# Long-Term Mode and Timing of Premature Ventricular Complex Recurrence Following Successful Catheter Ablation

Running Title: *Long Term PVC Recurrence*

**Authors:**
Derek Lee, BS, Kurt S. Hoffmayer, MD, PharmD., Jonathan C. Hsu, MD, MAS, Amir Schricker, MD, Ulrika Birgersdotter-Green, MD, Farshad Raissi, MD, Gregory K. Feld, MD, and David E. Krummen, MD

**Authors Affiliation:**
Department of Medicine, Division of Cardiology, University of California San Diego, San Diego, CA and VA San Diego Healthcare System, San Diego, CA

**Address for Correspondence:**
David E. Krummen, MD
3350 La Jolla Village Drive
Cardiology Section 111A
San Diego, CA 92161
Email: dkrummen@ucsd.edu
Office: 858-642-3539
Fax: 858-552-7490

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**Abstract**

**Background:**

Catheter ablation of PVCs is highly successful and has become the hallmark treatment for symptomatic or highly prevalent cases. However, few studies exist that evaluate the outcomes of ablation and likely mechanisms of PVC recurrence beyond 1 year of follow-up.

**Methods and Results**:

This study is a retrospective analysis of patients who underwent catheter ablation for symptomatic PVCs with acute procedural success and had clinical follow-up ≥ 12 months. 44 patients (24 women; age 53.5±4.8 years) following acutely successful PVC ablation with long-term follow-up were studied. At a mean of 36±6 months, overall long-term ablation success was 75% (33/44 patients). Notably, recurrence of the targeted PVC focus was low (6.8%, 3/44 patients); the majority of recurrences were from a new source location (18.2%, 8/44 patients). The time course for targeted versus *de novo* PVC recurrences was significantly different: recurrence of a PVC similar to the targeted PVC morphology occurred at a mean of 5.0±2.0 months, while recurrence of a PVC different from the index case occurred at a mean of 35.8±17.1 months (p=0.01). Nonischemic cardiomyopathy was associated with increased risk of PVC recurrence (odds ratio [OR] 18.43 (95% confidence interval [CI] 1.69-201.1, p=0.02)), while RVOT location at index procedure was associated with reduced probability of PVC recurrence (OR 0.06 (95% CI 0.004-0.89, p=0.04).

**Conclusion**s:

The majority of long-term PVC recurrences occur late in follow-up, at locations remote from the targeted PVC source or sources. Such sites may represent ongoing substrate evolution; additional

work is required to determine the precise substrate alterations which promote such arrhythmogenic changes.

**Key Words**:
Premature Ventricular Contractions
Ablation
Long Term Follow-up

**Abbreviations:**
Electrocardiogram: ECG
Premature Ventricular Contraction: PVC
Right Ventricular Outflow Tract: RVOT
Left Ventricular Outflow Tract: LVOT

## Introduction

Frequent premature ventricular contractions (PVC) are common and may occur in 1-4% of the general population[1]. An elevated PVC burden may cause significant palpitations and lead to left ventricular dysfunction or enlargement[1-5]. Prior seminal work has demonstrated that catheter ablation of PVCs is feasible, safe, and may reverse LV dysfunction due to tachycardia-mediated cardiomyopathy. Current guidelines recommend PVC ablation for drug-refractory cases of symptoms or LV dysfunction[5-20].

The success of PVC ablation at 6 months has been reported as 80-95%. However, limited data exist regarding the outcomes of PVC ablation beyond 1 year. Additionally, risk factors for late PVC recurrence are uncertain. We hypothesized that ongoing substrate changes may result in late PVC recurrences at sites remote from the index procedure. The purpose of this study was to investigate the mode and timing of long-term PVC recurrence following successful ablation.

## Methods

### *Study design*

This study was conducted under an institution review board-approved protocol for the retrospective analysis of patients following catheter ablation of PVCs between May 2010 and May 2015 at University of California San Diego Medical Center. Data were obtained from the UCSD procedural database (Perminova, Inc., San Diego, CA, USA) and electronic medical record (Epic Systems Corporation, Verona, WI, USA).

### *Patient Characteristics*

Patients with a high PVC burden and either symptoms or reduced ejection fraction who underwent acutely successful ablation with long-term follow-up greater than or equal to 12 months were included. Acutely successful ablation was defined as elimination of PVCs without intraoperative recurrence on or off an isoproterenol challenge. Recurrence was defined as any of the following: recurrent symptoms due to PVCs at clinical follow-up, ECGs demonstrating PVC recurrence during follow-up visits, or ambulatory monitors (24/48 Holter, 2 week event monitoring) showing >1% PVC burden. Patients were excluded if clinical follow-up was less than 12 months.

*Mapping and ablation*

A standard electrophysiology study was performed in all patients. Monitored anesthesia care was used to avoid PVC suppression by general anesthesia. Three dimensional electroanatomic mapping was used in all subjects. PVC mapping and ablation technique and equipment were left to the discretion of the attending electrophysiologist.

In general, the clinical PVC templates were captured for pace-map matching prior to sedation. If no PVCs were seen at baseline, then isoproterenol and/or phenylephrine was given to induce PVCs. A combination of pace-map matching and activation mapping was performed when possible to localize PVC sources. After successful ablation of the PVC site, a 30-minute waiting period was observed, during which high dose isoproterenol (up to 30mcg/min) was administered. Ablation success was defined as absence of intra-procedural PVC recurrence.

*Comparison of Index versus Recurrent PVC Source Locations*

Index source locations were identified as the site of PVC termination from intraprocedural mapping and ablation. If the patients had clinical recurrence of PVCs during long term follow-up, recurrent source location was similarly defined as the site of successful PVC termination during repeat ablation. If repeat ablation was not pursued, source location was determined using standard 12-lead ECG PVC localization technique[2, 4, 11, 12, 17, 19-30].

For statistical analysis, PVC sources were grouped into the following four categories: (1) right ventricular outflow tract (RVOT), (2) right ventricle (non-outflow tract), (3) left ventricular outflow tract and coronary cusps (LVOT), and (4) left ventricle (non-outflow tract).

*Statistical analysis*

Continuous variables were expressed as mean ± standard deviation and were compared with Student's *t*-test. Categorical variables were compared with the $\chi^2$ test; Fisher's exact test was used when expected values in contingency tables were less than 5. One-way ANOVA was used to determine the effect of source location on probability of PVC recurrence, using Bonferroni correction for multiple comparisons. Multivariate logistic regression was used to determine predictors which were associated with PVC recurrence. Predictors exhibiting differences between groups with a p value of $<0.05$ in the univariate analysis were incorporated into the multivariate model. A two-tailed p value of $<0.05$ was considered statistically significant. Statistical analysis was performed using Stata (Statacorp, College Station, TX, USA).

**Results**

The study included 44 patients (age 53.5±4.8 years, 24 female) with acutely successful PVC ablation and greater than or equal to 12 months of clinical follow-up. Mean ejection

fraction was 56.4±3.8%. PVC burden by Holter monitoring was reduced from mean 19.7±3.3% to mean 2.3±1.7% PVCs following successful ablation. Patient characteristics were similar between the long-term ablation success and failure groups for age, co-morbidities, echocardiographic parameters, and antiarrhythmic drugs (Table 1).

Long-term ablation success (mean follow-up time after index ablation 36.1±5.9 months) of the index PVC was achieved in 93.2% (41/44) of the cases. 8/44 (18.2%) had symptomatic recurrence from different PVC from the index case. Thus, overall 3-year freedom from PVCs was 75% (33/44) following ablation. To date, 8 of 11 patients with PVC recurrence (72.7%) have presented for repeat ablation.

*Index PVC Source Location and Procedural Success*

The most common PVC source locations identified and ablated were RVOT (50%) and LVOT/coronary cusps (30%, Table 2). The RVOT source location had a 95% (21/22) long-term ablation success rate.

*Mode, Location, and Time Course of PVC Recurrence*

Three patients (3/44, 6.8%) had recurrence of the index procedure PVC location at a mean 5.0 +/- 2.0 months. Of the three recurrences of the same PVC, 2/3 were from the LVOT/coronary cusp and 1 in the RVOT. In contrast, 8 patients (8/44, 18.2%) presented with recurrence of a PVC source location distinct from the index procedure at a mean on 35.8 +/- 17.1 months (p=.01), Table 3. The average annual risk of new PVC source development was 6.1%.

Of the 8 patients with recurrence of a new PVC, the LVOT/coronary cusp location during the index case (4/8, 50%) was most common. None of the recurrent PVC sources were identified or mapped during the index procedure.

*Univariate Analyses*

Univariate analyses of baseline characteristics identified 2 predictors of PVC recurrence or non-recurrence (Table 4). Non-ischemic cardiomyopathy was associated with a greater than 5-fold risk of PVC recurrence (RR of 5.29, 95% CI 1.71-16.3**,** p=0.01), while RVOT source location was associated with a lower risk (RR of 0.14, 95% CI (0.02-0.98), p=0.04).

*Multivariate Analyses*

Non-ischemic cardiomyopathy and RVOT source location remained statistically significant in multivariate analysis (Table 5). Non-ischemic cardiomyopathy significantly increased the odds of PVC recurrence (OR 18.43, 95% CI 1.69-201.1, p=0.02). RVOT location at index procedure decreased the odds of PVC recurrence (OR 0.06, 95% CI 0.004-0.89, p=0.04).

*Comparison of Patients With and Without Long Term Follow-up*

We evaluated whether there were differences between patients with and without long-term follow-up following PVC ablation. Results are detailed in the online supplement, Table S1. In summary, there were no observed differences between groups.

**Discussion**

There are 3 major findings from this long-term study of PVC ablation outcomes. First, we found that while the long-term freedom from the index PVC focus remains excellent at 3 years (approximately 93%), the majority of PVC recurrences at 3 years were due to new foci developing remote from the targeted site (18%). Second, we found that the recurrence of the index PVC focus primarily occurs within the first 6 months, while new PVC source development occurs after 6 months, at a rate of approximately 6.1% per year. Third, we found that non-ischemic cardiomyopathy is a significant risk factor for PVC recurrence after ablation, while patients with RVOT PVCs enjoyed greater freedom from PVCs after their procedure. These findings represent novel insight into the natural history of PVCs following ablation, and may help to inform decisions for patients undergoing this procedure.

*Long-Term PVC Ablation Outcomes*

Since the seminal studies of PVC ablation, the excellent acute success of the procedure has been well documented[2, 4]. Baser and colleagues reported an 80% success at 3 months in a general population undergoing PVC ablation [31]. In a study limited to RVOT PVC ablation, Zhang and colleagues found an 86.8% long-term success.[32] However, the long-term results, modes, and timings of recurrence in a general population undergoing PVC ablation remained uncertain.

In this study, we focused on patients presenting with high PVC burdens and either symptoms or reduced ejection fractions who had acute procedural success and long-term follow-up (≥12 months). During extended follow-up, we found that recurrence of the original PVC source remains low, <7%. These results suggest durable long-term success for most patients

undergoing PVC ablation which continues long beyond the previously reported studies of 3-12 months.

Importantly, with extended long-term follow we found a significant amount (18.2%) of patients had symptomatic PVC recurrence from a different PVC location. None of these recurrent PVCs were identified or mapped during the initial ablation. Because the identified anatomic locations were distant from the index PVC source, our work strongly supports that they are not the result of "changing the exit" from the index procedure, but rather likely represent ongoing changes in ventricular substrate. The precise changes and factors underlying such progression require further study in order to develop effective therapies to prevent such alterations.

*Time course of PVC Recurrence*

The limited follow-up in prior work had not detailed the time course or mode of PVC recurrence following successful catheter ablation. As a result, it had been unclear whether such cases represented ablation failure or development of new sources.

In this work, we methodically localized index PVC sources and compared these sites with those of recurrent PVCs. We were thus able to identify a bimodal pattern for the mechanism of PVC recurrence following ablation. Early in follow-up, recurrent PVCs are most likely to be due to resumption of activity of the index PVC site. This may represent an incomplete, or "missed" ablation in which ablation stunned or suppressed the PVC source, but did not completely eliminate triggering tissue, similar to studies of atrial fibrillation source ablation[33].

In contrast, *de novo* sources predominate in late PVC recurrence, consistent with work in other arrhythmias supporting a link between ongoing substrate remodeling and arrhythmia risk[34].

Such data are useful in counseling patients regarding PVC ablation. Furthermore, this finding may be hypothesis generating in that future work may study lifestyle interventions and risk factor modifications to potentially slow or prevent subsequent PVC source development, as has been shown in AF[35].

*Risk Factors for PVC Recurrence*

Finally, we analyzed clinical factors associated with greater and reduced risk of PVC recurrence. Notably, patients with non-ischemic cardiomyopathy, defined as reduced ejection fraction without patient history of myocardial infarction or echocardiographic evidence of regional scar, are significantly more likely to have PVC recurrence. This finding is consistent with prior work in PVC ablation demonstrating that PVC sources were often associated with remodeled substrate[36]. Notably, prior work has demonstrated that the ventricles of patients with non-ischemic cardiomyopathy are significantly remodeled[37]and have elevated levels of biomarkers associated with myocyte stretch and necrosis[38] compared with patients without non-ischemic cardiomyopathy. Thus, substrate progression in such patients may occur at an accelerated rate, and is thus detectable in our cohort of patients during the timescale of this study.

In contrast, PVC recurrence is reduced in patients with initial RVOT source location. PVCs from a patient with idiopathic RVOT PVCs have been previously shown to be a cyclic-AMP mediated process[2, 4, 13, 39-42], rather than related to fibrosis and scar. Thus, such patients may not be at risk for accelerated substrate evolution and PVC recurrence at a mean follow-up of 3 years.

These factors may play an important role in pre-ablation counseling and education as they represent clinical characteristics that predict PVC recurrence. Such data can help inform a more precise discussion of the expected success rate of an invasive PVC ablation.

### *Limitations*

The main limitation of this study was a small study population due to our strict inclusion criteria of a minimum of 12 months of follow-up after successful PVC ablation. Despite this limitation, we were able to identify sufficient patients to detect the bimodal pattern and timing of PVC recurrence (e.g. index versus *de novo*). Furthermore, there was no statistical difference in our database between patients who did and did not have long-term follow-up. This provides reassurance regarding the generalizability of our findings. Ongoing prospective series are required to confirm these results.

## Conclusions

Long-term success of PVC ablation is good; the majority of patients remain PVC free at a mean follow-up of 3 years. Most recurrences after the first year occur at a site anatomically distinct from the targeted focus. Non-ischemic cardiomyopathy is associated with increased PVC recurrence, while RVOT location is associated with decreased probability of PVC recurrence.

**Table 1: Patient Characteristics and Long-Term Ablation Outcome**

| Characteristics | Successful Long-term Outcome | Unsuccessful Long-term Outcome | p value |
|---|---|---|---|
| Patients, n | 33 | 11 | |
| Women/men | 20/13 | 4/7 | 0.29 |
| Age (years, ±SD) | 53.4±5.6 | 53.9±9.2 | 0.92 |
| LV EF (%, ±SD) | 58.0±4.3 | 52.3±.7.0 | 0.35 |
| Pre-ablation PVC Burden (%, ±SD) | 21.1±8.9 | 19.2±3.5 | 0.60 |
| Ischemic CMP (n, %) | 2 (6%) | 2 (18%) | 0.3 |
| NICM (n, %) | 3 (9%) | 4 (36%) | 0.07 |
| Hypertension (n, %) | 14 (42%) | 3 (27%) | 0.32 |
| Diabetes Mellitus (n, %) | 4 (12%) | 1 (9%) | 1 |
| Dyslipidemia (n, %) | 12 (36%) | 2 (18%) | 0.28 |
| CAD (n. %) | 6 (18%) | 2 (18%) | 1 |
| Medications: Antiarrhythmics pre-ablation (n, %) | 4 (12%) | 0 | 0.32 |
| Antiarrhythmics post-ablation (n, %) | 4 (12%) | 0 | 0.32 |

**Table 2: PVC Source Location and Ablation Success**

| **Index PVC Source Location** | **Successful Long-term Outcome** |
|---|---|
| **LVOT, including Coronary Cusps †** | **7/13 (54%)** |
| a. LVOT (n, %) | 3/6 (50%) |
| b. Coronary cusps (n, %) | 4/7 (57%) |
| | |
| **Left Ventricular** | 5/7 (71%) |
| a. Mitral annulus (n, %) | 2/3 (67%) |
| b. Mid posterior LV (n, %) | 2/2 (100%) |
| c. Septal basal LV (n, %) | 1/1 (100%) |
| d. Anterolateral papillary muscle base (n, %) | 1/1 (100%) |
| | |
| **RVOT († p=0.001)** | **21/22 (95%)** |
| | |
| **Right Ventricular** | 0/2 (0%) |
| a. Tricuspid annulus | 0/1 (0%) |
| b. Anterior apical RV wall | 0/1 (0%) |

**Table 3: PVC Recurrence at Similar vs. Distant Source Locations**

| **Recurrence at Similar Source Location Compared with Index Ablation** | | | | |
|---|---|---|---|---|
| **Patient** | **Age (years)** | **Initial source location** | **Recurrent source location** | **Timing of Recurrence** |
| 1 | 41 | Left coronary cusp | similar | 6 months |
| 2 | 51 | LVOT | similar | 3 months |
| 3 | 44 | Anterior apical RV wall | similar | 6 months |
| **Recurrence at Distant Source Location Compared with Index Ablation** | | | | |
| **Patient** | **Age (years)** | **Initial source location** | **Recurrent source location** | **Timing of Recurrence** |
| 1 | 64 | LVOT/Left coronary cusp | Posterior basal septal RV | 54 months |
| 2 | 55 | Left coronary cusp | RVOT free wall | 58 months |
| 3 | 31 | Anterior TVA | RVOT under pulmonic valve | 48 months |
| 4 | 60 | LVOT | R/L JXN Left/right coronary cusp | 46 months |
| 5 | 55 | Superior MVA | RVOT | 6 months |
| 6 | 77 | Posteroseptal RVOT | Mid-posterior LV | 39 months |
| 7 | 59 | Mid-posterior LV | RVOT posterior wall | 33 months |
| 8 | 52 | Left coronary cusp | Posterior medial papillary muscle + anterolateral basal LV | 2 months |

**Table 4: Predictors of Recurrence: Univariate Analysis**

| **Characteristic** | **RR** | **95% CI** | **p-value** |
|---|---|---|---|
| Male | 3.60 | 0.81-15.9 | 0.11 |
| Reduced ejection fraction (EF<50) | 0.71 | 0.09-5.34 | 0.74 |
| ICM | 3.33 | 0.98-11.4 | 0.15 |
| NICM | 5.29 | 1.71-16.3 | **0.01** |
| HTN | 0.53 | 0.12-2.33 | 0.45 |
| DM | 1.11 | 0.17-7.28 | 1.00 |
| HLD | 0.31 | 0.04-2.26 | 0.25 |
| CAD | 1.50 | 0.37-6.11 | 0.62 |
| PVC Sources | | | |
| LVOT+cusp | 2.38 | 0.70-8.12 | 0.21 |
| RVOT | 0.14 | 0.02-0.98 | **0.04** |
| LV not OT | 1.76 | 0.44-7.01 | 0.6 |
| RV not OT | 3.00 | 0.64-14.0 | 0.33 |

**Table 5: Predictors of Recurrence: Multivariate Analysis**

| Characteristic* | OR | 95% CI | p-value |
|---|---|---|---|
| NICM | 18.43 | 1.69-201.1 | **0.02** |
| RVOT | 0.06 | 0.004-0.89 | **0.04** |

*****Only variables exhibiting differences between groups with a p value of <0.05 in the univariate analysis were incorporated into the multivariate model.

**Author contributions:**

Derek Lee: Data analysis/interpretation, Drafting article, Statistics

Kurt S. Hoffmayer: Critical revision of article, Statistics, Approval of article

Jonathan C. Hsu: IRB approval secured by, Data collection, Approval of article

Amir Schricker: Data generation, Approval of article

Ulrika Birgersdotter-Green: Critical revision of article, Approval of article

Farshad Raissi: Data generation, Approval of article

Gregory K. Feld: Data generation, Approval of article

David E. Krummen: Funding secured by, Concept/design, Data generation, Drafting article, Critical revision of article, Approval of article

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**Online Supplement:**

# Long-Term Mode and Timing of Premature Ventricular Complex Recurrence Following Successful Catheter Ablation

**Authors:**
Derek Lee, BS, Kurt S. Hoffmayer, MD, PharmD., Jonathan C. Hsu, MD, MAS, Amir Schricker, MD, Ulrika Birgersdotter-Green, MD, Farshad Raissi, MD, Gregory K. Feld, MD, and David E. Krummen, MD

**Address for Correspondence:**
David E. Krummen, MD
3350 La Jolla Village Drive
Cardiology Section 111A
San Diego, CA 92161
Email: dkrummen@ucsd.edu
Office: 858-642-3539
Fax: 858-552-7490

**Differences Between Patients With and Without Long-Term Follow-up**

To address the possibility of significant differences between patients with (≥12 months) and without (<12 months) long-term follow-up, we compared available demographic information for the two groups. Data are summarized in table S1, below.

**Table S1: Comparison of Excluded Patients (<12 months of follow-up) and Study Patients**

| Characteristics | <12 months of follow-up | ≥12 months of follow-up | p value |
|---|---|---|---|
| Patients, n | 27 | 44 | |
| Women/men | 11/16 | 24/20 | 0.26 |
| Age (years, ±SD) | 56.6±10.2 | 53.5±4.7 | 0.45 |
| LV EF (%, ±SD) | 57.9±4.7 | 56.4±3.8 | 0.63 |
| Ischemic CMP (n, %) | 0 | 4 (9%) | 0.16 |
| NICM (n, %) | 4 (15%) | 7 (16%) | 1.00 |
| Hypertension (n, %) | 12 (44%) | 17 (39%) | 0.63 |
| Diabetes Mellitus (n, %) | 1 (4%) | 5 (11%) | 0.40 |
| Dyslipidemia (n, %) | 9 (33%) | 14 (32%) | 0.89 |
| CAD (n. %) | 4 (15%) | 8 (18%) | 0.76 |
| Medications: Antiarrhythmics pre-ablation (n, %) | 4 (15%) | 4 (9%) | 0.47 |
| Antiarrhythmics post-ablation (n, %) | 3 (11%) | 4 (9%) | 1.00 |

In summary, there were no significant differences between the two groups. Notably, the characteristics of both groups are consistent with those reported in contemporary studies of PVC ablation[1].

This similarity between groups addresses concern regarding bias present in the studied population. Because patients with recurrent symptoms are more likely to have ongoing, long-term follow-up, our study thus represents an upper limit for the rate of PVC recurrence. However, because the studied population is similar to excluded patients, and similar to

contemporary cohorts undergoing PVC ablation, our findings are more likely to be generalizable to contemporary practices who treat such patients.

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