 (0.001, 999)		

CV, cardiovascular; LV, left ventricular.

* Chi-square test.

# p < 0.05 is significant; † p < 0.01 is highly significant.

‡ Multivariable logistic regression analysis was performed to mutually adjusted relevant factors including age, sex, body height, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP) comorbidities of diabetes, hypertension, and atrial fibrillation.

Dyssynchrony of PVC

Echocardiography is an easily accessible tool to evaluate PVC disturbance. One study reported reduced LV stroke volume after PVC coupling.[7] Another study used segmental myocardial circumferential strain to explain how PVC causes synchronization disorder.[8] Billet et al. proposed that PVC could have a detrimental effect on hemodynamics (low systolic arterial pressure) in patients with PVC cardiomyopathy;[32] and Salem et al. provided evidence that PVC may be associated with an elevation in LV filling pressure,[6] although we did not find this in our study. Another study demonstrated that idiopathic PVC might increase ventricular wall stress even when LV systolic function is appropriate.[23] Nonetheless, these negative consequences created by PVC seem to be reversible. A clinical study at our center showed a slight reduction in left atrium and LV sizes when PVC burden decreased after medical treatment or catheter ablation.[33]

Hemodynamic sequelae of idiopathic PVC

There is a lack of direct evidence about how PVC impacts LV hemodynamics. Our study provides evidence that a higher idiopathic PVC burden is linked to the disturbance of LV hemodynamics (lower peak and mean LVOT velocity, PG, LVOT VTI and LVSI, all $p < 0.05$), which may increase afterload and lead to LV volume overload; thus, LV dilatation (increase in LVIDs associated with PVC burden; $p = 0.0006$ by bivariate regression analysis) and, ultimately, a decrease in LVEF ($p < 0.0001$ by bivariate regression analysis). A possible explanation is that an ectopic ventricular beat contracts inefficiently and generates intraventricular dyssynchrony; the greater the number of PVCs, the greater the intraventricular dyssynchrony and intraventricular blood stasis. All of these events occur in the early stage of idiopathic PVC normal systolic function. It is important to note that hemodynamic alterations precede LV remodeling. Additional research, such as myocardial strain for idiopathic PVC, is required to confirm our hypothesis.

Limitations

Due to the retrospective and cross-sectional design of the study, patient selection was based on PVC records and echocardiographic findings. First, the patient selection may have been biased. A total of 125 (21.5%) patients were not included in this study because of a lack of echocardiography data. The actual percentage of idiopathic PVC in a single center was also unclear. In addition, 78 patients with dilated LV and depressed LVEF were not enrolled; however, how many of them had late-stage idiopathic PVC is unknown. Second, most of the PVC burden fell within groups G1 to G2 (5% to 20%). The number of patients in groups G3 was lower than that in the other groups, and this may have introduced statistical bias. This may be the reason for the small R square when linear bivariate regression was performed in our study. However, R square is a descriptive measure which by itself does not measure the quality of the regression model, and the validity of the regression model is still determined by the p value. Nevertheless, the number of extremely high burden patients (G3) should be increased in further investigations. The major limitation of this study is its cross-sectional nature. Whether the changes in LV dimensions and hemodynamics are consequences or etiologies is not clear. Also, controlling for confounders is crucial in casual observational studies, and adjustments for confounders and another longitudinal observation study are mandatory in the future.

CONCLUSION

To the best of our knowledge, this is the first study to examine the relationship between PVC burden and intraventricular hemodynamic alterations. Our results suggest a negative relationship between PVC burden and LVIDs, LVEF, LVOT velocity, PG, VTI and LVSI, even in the structurally normal heart with normal systolic function. LVOT VTI and LVSI were significantly reduced when the PVC burden $\geq$ 20%. Future research should include a larger number of participants with a high PVC burden (20%). These unfavorable hemodynamic manifestations were considerable and occurred before LV remodeling. Further research is required to determine whether this connection is the result of high PVC burden. Nevertheless, early medical or interventional treatment is definitely suggested to reduce PVC load.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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