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# Post-Extrasystolic Potentiation as a Predictor of Recovery of Left Ventricular Dysfunction After Radiofrequency Catheter Ablation

Balaji Krishnan, MD, MS, Ashwini Sankar, MA, Inder Anand, MD, DPHIL, Selcuk Adabag, MD, MS, Jian-Ming Li, MD, PHD, Edward O. McFalls, MD, PHD, David G. Benditt, MD, Kalyanam Shivkumar, MD, PHD, Venkatakrishna N. Tholakanahalli, MD

## ABSTRACT

**OBJECTIVES** This study hypothesizes that post-extrasystolic potentiation reflects left ventricle contractile reserve and therefore may predict an improvement of premature ventricular contraction (PVC)-induced cardiomyopathy after PVC ablation.

**BACKGROUND** Post-extrasystolic potentiation is a physiologic phenomenon of blood pressure accentuation after a PVC beat.

**METHODS** We performed a retrospective study of patients with a PVC burden of ≥10% PVC/24 h and left ventricular ejection fraction (LVEF) of <50% who underwent successful ablation between January 1, 2009, to June 30, 2015. Subjects were classified as having reversible (a final LVEF ≥50%) or irreversible (final LVEF <50%) LV dysfunction on a follow-up echocardiogram. A reference (control) group with ≥10% PVC but normal LV function was also identified.

**RESULTS** Sixty-one patients (age 68 ± 11 years, 98% male) were studied: 30 with preserved and 31 with reduced LVEF. During median follow-up of 9.4 months, the LVEF of 17 of 31 reduced EF patients improved (reversible) but 14 did not (irreversible). The post-PVC beat systolic blood pressure (SBP) (mm Hg) increase ranged from 12.1 in control subjects (LVEF >50%) to 11.5 in reversible patients to 5 in irreversible patients. In multivariate analysis, the independent predictors of reversible LV function were post-PVC SBP rise (odds ratio [OR]: 4.61; 95% confidence interval [CI]: 1.45 to 15.83 per 5-mm Hg increase; $p < 0.001$), post-PVC pulse pressure change (OR: 5.2; 95% CI: 2.3 to 18.6 per 5-mm Hg increase; $p < 0.001$), and PVC QRS duration (OR: 2.78; 95% CI: 1.63 to 10.94 per 10-ms increase; $p < 0.001$).

**CONCLUSIONS** In patients with LV dysfunction and frequent PVC, post-PVC SBP accentuation may be a marker for subsequent recovery of LVEF after ablation in presumed PVC-induced cardiomyopathy. (J Am Coll Cardiol EP 2017;3:1283–91) Published by Elsevier on behalf of the American College of Cardiology Foundation.

Idiopathic premature ventricular complexes (PVC) are generally considered benign and most often are treated conservatively. However, sustained ventricular tachycardia, symptomatic PVC resistant to medical therapy, and PVC thought to contribute to an underlying cardiomyopathy are often treated with radiofrequency ablation.

A high burden of PVC has been associated with left ventricular (LV) dysfunction in prior studies of patients referred for ablation (1–5). A longitudinal study (6) found subclinical deterioration in LV function over 5 years in those with a high PVC burden (≥10% to 20%). Yet many patients with long-standing, frequent PVC have no evidence of LV dysfunction. Furthermore, a

From the Cardiac Arrhythmia Center and Cardiovascular Division, University of Minnesota and Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota. Dr. Adabag has received a research grant from Medtronic. Dr. Benditt is supported in part by a grant from the Dr. Earl E Bakken family in support of Heart-Brain research. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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**ABBREVIATIONS AND ACRONYMS**

**CI** = confidence interval

**DBP** = diastolic blood pressure

**IQR** = interquartile range

**LV** = left ventricle

**LVEF** = left ventricular ejection fraction

**MAP** = mean arterial pressure

**OR** = odds ratio

**PESP** = post-extrasystolic potentiation

**PVC** = premature ventricular complex(es)

**SBP** = systolic blood pressure

**VT** = ventricular tachycardia

significant proportion of patients with frequent PVC and LV dysfunction show no significant improvement in ventricular function despite the elimination of PVC. A few studies have suggested that PVC coupling interval (4), QRS duration of PVC (6), or origin of PVC from epicardial (7) or right ventricular outflow tract (3,5) might predict recovery of LV function post-ablation.

In a normal heart, the post-PVC initiated systolic blood pressure (SBP) is typically higher than the preceding sinus rhythm-initiated SBP. This phenomenon has been termed post-extrasystolic potentiation (PESP). Although the mechanisms are not entirely clear, and a longer diastolic filling period might contribute to the "potentiation," most of the evidence suggests that calcium movement within the sarcoplasmic reticulum is responsible for the increase in myocardial contractility associated with PESP. We hypothesized that the relative change in SBP and mean arterial pressure (MAP) may indicate the LV contractile reserve, and this response in patients before PVC ablation might identify patients in whom PVC-associated LV dysfunction is reversible or irreversible following ablation.

Hence, the purpose of this study was to examine whether post-PVC blood pressure rise is a predictor of the reversibility of LV dysfunction after the successful elimination of PVC by ablation.

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## METHODS

**PATIENT POPULATION.** A total of 150 consecutive patients underwent successful first-time ablation of frequent PVC at the Minneapolis Veterans Affairs Medical Center from January 1, 2009, to June 30, 2015. After satisfying all the exclusion and inclusion criteria, 61 patients were included in this study (**Figure 1**).

We noted those who had a documented left ventricular ejection fraction (LVEF) of <50% on pre-procedure echocardiography. As existing data suggest that very frequent PVC are associated with LV dysfunction (8), we restricted our cohort to patients with ≥10% PVC on pre-procedure 24-h Holter monitoring. Successful ablation was defined as 80% reduction in the 24-h burden of PVC, verified by 24-h Holter monitoring, 3 months post-procedure (9). Patients were excluded if they had a known cause of LV dysfunction or a history of sustained ventricular tachycardia, appropriate implantable defibrillator discharges, or sudden cardiac death. Only subjects with complete Holter and echocardiographic follow-up were eligible. Subjects with unsuccessful ablation were excluded from the analysis. All antiarrhythmic agents were discontinued after ablation. All patients with LV dysfunction before ablation received standard therapy with beta blockade and renin-angiotensin inhibition prior to ablation. Those patients with ongoing LV dysfunction after ablation continued to receive standard therapy for heart failure.

To evaluate characteristics associated with LV dysfunction in the presence of frequent PVC, we also identified a reference group of patients with ≥10% PVC on pre-procedure Holter monitoring but with preserved LV function (echocardiographic LVEF of ≥50%) who underwent ablation during the study period. These patients had the procedure performed for significant worsening of quality-of-life related to symptoms of shortness of breath or palpitations.

**DATA COLLECTION.** Baseline demographic, historical, and clinical characteristics were collected, retrospectively, through detailed chart review. All electrocardiographic and blood pressure measurements were performed, using digital calipers at 100 mm/s on CardioLab (version 6.5.4.1858, GE Medical Systems, Waukesha, Wisconsin). To limit heterogeneous within-subject variances, all electrocardiographic and blood pressure measurements were repeated on 3 separate PVC, occurring at least 10 min apart during intracardiac catheterization and arterial blood pressure monitoring (**Figure 2**). The measurements were taken prior to anesthesia induction and administration of inotropes. The mean of the 3 measurements was used for analysis. In the case of multiple PVC morphologies, the dominant/targeted PVC was measured.

The following equations were used:

$$\text{PESP SBP change} = \text{post-PVC SBP} - \text{sinus SBP}$$

$$\text{PESP DBP change} = \text{post-PVC DBP} - \text{sinus DBP}$$

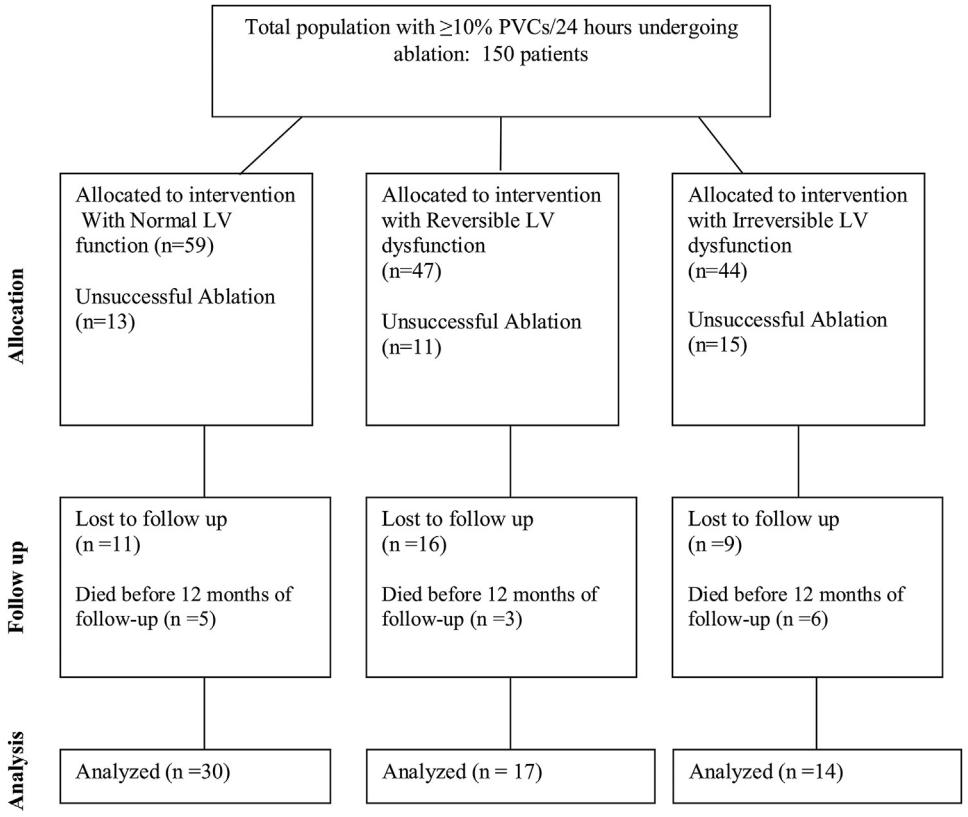
$$\text{MAP} = \frac{\text{SBP} - 2(\text{DBP})}{3}$$

$$\text{MAP change} = \text{MAP}_{\text{post-PVC beat}} - \text{MAP}_{\text{sinus}}$$

$$\text{Pulse pressure change} = \left(\text{SBP}_{\text{post-PVC}} - \text{DBP}_{\text{post-PVC}}\right) - \left(\text{SBP}_{\text{sinus}} - \text{DBP}_{\text{sinus}}\right)$$

As quantitative echocardiographic methods of assessment of LV function may be inaccurate in the setting of frequent PVC, visual estimation was used to determine LVEF. All echocardiographic assessments were blinded to electrophysiologic and procedural characteristics. If the interpreter reported a range, the lower value was used for all analyses.

**FIGURE 1 The Patient Flow for the Study Is Depicted as a CONSORT Diagram**




Note that successful ablation was defined as at least an 80% reduction in the burden of ectopy on postablation 24-h Holter monitoring.
LV = left ventricular; PVC = premature ventricular contraction.

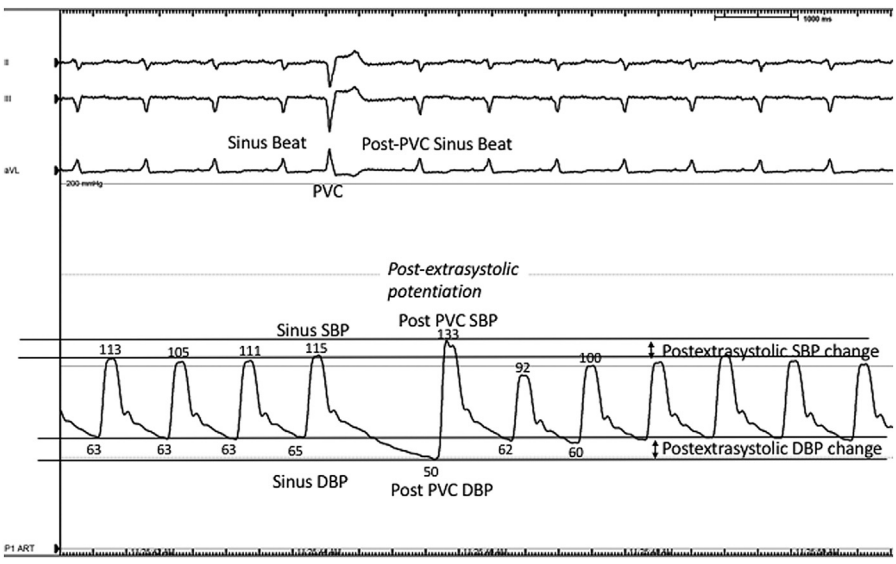
Pre-ablation echocardiographic measurements were made by using stored loops of 3 cardiac cycles without ectopic beats, where possible.

The site of origin of the PVC was classified at the time of successful ablation. In the absence of a standard classification scheme, we initially classified PVC into the following groups on the basis of the anatomic structure giving rise to the PVC: 1) right ventricular outflow tract, right ventricle inflow and other right ventricle sites; 2) left ventricular outflow tract, right coronary cusp, left coronary cusp, right coronary cusp-left coronary cusp commissure, aortomitral continuity; 3) anterior mitral annulus; 4) papillary muscles; 5) other LV sites; and 6) epicardial site.

**PATIENT CLASSIFICATION.** There is no accepted disease definition for PVC-induced cardiomyopathy. We therefore characterized patients with impaired LV function into 2 groups on the basis of their response to therapy with ablation: reversible (a final LVEF ≥50% and change in LVEF ≥10%) or irreversible (final LVEF <50%) LV dysfunction on a follow-up echocardiogram. The minimum change in LVEF of 10% to be considered reversible was chosen as the interobserver variability in determining LVEF by echocardiography ranges from 9% to 14% (4). Given the small number in the partially reversible group, these were included with the irreversible group for the primary analysis. In a sensitivity analysis, they were instead included with the reversible group to assess the robustness of the findings.

**PROCEDURE PROTOCOL.** Antiarrhythmic medications were discontinued at least 48 h before the procedure as per protocol at the participating institutions. A standard diagnostic electrophysiological study was then performed using several percutaneously placed multielectrode catheters. If needed, isoproterenol infusion was used to increase the frequency of PVC. A bipolar voltage map was obtained of the left and right ventricles if the PVC had a left bundle branch block morphology and of the LV if the PVC had a right bundle branch block morphology. Bipolar electrogram amplitudes >1.5 mV were defined

**FIGURE 2 Intra-Arterial Blood Pressure Measurements Demonstrating Post-Extrasystolic Potentiation From Sinus Beat Before and Sinus Beat After PVC**




DBP = diastolic blood pressure; PVC = premature ventricular contraction; SBP = systolic blood pressure.

as normal endocardial voltage. Mapping of the PVC origin was performed targeting the earliest site of activation compared with the onset of the surface PVC QRS complex, after which radiofrequency ablation was attempted using standard or irrigated radiofrequency energy after excluding an unacceptable proximity to a major coronary artery (e.g., epicardial mapping at the LV base). In all cases, advanced mapping systems such as CARTO version 3.0 (Biosense Webster, Diamond Bar, California) or NavX version 3.0 (St. Jude Medical, Minneapolis, Minnesota) were used to facilitate mapping.

**STATISTICAL METHODS.** Differences in baseline characteristics across the groups of interest were carried out first in a univariate fashion by using the Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

To determine independent predictors of the presence of both LV dysfunction and reversibility of LV dysfunction, multivariate logistic regression was used. All covariates were initially assessed in a univariate fashion, and variables were introduced into the multivariate model if the likelihood ratio test p value was $<0.20$. The percentage of PVC/24 h and PVC QRS duration were included in the preliminary main effects models, given their clinically plausible influence on outcomes. For the model evaluating reversibility of LV dysfunction, baseline LVEF was also included in the preliminary main effects model. All variables from the univariate analysis were added in a stepwise fashion, and interaction variables were introduced to identify effect modification. The influence of each variable on the model was assessed by using a likelihood-ratio test. All analyses were performed by using STATA version 9.2 (StataCorp, College Station, Texas).

## RESULTS

There were 61 consecutive patients with ≥10% PVC who underwent successful ablation of PVC. Of these, 31 (50.9%) had impaired LV function at baseline and the remaining 30 (49.2%) had normal LV function and served as control subjects. All the patients had post-procedure Holter monitoring to verify change in PVC burden. The acute procedural success rate (no observed targeted PVC during a 30-min waiting period after ablation) was achieved in 53 of 61 (86.9%) in the overall study population and 28 of 31 (90.4%) in those with impaired LV function. None of the patients with impaired LV function was noted to have scar based on voltage mapping.

The median echocardiographic follow-up among patients with impaired LV function was 4.1 months (interquartile range [IQR]: 3.2 to 6.2 months). Post-procedure Holter monitoring was performed at a median of 3.1 months (IQR: 2.6 to 5.4 months).

The median first clinic follow-up among patients was 3.6 months (IQR: 3.2 to 5.2 months). Success (at least an 80% reduction in PVC burden) for ablation among patients with LV dysfunction was 87.1% (27 of 31), with second procedures required for success in 4 of 31 (18.2%). Of the 31 patients with successful ablation, 17 (54.9%) patients had reversible LV dysfunction and 14 (45.2%) had irreversible LV dysfunction.

**BASELINE CHARACTERISTICS.** The baseline characteristics across the 3 groups of normal LV function, reversible LV function, and irreversible LV function are presented in Table 1. Among the historical variables, the following were noted to be significant.

The median improvement in LVEF was 17.5% (IQR: 2% to 4%) for patients with reversible LV dysfunction. The median change in LVEF in the irreversible group was 1% (IQR: 3% to 5%).

The presence and nature of symptoms differed markedly across the groups. Subjects with LV dysfunction were more likely to be symptomatic (6.7% with normal LV function, 47.1% with reversible LV function, and 35.8% with irreversible LV function; $p = 0.001$). Patients with LV dysfunction were more likely to have heart failure symptoms ($p = 0.005$) and to be on an antiarrhythmic ($p < 0.001$).

**HEMODYNAMIC AND ELECTROPHYSIOLOGIC CHARACTERISTICS.** Among the intra-arterial blood pressure monitoring characteristics, there was a significant difference in post-PVC SBP rise among the control, reversible, and irreversible groups (SBP: 12.1 ± 3.5, 11.5 ± 6.3, 5 ± 2.8 mm Hg, respectively; $p < 0.001$). Even though post-PVC DBP rise among the groups did not achieve statistical significance of 0.05, it was close and there was an appreciable difference (-24.8 ± 7.7, -19.9 ± 3.7, -14.5 ± 3.3; $p = 0.059$). Therefore, the composite pulse pressure showed the most significant difference (33.5 ± 7.1, 31.4 ± 5.4, 19.6 ± 7.7; $p < 0.001$). Among electrophysiologic characteristics, there was a significant difference in mean PVC QRS duration ($p < 0.001$), with longer durations seen in the LV dysfunction groups.

The distribution of the site of origin of the PVC was similar across the 3 groups with the exception of papillary muscle LV sites and outflow tract LV sites. The papillary muscle LV sites were significantly higher in the normal LV function group (23.4%, $p = 0.046$), compared with the reversible and irreversible groups (5.9% and 0%, respectively). The outflow tract LV sites were significantly higher in the reversible and irreversible groups (17.7% and 28.6%, respectively) compared with the normal LV function group (6.7%; $p = 0.036$) (Table 2). Figure 3 represents a scatter plot showing the distribution of post-PVC systolic pressure among the 3 groups with the y-axis representing the systolic pressure differential and x-axis representing the total patients in each group.

**TABLE 1 Baseline Characteristics Prior to Ablation**

| | Normal LV Function (n = 30) | Reversible LV Dysfunction (n = 17) | Irreversible LV Dysfunction (n = 14) | p Value for Comparison Across All Groups |
|---|---|---|---|---|
| Demographics | | | | |
| Age, yrs | 69.2 ± 10.5 | 68.9 ± 12.5 | 67.8 ± 8.1 | 0.8122 |
| Male | 30 (100.0) | 16 (94.2) | 14 (100.0) | 0.5082 |
| BMI, kg/m$^2$ | 32.6 ± 6.8 | 31.8 ± 6.8 | 28.6 ± 3.3 | 0.1436 |
| Medical history | | | | |
| History of hypertension | 18 (60.0) | 8 (47.0) | 8 (57.0) | 0.7497 |
| History of diabetes | 9 (30.0) | 4 (23.6) | 2 (14.3) | 0.5888 |
| History of CHF | 3 (10.0) | 9 (53.0) | 9 (64.3) | 0.0050 |
| History of CAD | 4 (13.4) | 9 (53.0) | 4 (28.6) | 0.0135 |
| Medications | | | | |
| Beta-blocker | 30 (100.0) | 16 (94.1) | 14 (100.0) | 0.675 |
| Antiarrhythmic | 1 (3.3) | 6 (47.1) | 8 (57.1) | 0.001 |
| ACE inhibitor/ARB | 18 (67.7) | 17 (100.0) | 14 (100.0) | 0.386 |
| Symptoms | | | | |
| Asymptomatic | 2 (6.7) | 8 (47.1) | 5 (35.8) | 0.001 |
| Palpitations/skipped beats | 18 (60) | 5 (29.5) | 5 (35.8) | 0.032 |
| Other symptoms | 10 (33.4) | 4 (23.6) | 4 (28.6) | 0.629 |
| Holter monitoring | | | | |
| % VPD | 23.0 ± 14.6 | 23.0 ± 8.8 | 22.4 ± 12.0 | 0.942 |
| NSVT ≥5 beats | 11 (36.7) | 7 (41.2) | 5 (35.8) | 0.268 |
| Echocardiography | | | | |
| LVEF pre-ablation, % | 55.5 ± 2.4 | 33.9 ± 12.0 | 37.2 ± 10.4 | 0.001 |
| LVEF post-ablation, % | 54.0 ± 5.4 | 47.1 ± 10.1 | 35 ± 12 | 0.015 |
| LVIDd, mm | 33.9 ± 12.0 | 37.2 ± 10.4 | 45.5 ± 2.4 | 0.090 |
| LVESd, mm | 53.1 ± 2.1 | 61.1 ± 1.8 | 64.3 ± 1.0 | 0.176 |
| LVH by echo, mm | 3.9 ± 1.4 | 4.3 ± 1.2 | 4.5 ± 1.2 | 0.287 |
| Coronary angiography | | | | |
| Performed | 10 (33.4) | 17 (100.0) | 14 (100.0) | 0.001 |
| Abnormal | 1 (3.4) | 0 (0.0) | 0 (0.0) | 0.577 |
| Nuclear stress test | | | | |
| Performed | 15 (50.0) | 8 (47.1) | 6 (42.9) | 0.394 |
| Abnormal | 2 (6.7) | 0 (0.0) | 0 (0.0) | 0.147 |
| CMR | | | | |
| Performed | 3 (10.0) | 1 (5.9) | 1 (7.2) | 0.385 |
| Abnormal | 1 (3.4) | 0 (0.0) | 0 (0.0) | 0.453 |

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CMR = cardiac magnetic resonance; LV = left ventricle; LVESd = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVIDd = left ventricular internal dimension-diastole; NSVT = nonsustained ventricular tachycardia; VPD = ventricular premature depolarization.

**CHARACTERISTICS ASSOCIATED WITH REVERSIBILITY OF LV DYSFUNCTION.** In the final multivariate model (Tables 3 and 4), adjusted for baseline LVEF, the independent predictors of reversible LV function were post-PVC systolic pressure rise (odds ratio [OR]: 4.61; 95% confidence interval [CI]: 1.45 to 15.83, per 5-mm Hg increase; $p < 0.001$), post-PVC pulse pressure change (OR: 5.2; 95% CI: 2.3 to 18.6, per 5-mm Hg increase; $p < 0.001$), and PVC QRS

**TABLE 2 Intra-Arterial Blood Pressure and Electrophysiologic Monitoring Characteristics**

| | Normal LV Function (n = 30) | Reversible LV Dysfunction (n = 17) | Irreversible LV Dysfunction (n = 14) | p Value for Comparison Across All Groups |
|---|---|---|---|---|
| Blood pressure parameters | | | | |
| Sinus SBP | 166.4 ± 15.9 | 165 ± 12 | 164.0 ± 12.1 | 0.6243 |
| Sinus DBP | 86.3 ± 16.6 | 80.7 ± 15.6 | 75.7 ± 8.8 | 0.147 |
| Sinus MAP | 139.7 ± 12.3 | 136.9 ± 11.2 | 134.6 ± 9.2 | 0.1126 |
| Post-PVC SBP | 178.5 ± 15.4 | 176.5 ± 16.6 | 168.9 ± 14.0 | <0.001 |
| Post-PVC DBP | 58.5 ± 13.0 | 54.8 ± 15 | 51.3 ± 7.9 | 0.1707 |
| Post-PVC MAP | 145.1 ± 11.8 | 142.6 ± 14.1 | 136.4 ± 10.4 | 0.104 |
| SBP change | 12.1 ± 3.5 | 11.5 ± 6.3 | 5.0 ± 2.8 | <0.001 |
| DBP change | −24.8 ± 7.7 | −19.9 ± 3.7 | −14.5 ± 3.3 | 0.059 |
| MAP change | 9.2 ± 5.6 | 7.8 ± 3.7 | 4.7 ± 2.4 | 0.065 |
| Pulse pressure change | 33.5 ± 7.1 | 31.4 ± 5.4 | 19.6 ± 7.7 | <0.001 |
| Electrocardiographic parameters | | | | |
| PVC QRS width, ms | 138.8 ± 9.3 | 159.4 ± 12.6 | 169.5 ± 11.9 | <0.001 |
| PVC coupling interval, ms | 528.4 ± 12.3 | 560.1 ± 23.6 | 575.0 ± 21.2 | 0.087 |
| PVC site of origin | | | | |
| RVOT, RV inflow, other RV sites | 11 (36.7) | 7 (41.2) | 5 (35.8) | 0.640 |
| LVOT, RCC, LCC, RCC-LCC commissure, aortomitral continuity | 2 (6.7) | 3 (17.7) | 4 (28.6) | 0.036 |
| Anterior mitral annulus | 5 (16.7) | 2 (11.8) | 3 (21.5) | 0.213 |
| Papillary muscles | 7 (23.4) | 1 (5.9) | 0 (0) | 0.046 |
| Other LV sites | 5 (16.7) | 3 (17.7) | 2 (14.3) | 0.812 |
| Epicardial sites | 0 (0) | 1 (5.9) | 0 (0) | 0.195 |

Values are mean ± SD or n (%).

DBP = diastolic blood pressure; LCC = left coronary cusp; LV = left ventricle; LVOT = left ventricular outflow tract; MAP = mean arterial pressure; PVC = premature ventricular complexes; RCC = right coronary cusp; RV = right ventricle; RVOT = right ventricular outflow tract; SBP = systolic blood pressure.

duration (OR: 0.78; 95% CI: 0.63 to 0.94, per 10-ms increase; p = 0.001). We performed a separate multivariate model to determine predictors of LV dysfunction. The independent predictor of LV dysfunction were percentage of PVC on Holter monitoring, per 1% increase (OR: 1.995; 95% CI: 0.932 to 2.063; p < 0.039).

## DISCUSSION

The main finding in this study is that in patients with LV dysfunction and frequent PVC, PESP SBP rise is an independent predictor for recovery of LV function after ablation. Furthermore, the post-PVC blood pressure rise between normal LV function and reversible LV dysfunction were comparable and a significant difference was seen when compared with the rise seen with irreversible LV dysfunction. Notably PVC burden was not predictive. The significance of PVC QRS duration in this study is consistent with a prior study in that those with a prolonged PVC QRS duration are unlikely to normalize their LV function (6).

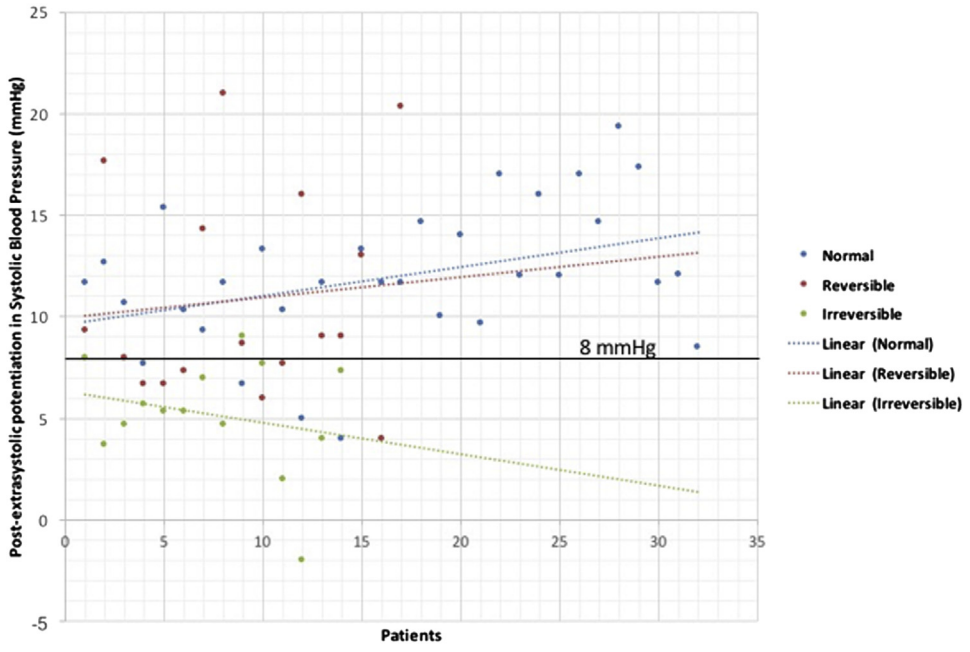
PVC frequently coexist in patients who have other forms of cardiomyopathy. Improvement in LVEF with ablation of PVC has been reported in such patients (4). This study sought to primarily define improvement in those patients who do not have an apparent other form of cardiomyopathy. Efforts were made to use cardiac magnetic resonance imaging tissue characterization to identify patients with coexisting ischemic cardiomyopathy prior to ablation. The use of voltage mapping during ablation can also provide information regarding local voltage abnormalities that may be used as a surrogate marker for myocardial health. Specific bipolar and unipolar voltage cutoff values have been reproducibly shown to accurately identify scar and/or fibrosis in the ventricles (10). In this study, using voltage mapping no scar was demonstrated in patients with impaired LV function. These results support a causal effect of PVC on cardiomyopathy in the absence of other coexisting cardiomyopathy.

Since it was first reported in 1998, the concept that frequent PVC may produce a potentially reversible form of LV dysfunction has generated increasing interest (11). Moreover, the growing success of the electrophysiologists in eliminating certain PVC with ablation has raised the expectations that this might improve tachycardia-induced cardiomyopathy (6,9). However, much of the natural history and pathophysiology of PVC-associated ventricular dysfunction remains unclear. Most observational studies report an association of LV dysfunction with PVC burden, duration, coupling interval, or location but, to our knowledge, no studies have documented specific mechanisms to explain how PVC depress LV function.

Our hypothesis was derived from observations in blood pressure patterns during arterial pressure monitoring recorded with PVC that are known as PESP (12). The blood pressure generated by a PVC is very small. The sinus beat after a PVC generates a significant rise in blood pressure due to prolonged ventricular filling time and timing of the cardiac cycle related to the previous PVC. PESP has been applied extensively in diagnosis in coronary heart disease and valvular heart disease. The effects of PESP on global LV function in cardiomyopathy are somewhat paradoxical, as several studies have reported increased potentiation in cardiomyopathic ventricles (12). Our study shows that PVC cardiomyopathy produces increased potentiation when there is reversibility in cardiomyopathy, but it produces a PESP response in these ventricles because it depends on inotropy.

Cardiac afterload affects the rate of cardiac relaxation in both animal models and humans (13,14) with increases in load occurring during late ejection being

**FIGURE 3** Scatter Plot Showing the Distribution of Post-PVC Systolic Pressure Among the 3 Groups




Scatter plot showing the distribution of post-premature ventricular contraction (PVC) systolic pressure among the 3 groups with the y-axis representing the systolic pressure differential and x-axis representing the total patients in each group.

particularly deleterious. This is important because vascular aging typically imposes increased late systolic loading due to the rapid return of reflected pressure waves and can thus further impair relaxation. PESP may lead to cardiomyopathy similar to hypertensive cardiomyopathy with an initial stage of diastolic dysfunction (15) and later systolic heart failure. The mechanism of reversible PVC cardiomyopathy is likely a state of latent myocardium similar to tachycardia-associated cardiomyopathy or likely a stunned or fatigued myocardium in the initial stages of hypertensive cardiomyopathy, perhaps remodeled or fibrotic at later stages. This is different from the irreversible PVC cardiomyopathy where the hypothesis is myofibril disarray and fibrosis of the underlying mechanism, the dominant pathologic findings in idiopathic LV cardiomyopathy (16,17). It is our hypothesis that the interval between the sinus beat preceding sinus beat and the post-PVC sinus beat allows the LV to transiently regain LV contractility in reversible cardiomyopathy. However, patients with greater substrate abnormality are unable to produce such a robust response and consequently are less likely to recover after PVC elimination.

Prior studies have demonstrated an improvement in the majority of patients with LV dysfunction and frequent PVC undergoing ablation (1,2). However, the lack of improvement in a substantial proportion of patients (23% of the patients in this cohort) remains unexplained. In this series, patients who have reversible LV systolic dysfunction in our study show a preserved PESP compared with patients with a normal EF. We believe this is a marker of the contractile reserve and hence the reversibility after ablation. Similarly, those with irreversible LV systolic dysfunction may have less or no contractile reserve.

Our findings correlate with the heart rate turbulence reports. In their elegant study, Wichterle et al. (18) show that heart rate turbulence and baroreflex

**TABLE 3** Multivariate Analysis of Characteristics Associated With the Presence of Reversible LV Dysfunction

| | Adjusted OR for Reversible LV Dysfunction (95% CI) | Likelihood Ratio Test p Value |
|---|---|---|
| Delta SBP (post-PVC SBP rise), per 5-mm Hg increase | 4.61 (1.448–15.833) | 0.001 |
| Pulse pressure rise, per 5-mm Hg increase | 5.20 (2.30–18.67) | 0.001 |
| PVC QRS duration, per 10-ms increase | 0.782 (0.632–0.942) | <0.001 |
| Percentage of PVC on Holter monitoring, per 1% increase | 1.015 (0.956–1.079) | 0.622 |
| PVC coupling interval, per 10-ms increase | 0.842 (0.545–1.165) | 0.834 |

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

**TABLE 4 Multivariate Analysis for Predictors of LV Dysfunction**

| | Adjusted OR for LV Dysfunction (95% CI) | Likelihood Ratio Test p Value |
|---|---|---|
| Post-PVC SBP (MAP) rise, per 1-mm Hg increase | 1.431 (0.280–0.664) | 0.883 |
| Post-PVC DBP (MAP) rise, per 1-mm Hg increase | 1.048 (0.992–1.108) | 0.1963 |
| Percentage of PVC on Holter monitoring, per 1% increase | 1.995 (0.932–2.063) | 0.039 |
| PVC QRS duration, per 10-ms increase | 1.631 (0.542–1.967) | 0.052 |
| PVC coupling interval, per 10-ms increase | 1.275 (0.846–1.857) | 0.387 |

Abbreviations as in Tables 1 to 3.

sensitivity indices are highly correlated and depressed in patients with LV dysfunction, and that the late SBP dynamics results from a delayed sympathetically mediated vasomotor response to the initial loss of cardiac output after VPC. They also demonstrate that, apart from the first potentiated post-VPC sinus beat, there was no increase of stroke volume in the late phase of heart rate turbulence. Even lesser decrease of stroke volume was observed in patients with LV dysfunction. This correlates strongly with our data, but what is more important is that our data show the translational importance of PVC ablation in treating PVC-induced cardiomyopathy. We show the clinical impact of using such first potentiated post-PVC sinus beat in assessed reversibility of PVC-induced cardiomyopathy.

**STUDY LIMITATIONS.** This is a retrospective study, as are many prior studies. The patient cohort is small, despite being a high-volume center that does approximately 200 ventricular tachycardia/PVC ablations a year, given the inclusion and exclusion criteria, we studied 150 patients. That is the challenge with studying outcomes in a single center. Also, only subjects undergoing ablation were included and therefore the findings may be influenced by referral bias. We were unable to track patients not referred for or who refused ablation. We attempted to minimize the influence of referral bias by restriction of our cohort to only those with ≥10% PVC, as there is likely a bias against ablation among patients with impaired LV function who have infrequent (<10%) PVC. We were unable to evaluate clinical outcomes such as heart failure or arrhythmic death. Electrophysiological and blood pressure measurements taken during the procedure given may tend to be simplified by taking the mean of 3 measures. In the future, it may be worthwhile to acquire a large series of measurements from the procedure and perform a hierarchical model to limit within-subject variances. Although PVC is frequently seen in the general population, a systematic large study involving a nonhomogeneous group may be helpful to understand the pathophysiology of PVC-induced cardiomyopathy. There is a possibility that LVEF may be inaccurately assessed particularly with a high PVC burden. Future studies may involve assessing post-PVC velocity time integral to assess the LV contractile reserve.

## CONCLUSIONS

PVC-associated cardiomyopathy data, so far described in the published reports, are mainly from association studies with either burden or coupling interval or possibly interpolated timing. This may be the first observational study that describes likely pathophysiology. It is still unclear as to why some PVC demonstrate this behavior in some patients. This concept is very helpful to understand when and why patients need intervention when they present with PVC and perhaps it could be answered in a larger study.

**ADDRESS FOR CORRESPONDENCE:** Dr. Venkatakrishna N. Tholakanahalli, University of Minnesota, Minneapolis Veterans Affairs Medical Center, 1 Veterans Drive, Minneapolis, Minnesota 55417. E-mail: thola001@umn.edu.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE 1:** Frequent PVC may produce a potentially reversible form of LV dysfunction.

**COMPETENCY IN MEDICAL KNOWLEDGE 2:** Decreasing burden of frequent PVC in patients with suspected PVC-associated cardiomyopathy have shown reversible form of LV dysfunction. If PVC cardiomyopathy has been identified and therapy with antiarrhythmics has failed, then electrophysiology consultation should be considered for radiofrequency ablation.

**TRANSLATIONAL OUTLOOK 1:** Although this is a relatively short-term study (median of 1 years), predicting patients who will recover from PVC ablation may better help select patients who may benefit from radiofrequency ablation.

**TRANSLATIONAL OUTLOOK 2:** Much of the natural history and pathophysiology of PVC-associated ventricular dysfunction remains unclear. We present a case that PVC cardiomyopathy is a progressive disease that may represent a progression of hypertensive cardiomyopathy.

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**KEY WORDS** **blood pressure, contractile reserve, hypertension, premature ventricular complex**