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ORIGINAL RESEARCH

Electrophysiological Characteristics and Ablation Outcomes in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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BACKGROUND: Catheter ablation of premature ventricular contractions (PVCs) that trigger polymorphic ventricular tachycardia (PVT) or ventricular fibrillation has been reported as a novel therapy to reduce the syncope events in patients with catecholaminergic PVT, whereas the long-term ablation outcome and its value in improving exercise-induced ventricular arrhythmias remain unclear.

METHODS AND RESULTS: Fourteen consecutive selected patients with catecholaminergic PVT (mean±SD age, 16±6 years; 43% male patients) treated with maximum β-blockers with no possibility of adding flecainide were prospectively enrolled for catheter ablation. The primary end point was syncope recurrence, and the secondary end point was the reduction of the ventricular arrhythmia score during exercise testing. Twenty-six PVT/ventricular fibrillation–triggering PVCs were identified for ablation. The trigger beats arose from the left ventricle in 50% of the cases and from both ventricles in 36% of the cases. Purkinje potentials were observed at 27% of the targets. After a mean follow-up of 49 months after ablation, 8 (57%) patients were free from syncope recurrence. Ablation of trigger beat significantly reduced the syncope frequency (mean±SD, 4.3±1.6 to 0.5±0.8 events per year; $P<0.001$) and improved the ventricular arrhythmia scores at the 3-month (5 [range, 3–6] to 1.5 [range, 0–5]; $P=0.002$) and 12-month (5 [range, 3–6] to 2 [range, 0–5]; $P=0.014$) follow-ups. The induction of nontriggering PVCs postablation was closely associated with syncope recurrence (hazard ratio, 6.8 [95% CI, 1.3–35.5]; $P=0.026$).

CONCLUSIONS: Catheter ablation of PVT/ventricular fibrillation–triggering PVCs in patients with catecholaminergic PVT who cannot receive flecainide treatment seems to be a safe and feasible adjunctive treatment that may reduce the syncope burden and improve exercise-related ventricular arrhythmias. Induction of nontriggering PVCs after ablation is associated with a higher risk of syncope recurrence.

Key Words: catecholaminergic polymorphic ventricular tachycardia ■ catheter ablation ■ exercise testing ■ polymorphic ventricular tachycardia ■ premature ventricular contraction ■ ventricular fibrillation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but lethal inherited channelopathy characterized by adrenergic-induced bidirectional and polymorphic ventricular arrhythmias (VAs) in patients with a structurally normal heart.[1] It mainly presents with recurrent episodes of syncope or cardiac arrest during exercise or emotional stress.[2,3] Mutations of calcium channel proteins, such as RYR2

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CLINICAL PERSPECTIVE

What Is New?

- Our data show that the induced premature ventricular contractions (PVCs) during stress testing were closely associated with the onset of polymorphic ventricular tachycardia/ventricular fibrillation events in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).
- The polymorphic ventricular tachycardia/ventricular fibrillation–triggering PVCs in CPVT mainly originated from the left ventricle, and one-third of the cases had biventricular triggering beats.
- Catheter ablation of triggering PVCs in CPVT reduced the episode of syncope and improved the ventricular arrhythmia burden during exercise; induction of nontriggering PVCs after ablation is associated with a higher risk of syncope recurrence.

What Are the Clinical Implications?

- As flecainide and nadolol are not available in some countries and regions, catheter ablation can be considered as an adjunctive treatment for patients with CPVT and recurrent syncope despite the maximum use of β-blockers.
- Elimination of polymorphic ventricular tachycardia/ventricular fibrillation–triggering PVCs in CPVT seems to be a safe and feasible therapy that may reduce the syncope burden and improve exercise-related ventricular arrhythmias.
- Patients for whom nontriggering PVCs are inducible after ablation have a high risk of syncope recurrence and may need further interventions, such as cardiac sympathetic denervation or implantable cardioverter-defibrillator implantation.

Nonstandard Abbreviations and Acronyms

CASQ2	calsequestrin 2
CPVT	catecholaminergic polymorphic ventricular tachycardia
LCSD	left cardiac sympathetic denervation
PVT	polymorphic ventricular tachycardia
RYR2	ryanodine receptor 2
TECRL	trans-2,3-enoyl-CoA reductase-like gene
VA	ventricular arrhythmia

(cardiac ryanodine receptor 2) and cardiac CASQ2 (calsequestrin 2), are implicated in 60% of CPVT cases.[4,5] The disruptions of these channel proteins result in excessive release of sarcoplasmic reticulum calcium, thereby increasing the risk of VAs.[6]

β-Blocker is the recommended first-line therapy for this channelopathy, but it cannot completely suppress the arrhythmic events in all patients.[7–9] The additional use of flecainide or left cardiac sympathetic denervation (LCSD) has been reported to be effective.[10–12] Unfortunately, flecainide is not available in several countries, including China. As LCSD is an invasive surgery and most CPVT patients are children and teenagers, this procedure is only accepted by a limited number of patients. For medically refractory cases or patients who experienced an aborted cardiac arrest, an implantable cardioverter-defibrillator (ICD) implantation should be considered. However, the benefits of this therapy remain controversial. Previous data showed that ICDs could terminate ventricular fibrillation (VF) and significantly reduce mortality in patients with high-risk CPVT.[9,13] However, it cannot prevent the occurrence of VAs and has potentially proarrhythmic effects as appropriate or inappropriate discharges can trigger catecholamine release, evoking a self-induced vicious circle.[14] A recent registry study reported that ICD implantation in CPVT did not improve survival but was associated with a high rate of inappropriate ICD shocks and device-related complications.[15] Roston et al summarized that nearly 20% of ICD recipients in CPVT experienced an electrical storm, and 60% of (7) deaths were attributed to ICD-associated incessant ventricular tachycardias (VTs).[16]

Catheter ablation of premature ventricular contractions (PVCs) that triggered VF has been reported as a promising therapy for preventing VF in patients with CPVT.[17,18] However, these efficacy data are only derived from sporadic cases, and little is known about the electrophysiological features and long-term outcomes of trigger ablation in CPVT. Moreover, the effect of catheter ablation on exercised-induced VAs is also unclear. This study aimed to elucidate the aforementioned points using the results from a long-term follow-up in a prospective study.

METHODS

The data underlying this article cannot be shared publicly because of the privacy of study participants. The data will be shared on reasonable request to the corresponding author.

Study Population

This study complied with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee of Fuwai Hospital. From January 2016 to January 2021, consecutively selected patients with CPVT who experienced recurrent syncope despite the maximum β-blockers and could not add on flecainide

were enrolled for electrophysiological study and catheter ablation. The diagnosis of CPVT was established according to the Heart Rhythm Society consensus statement based on stress-induced bidirectional VT or polymorphic VT (PVT) with no detectable structural heart disease.[7] Recurrent syncope was defined as ≥2 episodes of syncope after drug therapy and exercise restriction. Individuals were excluded if they had an ablation history or if they selected the initial therapy of LCSD. Additional exclusion criteria included obstructive coronary artery disease, myocarditis, and ventricular cardiomyopathy (Figure S1). Informed consent was obtained from all participants or their guardians.

A baseline exercise treadmill test was performed at enrollment (with the maximum β-blockers). VA scores during exercise were evaluated using the following scoring system (modified from Rosso et al[19]) on an ordinal scale of VA observed during the worst 10-second period of the exercise test: 0, no PVC; 1, isolated PVCs (<10 per minute); 2, bigeminal PVCs, frequent PVCs (>10 per minute), or both; 3, ventricular couplets (2 consecutive beats); 4, monomorphic VT; 5, polymorphic VT; and 6, VF.

Electrophysiological Study, Mapping, and Ablation

The procedure was performed under local anesthesia and conscious sedation. Three-dimensional electroanatomic mapping was performed using the EnSite NavX system (St. Jude Medical, Abbott, St Paul, MN). During the electrophysiological study, intravenous isoproterenol was administered stepwise (from 0.025 to 0.1 μg/kg per minute) to provoke the VAs. The isoproterenol infusion was terminated once the PVC-triggered PVT/VF events appeared. Repeated isoproterenol stress testing was performed to reproduce the triggering events when the heart rate recovered to the baseline level. The induced PVCs that repeatedly triggered PVT/VF events were specifically ablated. They were localized by mapping the earliest local activation electrograms relative to the onset of the QRS complex. Pace mapping was further applied to identify the site with the best match to the QRS configuration according to the recorded ventricular ectopy on the 12-lead surface ECG. Electrical cardioversion or defibrillation was performed if the induced VAs led to unstable hemodynamics.

Radiofrequency catheter ablation was performed using an irrigated 4-mm flexible-tip catheter (FlexAbility, St. Jude Medical, Abbott) with an upper power limit of 30 to 40 W and a temperature limit of 45 °C. If acceleration or reduction of PVCs was observed during the initial 10 s of ablation, radiofrequency delivery was continued for 60 to 120 s.

The procedure end point was the noninducibility of PVT/VF-triggering PVCs during the administration of isoproterenol-escalating infusion until the maximum heart rate was reached. In this study, nontriggering PVCs were defined as induced ventricular beats that could not trigger PVT/VF events, and these PVCs were not targeted for ablation. Major procedural complications were pericardial tamponade, ventricular perforation, pulmonary thromboembolism, ischemic stroke, myocardial infarction, and severe vascular complications requiring surgical intervention.

Clinical Follow-Up

Patients were prescribed the same dose of β-blockers as they received before ablation and were followed up in the outpatient clinic or by telephone interviews. At the 3- and 12-month follow-ups, exercise treadmill tests were performed without interrupting β-blocker therapy to evaluate the inducibility of VAs.

The primary end point was the syncope recurrence. The secondary end point was the reduction of VA scores during follow-up exercise testing.

Statistical Analysis

Continuous data are summarized as mean±SD or median (interquartile range). Categorical variables are expressed as absolute frequencies and percentages. Comparisons between groups with and without syncope recurrence were performed with Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables. A matched-period analysis was applied to evaluate the effect of catheter ablation on syncope control. For each patient, periods of equal duration before and after ablation were identified, with patients serving as their own controls. The number of syncope episodes was determined for the matched periods. Syncope frequency was defined as the number of syncope events per year. The difference in syncope frequency before and after ablation was compared using the paired Wilcoxon signed-rank test. Comparisons of VA score at various time intervals were analyzed using the Friedman test and, if statistical significance was detected, multiple comparisons were done using the Wilcoxon signed rank test with a Bonferroni correction applied. Long-term syncope-free survival after ablation was assessed through time-to-event analysis using the Kaplan-Meier method. The effect of different clinical variables on syncope recurrence was investigated using the univariate Cox proportional hazards model. $P<0.05$ was considered statistically significant. All analyses were performed using SPSS software, version 22.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

Fourteen patients were enrolled in this study. The baseline characteristics of the study population are shown in Table 1. The mean±SD age was 16±6 years (median, 15 [range, 5–29] years), and 43% of the patients were male sex. The median disease course was 46 months. All patients received the maximum tolerated dosage of β-blockers. As nadolol is unavailable in China, these patients used propranolol or metoprolol instead. The syncope frequency was 4±2 events per year (median, 4 [IQR, 3–5]). Five patients had a history of aborted cardiac arrest (for the main features of each subject, see Table S1). Putative pathogenic mutations were identified in *RYR2* in 9 patients, *CASQ2* in 1 patient, and trans-2,3-enoyl-CoA reductase-like gene (*TECRL*) in 1 patient; 3 patients had negative genetic findings (Figure 1). Cardiac magnetic resonance imaging revealed normal cardiac structure and function in all patients. No distribution of late gadolinium enhancement was observed. Echocardiography showed a normal left ventricular (LV) ejection fraction (66±5%). Baseline ECG exhibited sinus rhythm (62±15 beats per minute), normal QRS duration (95±11 ms), and normal QTc interval (415±39 ms). None of the patients had conduction abnormalities or spontaneous cardiac arrhythmias.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Patient data (n=14)
Age at first symptom, y	12±7
Age at diagnosis, y	14±6
Age at baseline, y	16±6
Male sex, n (%)	6 (43)
Disease course, median (IQR), mo	46 (28–62)
Syncope frequency, n/y	4±2
Aborted cardiac arrest, n (%)	5 (36)
Putative pathogenic mutation, n (%)	
RYR2	9 (64)
CASQ2	1 (7)
TECRL	1 (7)
Not identified	3 (21)
SBP, mm Hg	117±14
DBP, mm Hg	65±11
ECG features	
Heart rate, bpm	62±15
PR interval, ms	132±16
QTc interval, ms	408±45
QRS duration, ms	95±11
LV ejection fraction, %	66±5
LVEDd, mm	45±9

Values are mean±SD, unless otherwise indicated. Bpm indicates beats per minute; *CASQ2*, gene encoding calsequestrin 2; DBP, diastolic blood pressure; IQR, interquartile range; LV, left ventricular; LVEDd, LV end-diastolic diameter; *RYR2*, gene encoding ryanodine receptor 2; SBP, systolic blood pressure; and *TECRL*, gene encoding trans-2,3-enoyl-CoA reductase-like.

Electrophysiological Characteristics of PVC Targets

During the electrophysiological study, VAs were induced in all patients. With increasing isoproterenol infusion, 12 patients (12/14 [86%]) developed PVT (Figure 2A), of whom 2 rapidly degenerated into VF (Figure 2B), and the remaining 10 self-terminated. In another 2 patients (2/14 [14%]), PVCs directly triggered VF (Figure 2C). On the basis of documented PVT/VF initiation on surface ECG, the PVT/VF events were triggered by bidirectional PVCs in 12 patients (12/14 [86%]) and monomorphic PVCs in 2 patients (2/14 [14%]). A total of 26 triggering ectopic beats were recorded: 9 exhibited right bundle-branch block configuration with inferior axis, 8 revealed right bundle-branch block configuration with superior axis, 4 showed left bundle-branch block configuration with inferior axis, and 5 exhibited left bundle-branch block configuration with superior axis (Figure 3).

These 26 PVT/VF-triggering PVCs were targeted for ablation under the guidance of perfect activation mapping and pace mapping. The mean±SD activation time at the ablation catheter preceding the onset of the QRS complex was 38±11 ms. Seventeen (17/26 [65%]) triggering PVCs originated from the left ventricle, and 9 (9/26 [35%]) originated from the right ventricle. Specifically, these targets were located in the LV basal anterior wall (7/26 [27%]), LV septal area (7/26 [27%]), LV inferior wall (2/26 [8%]), LV anterior free wall (1/26 [4%]), right ventricular (RV) outflow tract (3/26 [12%]), RV septal area (4/26 [15%]), RV inferior wall (1/26 [4%]), and RV anterior wall (1/26 [4%]) (Figure 4).

LV-originated triggering PVCs were observed in 12 patients (12/14 [86%]), and RV-originated triggering PVCs were observed in 7 patients (7/14 [50%]). In 5 patients (5/14 [36%]), triggering PVCs originated from both ventricles; in 7 patients (50%), triggering PVCs only originated from the LV; and in the remaining 2 patients (14%), triggering PVCs only originated from the RV (Table S2). Significant Purkinje potentials were recorded in 7 (27%) targets (Figure 5). No abnormal low-voltage area during endocardial substrate mapping was observed in any patient.

Ablation End Point and Complications

After eliminating the targeted beats, extended ablation around the focus was performed to minimize the recurrence. Isoproterenol was infused again to ensure the noninducibility of the targeted PVCs. Ultimately, 25 of the 26 PVC targets were ablated successfully. PVT/VF events were noninducible in 13 (13/14 [93%]) patients.

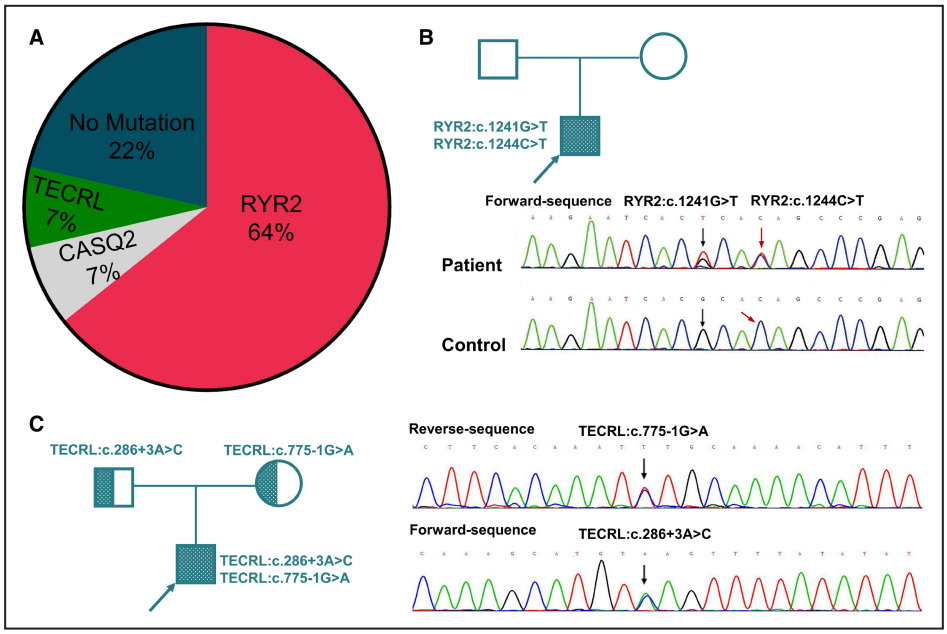

Figure 1. The genetic mutations of the study population.
A, Genotype distribution in this cohort with catecholaminergic polymorphic ventricular tachycardia. **B**, Pedigree of the ryanodine receptor 2 gene (*RYR2*) mutated family. **C**, Pedigree of the trans-2,3-enoyl-CoA reductase-like gene (*TECRL*) mutated family. *CASQ2* indicates the gene encoding calsequestrin 2.

In 1 patient (1/14 [7%]), the triggering PVCs (origin site: LV basal anterior wall) remained inducible even after additional radiofrequency applications. The total ablation time was 20 (range, 12–26) minutes, and total procedure time was 198 (range, 142–256) minutes. After ablation, nontriggering PVCs were induced in 6 patients (6/14 [43%]), among whom no one occurred VTs. As the amounts of these nontriggering PVCs were also limited, no further ablation was performed.

None of the patients developed severe complications during the electrophysiological mapping and ablation. One patient had a pseudoaneurysm after a femoral artery puncture, which was well managed with no surgical intervention.

Clinical Follow-Up

The mean±SD duration of risk exposure during matched periods before and after catheter ablation was 4±1 years. The syncope frequency was significantly reduced after ablation (from 4.3±1.6 to 0.5±0.8 events per year; $P<0.001$). After a mean±SD follow-up of 49±23 months (median, 49 [IQR, 34–58] months), 8 (8/14 [57%]) patients were free from syncope recurrence (Figure 6). Six patients had syncope events, including 3 who experienced a single episode and 3 who had multiple episodes. There was no significant difference in baseline clinical characteristics between patients with and without syncope recurrence (Table 2). More syncope recurrence was seen in patients who had nontriggering PVCs after ablation (5/6 [83%]) compared with patients in whom PVCs were absent (1/8 [13%]; log-rank $P=0.014$; Figure 7). Cox proportional hazards regression analysis showed that the PVC target sites did not impact the syncope recurrence, whereas the induction of nontriggering PVCs postablation indicated a high recurrent risk (hazard ratio, 6.8 [95% CI, 1.3–35.5]; $P=0.026$; Table S3).

Three patients experienced cardiac arrest, of whom 1 had sudden cardiac death during severe emotional stress; 1 further received LCSD therapy and reported no syncope recurrence after the procedure; and the remaining 1 implanted an ICD because of recurrent cardiac arrest after LCSD.

Elimination of Trigger Beats Reduces Exercise-Induced VAs

Baseline exercise treadmill testing (under β-blocker therapy) was performed on 13 patients; 1 patient could not exercise because of her young age (Table S4). The median baseline VAs score was 5 (range, 3–6). As demonstrated in Table 3, 11 participants experienced PVT or VF events. After eliminating PVT/VF triggers, exercise-related ventricular ectopy was significantly reduced at 3-month (VA score, 1.5 [range, 0–5] versus baseline; $P=0.002$) and 12-month (VA score, 2 [range, 0–5] versus baseline; $P=0.014$) follow-ups in the 12 patients with available data. One patient had no follow-up exercise testing data because of sudden cardiac death 20 days after discharge. Ten (10/12 [83%]) patients improved the VA score at 3- and 12-month follow-ups

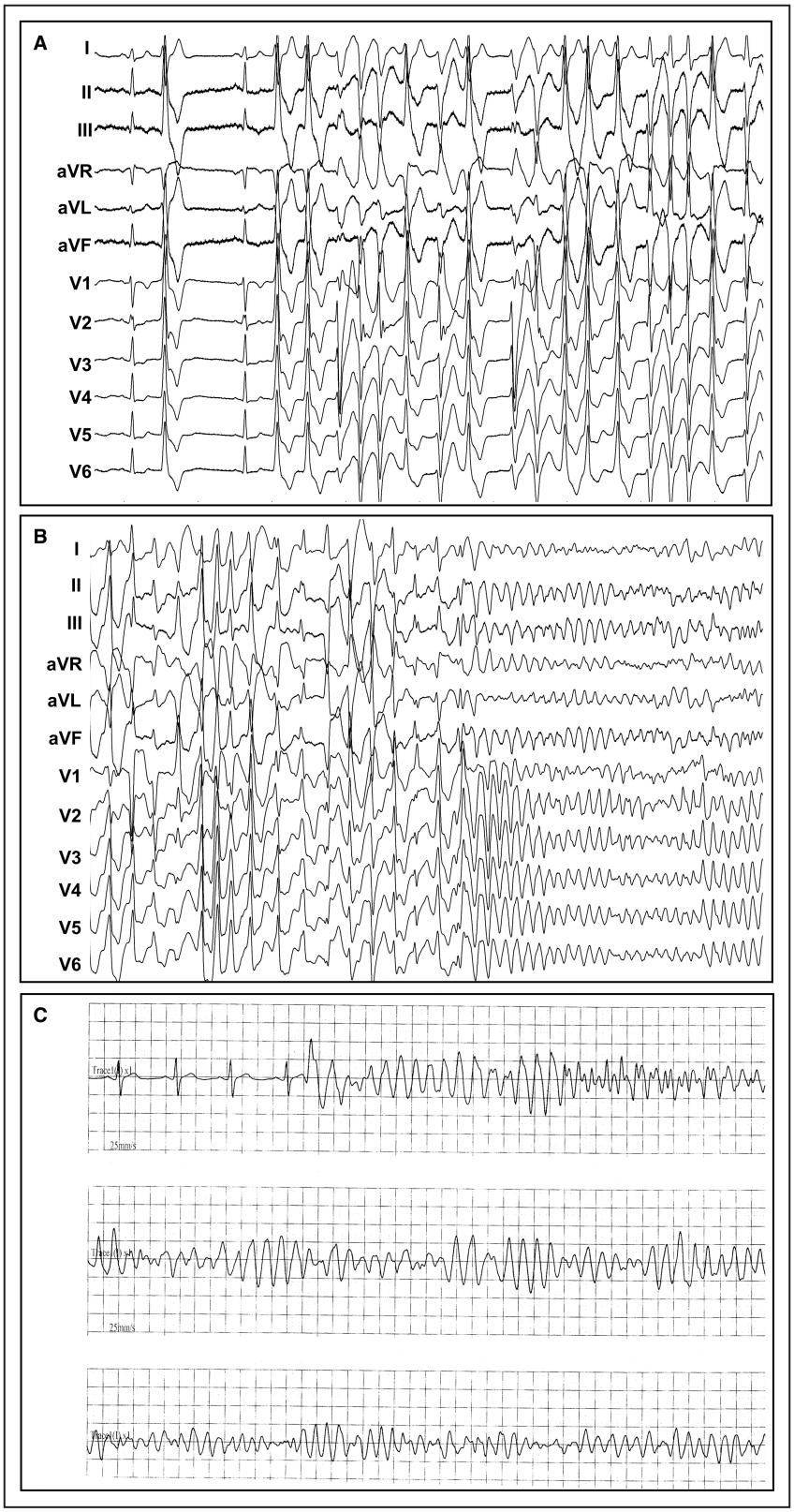

Figure 2. Electrocardiographic changes during catecholamine stress testing in patients with catecholaminergic polymorphic ventricular tachycardia (PVT).
A, Continuous intravenous infusion of isoproterenol induced premature ventricular contractions (PVCs) and further triggered PVT. **B**, PVT rapidly deteriorated into ventricular fibrillation (VF). **C**, PVCs can also directly trigger VF.

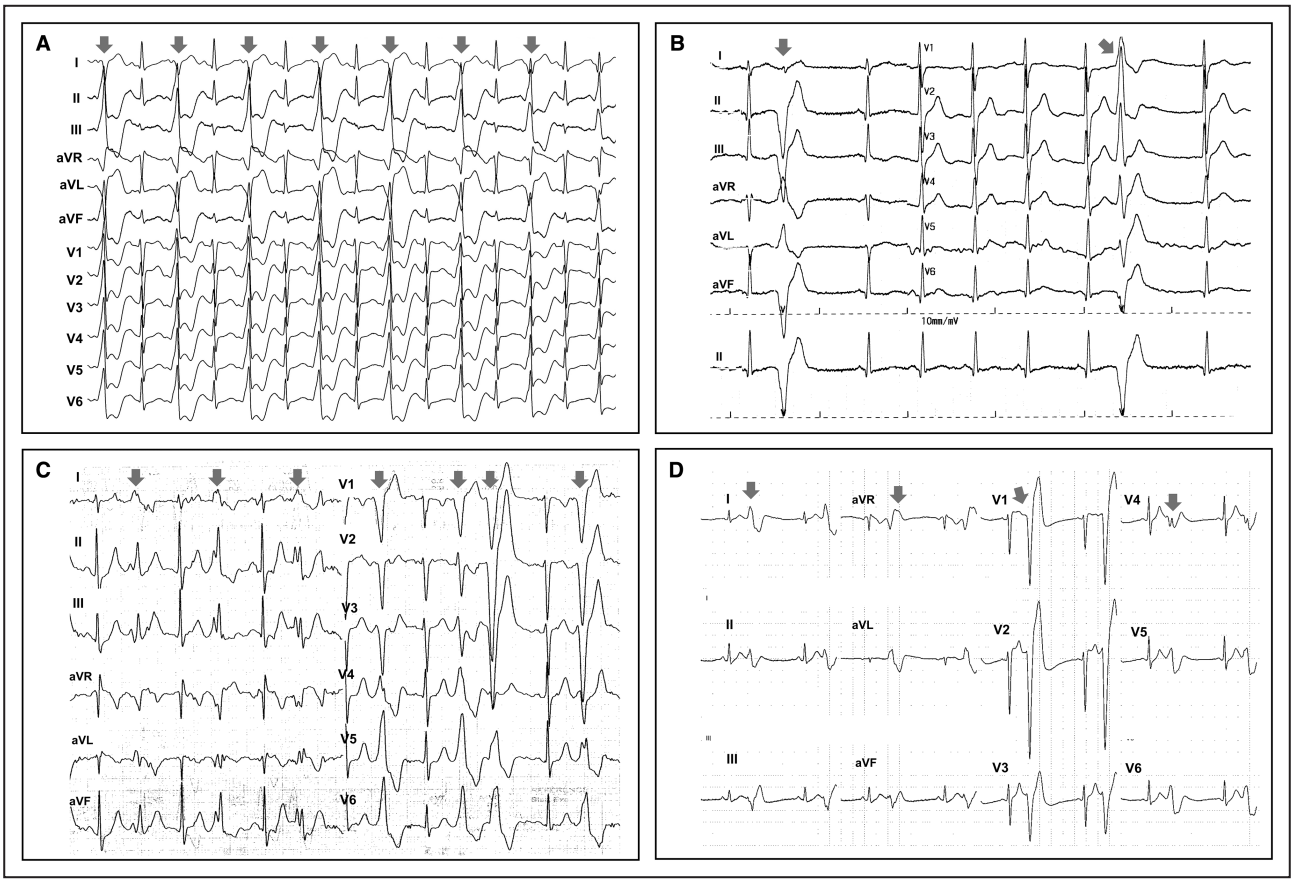

Figure 3. Polymorphic ventricular tachycardia/ventricular fibrillation–triggering ectopic beats.
A, Right bundle-branch block (RBBB) and inferior axis configuration (9/26 [35%]). **B**, RBBB and superior axis morphology (8/26 [31%]). **C**, Left bundle-branch block (LBBB) and inferior axis configuration (4/26 [15%]). **D**, LBBB and superior axis morphology (5/26 [19%]).

(Figure 8). In the last exercise test, the PVT event was induced in 2 patients, but none triggered the VF event. Compared with the 3-month exercise testing data, patients at the 12-month follow-up exhibited no differences in VA score (2 [range, 0–5] versus 1.5 [range, 0–5]; *P*=0.540).

DISCUSSION

Main Findings

To the best of our knowledge, this is the largest study to investigate the electrophysiological features and ablation outcomes in patients with CPVT. The main findings were as follows: (1) PVT/VF-triggering PVCs in CPVT mainly originated from the LV, and one-third of the cases had biventricular triggering beats; (2) LV basal anterior wall and LV septal area were the main sites of triggering beats, and 27% of ablation targets had Purkinje potentials; (3) eliminating triggering PVCs in CPVT reduced the syncope burden and improved the VA score during exercise; and (4) the induction of nontriggering PVCs after ablation indicated a high risk of syncope recurrence.

CPVT has a high prevalence of arrhythmic events, including syncope and sudden cardiac arrest. The use of flecainide and nadolol can effectively reduce these events, whereas these drugs are not approved for clinical use in some countries and regions. Catheter ablation of PVCs that trigger VF has been reported as an effective therapy for preventing VF in patients with long-QT syndrome and Brugada syndrome.[20,21] However, only sporadic cases have described this therapy for CPVT. The first such case reported by Szumowski et al[17] found that catheter ablation eliminated the VF trigger in a young patient with CPVT and suppressed the VAs during follow-up. Similarly, Kaneshiro et al ablated the bidirectional PVCs in an adult patient and prevented the episodes of syncope and ICD therapy.[18] Interestingly, a recent CPVT case series reported that 80% of ablated patients still experienced VAs requiring ICD or external defibrillator intervention.[22] That study only enrolled 5 patients, and all participants were female sex. The reported causes of recurrence include earthquake-induced emotional stress and inappropriate shock delivery for rapid atrial fibrillation. In this study, we enrolled 14 patients with

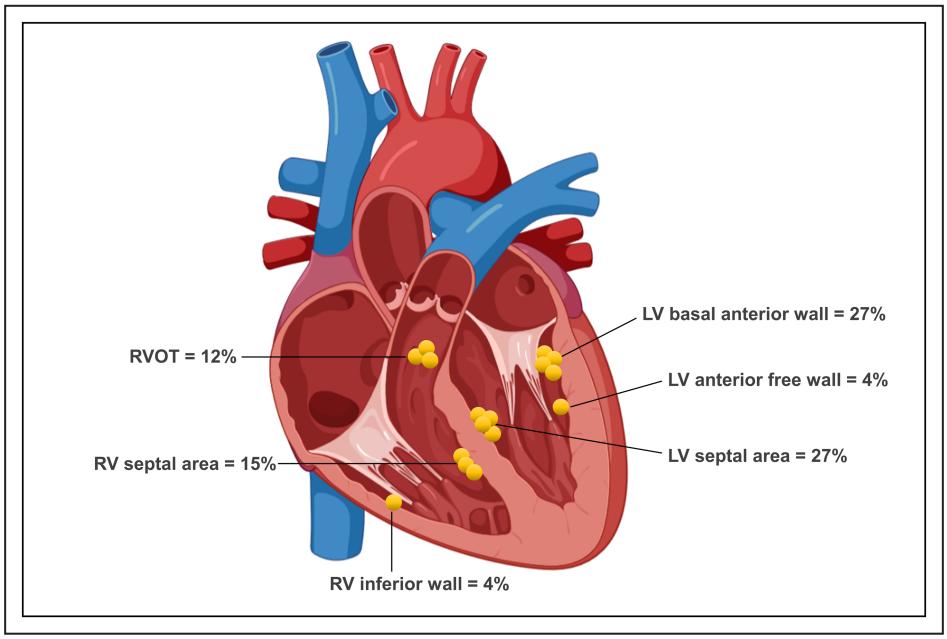

Figure 4. The origin sites of the polymorphic ventricular tachycardia/ventricular fibrillation–triggering premature ventricular contractions in patients with catecholaminergic polymorphic ventricular tachycardia.
LV indicates left ventricular; RV, right ventricular; and RVOT, RV outflow tract.

CPVT with a similar proportion of male and female participants. We observed that the induced PVCs during catecholamine stress testing were closely associated with the onset of PVT/VF events. Elimination of these trigger beats achieved the noninducibility of PVT/VF events in >90% of patients, and nearly 60% of the

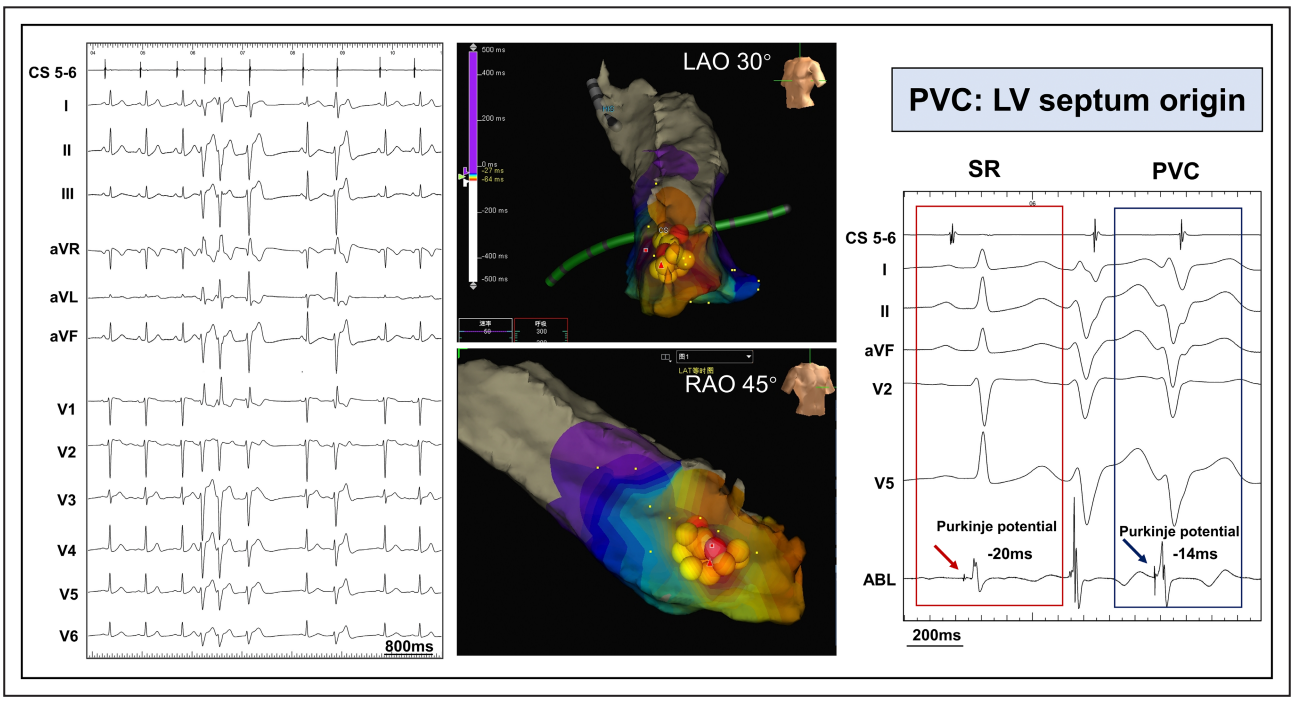

Figure 5. Intracardiac recordings and catheter position at a successful ablation site of a polymorphic ventricular tachycardia/ventricular fibrillation–triggering premature ventricular contraction (PVC).
A Purkinje potential was recorded from the left inferior septum area and preceded the QRS onset by 14 ms. Red points indicate the ablation sites. Yellow points indicate the sites with Purkinje potentials. ABL indicates ablation catheter; CS, coronary sinus; LAO, left anterior oblique; LV, left ventricular; RAO, right anterior oblique; and SR, sinus rhythm.

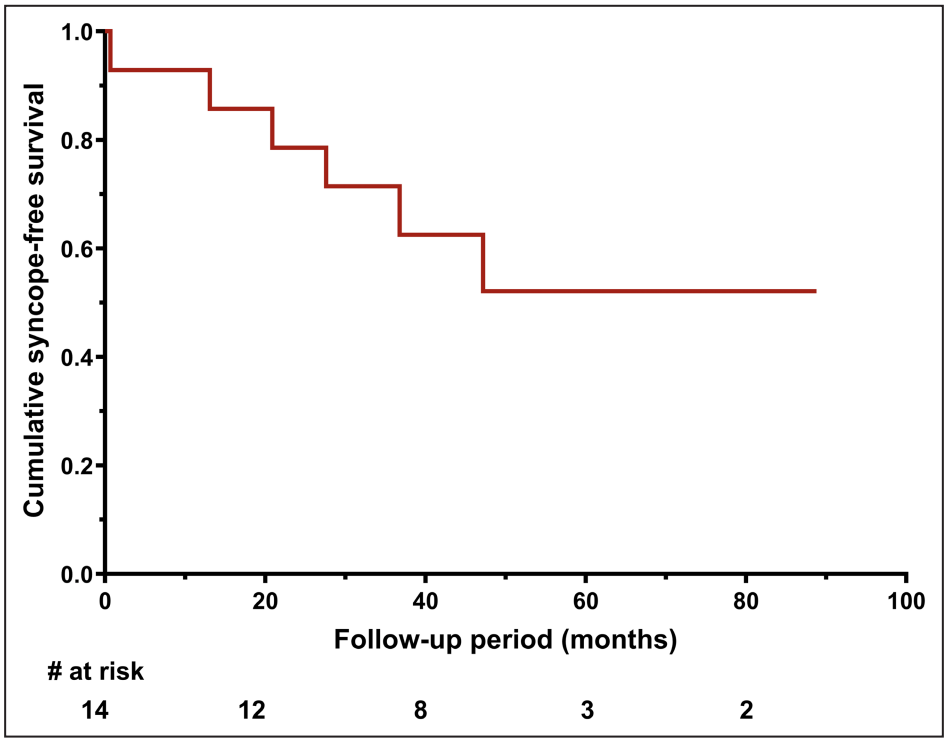

Figure 6. Kaplan-Meier curve of freedom from syncope recurrence after catheter ablation for catecholaminergic polymorphic ventricular tachycardia.

cases were free from syncope recurrence during follow-up. Although 6 patients still experienced syncope episodes, most recurrent events occurred ≥1 year after ablation, and 3 patients only experienced 1 episode during the entire follow-up period. Catheter ablation seems to reduce the syncope burden, suggesting that ablation of trigger beats may improve the quality of life in patients with CPVT. In this study, we observed that bidirectional PVCs were common in patients with CPVT. There is growing evidence that the origin sites of bidirectional PVCs in CPVT have a dominant-subordinate relationship. Eliminating the main PVC target can

Table 2. Comparison Between the 2 Groups for Clinical and Procedural Data

Variable	Syncope recurrence (n=6)	No syncope recurrence (n=8)	*P* value
Age at baseline, y	13±7	18±7	0.116
Male sex	2 (33)	4 (50)	0.627
Disease course, median (IQR), mo	53 (43–61)	34 (24–58)	0.491
Putative pathogenic mutation	6 (100)	5 (63)	0.209
RYR2 mutation	5 (83)	4 (50)	0.301
Baseline ECG features			
Heart rate, bpm	59±8	64±20	0.852
QTc interval, ms	400±37	414±53	0.512
QRS duration, ms	90±7	98±13	0.267
Triggering PVC site, n	11	15	0.646
LV basal anterior wall	4 (36)	3 (20)	0.407
LV fascicular area	2 (18)	5 (33)	0.658
RVOT	2 (18)	1 (7)	0.556
RV septal area	2 (18)	2 (13)	>0.999
Inducibility of nontriggering PVCs	5 (83)	1 (13)	0.035

Values are mean±SD or number (percentage), unless otherwise indicated. Bpm indicates beats per minute; IQR, interquartile range; LV, left ventricular; PVC, premature ventricular contraction; *RYR2*, gene encoding ryanodine receptor 2; RV, right ventricular; and RVOT, RV outflow tract.

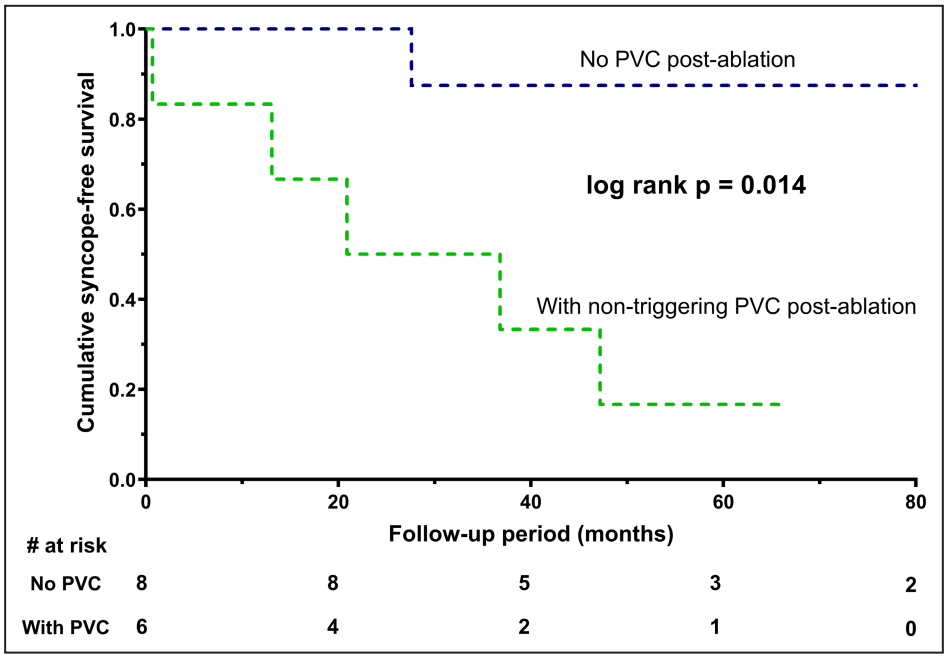

Figure 7. Survival analysis showing the comparison in the cumulative syncope-free survival between patients with and without nontriggering premature ventricular contraction (PVC) after ablation.

effectively inhibit the occurrence of secondary PVCs.[23] We ablated all bidirectional PVCs and observed that the elimination of both targets might be an efficient therapeutic option for reducing arrhythmic episodes.

Different from previous studies, which reported that the RV outflow tract was the main origin site of CPVT arrhythmias and most of the patients only had a single ventricular ectopic focus,[24–26] our investigation observed that the VAs in CPVT were mainly from the left ventricle. More than 30% of patients had biventricular PVCs. The specific origins of PVCs were primarily located in the LV basal anterior wall and ventricular septum. RV outflow tract as the origin was only observed in 12% of ablated targets. The RV septal area was another common origin site of PVCs in these patients with CPVT. Purkinje cell calcium dysregulation was reported as 1 of the mechanisms that underlay focally activated arrhythmias in CPVT.[27,28] However, Flores et al observed that the disruption of calcium homeostasis in the Purkinje network could not produce a CPVT phenotype.[29] Purkinje-myocardial junction was the anatomic origin of VAs, and the delayed afterdepolarizations in the ventricular myocardium could trigger full action potentials in adjacent Purkinje cells.[30] Isolated ventricular cardiomyocytes from CPVT models also exhibited spontaneous calcium release, delayed afterdepolarizations, and spontaneous action potentials in response to catecholaminergic stimulation.[31,32]

Table 3. VA Changes During Exercise Treadmill Stress Testing

VA (score)	No. (%) of patients		
	Baseline (n=13)	3-mo Follow-up (n=12)	12-mo Follow-up (n=12)
VF (6)	1 (8)	0	0
PVT (5)	10 (77)	2 (17)	2 (17)
MVT (4)	1 (8)	0	0
Couplets (3)	1 (8)	2 (17)	3 (25)
Bigeminy (2)	0	2 (17)	3 (25)
Isolated PVC (1)	0	4 (33)	3 (25)
No ectopy (0)	0	2 (17)	1 (8)

MVT indicates monomorphic ventricular tachycardia; PVC, premature ventricular contraction; PVT, polymorphic ventricular tachycardia; VA, ventricular arrhythmia; and VF, ventricular fibrillation.

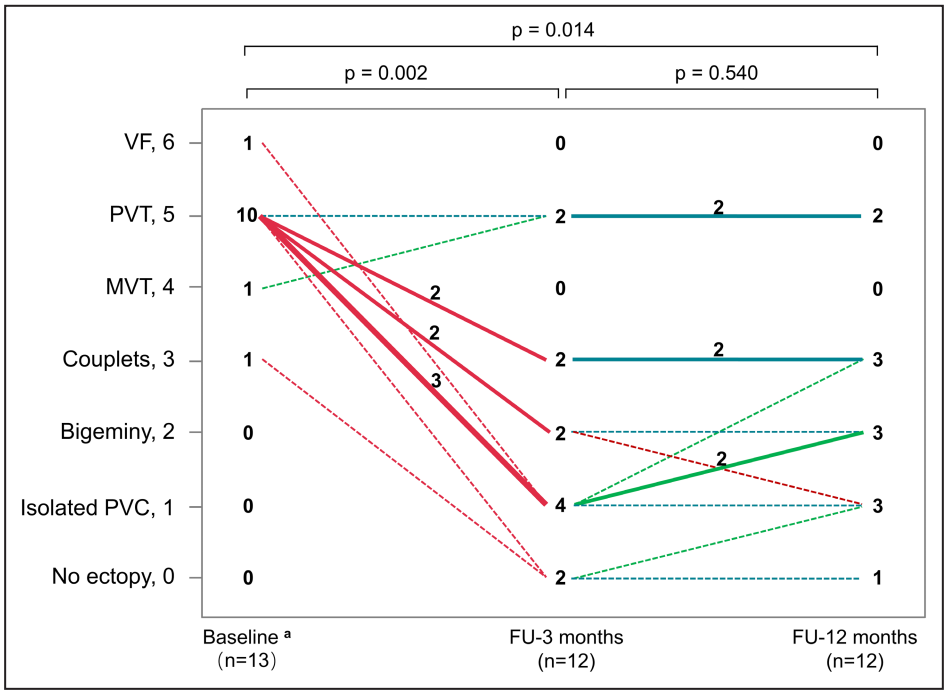

Figure 8. Efficacy of trigger beat elimination in reducing ventricular arrhythmias during exercise in patients with catecholaminergic polymorphic ventricular tachycardia.
The number of patients in each ventricular arrhythmia category and changes in ventricular arrhythmia category at 3- and 12-month follow-ups were shown. A dotted line represents 1 patient, and the solid line thickness indicates the number of patients. Exercise testing was performed using a treadmill. The median baseline ventricular arrhythmia (VA) score was 5 (range, 3–6), and the median 3- and 12-month VA scores were 1.5 (range, 0–5) and 2 (range, 0–5), respectively. [a]One patient died of sudden cardiac arrest 20 days after discharge. FU indicates follow-up; MVT, monomorphic ventricular tachycardia; PVC, premature ventricular contraction; PVT, premature ventricular tachycardia; and VF, ventricular fibrillation.

In this study, we did observe Purkinje potentials in several CPVT triggers, whereas >70% of ablated targets did not detect similar potentials. Moreover, we also observed the CPVT arrhythmias originated far from the Purkinje fiber system, such as the ventricular outflow tracts, where there is little or no distribution of Purkinje fibers. These findings suggested that the His-Purkinje system may not be the sole culprit for CPVT.

Nearly 40% of patients in this study induced nontriggering PVCs after ablation. Although the amounts of these PVCs were limited and did not trigger PVT/VF events during stress testing, patients inducing nontriggering PVCs had a high risk of syncope recurrence. This finding indicated that catheter ablation may reduce the VA risk but not completely eliminate the arrhythmogenic substrates in patients with CPVT, and β-blockers remain the therapeutic cornerstone for all patients, regardless of whether they received successful trigger beats ablation. For patients with induction of nontriggering PVCs after ablation, further early interventions, such as cardiac sympathetic denervation or ICD implantation, may be necessary.

Patients with CPVT were usually recommended to limit or avoid strenuous exercise.[33,34] This lifestyle change has demonstrated its significance in reducing arrhythmic events. However, the reality is that many patients no longer engage in daily physical exercise because of the fear of syncope episodes. Because most patients with CPVT are children and adolescents, the long-term restriction of physical exercise can lead to a series of concerns, such as obesity, growth retardation, psychological problems, and poor interpersonal relationships.[35,36] Recently, Ostby et al reported that a well-treated athlete following the diagnosis of CPVT had a comparable risk of arrhythmic events to nonathletes.[37] Exercise treadmill test is the cornerstone for the risk stratification and assessment of therapeutic efficacy in CPVT. Peltenburg et al studied 104 patients with CPVT with a repeated exercise-stress test and found that a decrease in VA score of at least 2 categories after a therapeutic modification suggests a positive effect.[38] In this study, we evaluated the exercise tolerance after catheter ablation. Interestingly, the elimination of trigger beats resulted in a remarkable reduction in the burden of VAs during exercise, even at

the 1-year follow-up. This result seems promising as it implies that patients with CPVT may have reduced VA events during physical exercise if they could well improve their arrhythmic risk, and catheter ablation for PVT/VF-triggering beats may be a valuable adjunctive therapy. Further investigations with larger sample sizes and longer follow-up durations are required to confirm these findings.

Limitations

This study had several limitations. First, the number of enrolled patients was small. For safety concerns, only limited parents accepted the catheter ablation for their children. To our knowledge, this is the largest known cohort for CPVT ablation until now. Second, the present study represented a single-center experience and did not report any major procedure-related complications. Larger studies are needed to determine the risks and benefits of catheter ablation for CPVT. Third, it would be of great interest to analyze the differences in outcomes between catheter ablation and medical treatment alone in a randomized manner. However, this requires a multicenter collaborative approach for rare diseases, such as CPVT. Fourth, flecainide and nadolol are not available in China, and it remains unclear whether these drugs could further improve the prognosis after CPVT ablation. Fifth, the small sample size may also limit us from revealing the impact of genetic variants, especially RYR2 mutation, on PVC targets and ablation outcomes. Sixth, the selection of patients who had positive responses to isoproterenol infusion may also limit the application population of this treatment strategy. Nevertheless, this is the first prospective study analyzing ablation outcomes in patients with CPVT. The efficacy of VA control observed during exercise testing might offer future perspectives for ameliorating stress-induced malignant arrhythmias.

CONCLUSIONS

Catheter ablation of PVT/VF-triggering PVCs in patients with CPVT who cannot receive flecainide treatment seems to be a safe and feasible adjunctive treatment that may reduce the syncope burden and improve exercise-related VAs. Induction of nontriggering PVCs after ablation is associated with a higher risk of syncope recurrence.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figure S1

REFERENCES

1. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106:69–74. doi: 10.1161/01.CIR.0000020013.73106.D8
2. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, Klug D, Hayashi M, Takatsuki S, Villain E, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2009;119:2426–2434. doi: 10.1161/CIRCULATIONAHA.108.829267
3. Giudicessi JR, Ackerman MJ. Exercise testing oversights underlie missed and delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia in young sudden cardiac arrest survivors. *Heart Rhythm*. 2019;16:1232–1239. doi: 10.1016/j.hrthm.2019.02.012
4. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, Potts JE, Maginot KR, Salerno JC, Cohen MI, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace*. 2018;20:541–547. doi: 10.1093/europace/euw389
5. di Barletta MR, Viatchenko-Karpinski S, Nori A, Memmi M, Terentyev D, Turcato F, Valle G, Rizzi N, Napolitano C, Gyorke S, et al. Clinical phenotype and functional characterization of CASQ2 mutations associated with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2006;114:1012–1019. doi: 10.1161/CIRCULATIONAHA.106.623793
6. Priori SG, Chen SR. Inherited dysfunction of sarcoplasmic reticulum Ca2+ handling and arrhythmogenesis. *Circ Res*. 2011;108:871–883. doi: 10.1161/CIRCRESAHA.110.226845
7. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963. doi: 10.1016/j.hrthm.2013.05.014
8. Peltenburg PJ, Kallas D, Bos JM, Lieve KVV, Franciosi S, Roston TM, Denjoy I, Sorensen KB, Ohno S, Roses-Noguer F, et al. An international multicenter cohort study on β-blockers for the treatment of symptomatic children with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2022;145:333–344. doi: 10.1161/CIRCULATIONAHA.121.056018
9. Mazzanti A, Kukavica D, Trancuccio A, Memmi M, Bloise R, Gambelli P, Marino M, Ortíz-Genga M, Morini M, Monteforte N, et al. Outcomes of patients with catecholaminergic polymorphic ventricular tachycardia treated with β-blockers. *JAMA Cardiol*. 2022;7:504–512. doi: 10.1001/jamacardio.2022.0219
10. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126. doi: 10.1093/eurheartj/ehac262
11. Kannankeril PJ, Moore JP, Cerrone M, Priori SG, Kertesz NJ, Ro PS, Batra AS, Kaufman ES, Fairbrother DL, Saarel EV, et al. Efficacy of

flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. *JAMA Cardiol*. 2017;2:759–766. doi: 10.1001/jamacardio.2017.1320
12. De Ferrari GM, Dusi V, Spazzolini C, Bos JM, Abrams DJ, Berul CI, Crotti L, Davis AM, Eldar M, Kharlap M, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. *Circulation*. 2015;131:2185–2193. doi: 10.1161/CIRCULATIONAHA.115.015731
13. Roses-Noguer F, Jarman JW, Clague JR, Till J. Outcomes of defibrillator therapy in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2014;11:58–66. doi: 10.1016/j.hrthm.2013.10.027
14. Miyake CY, Webster G, Czosek RJ, Kantoch MJ, Dubin AM, Avasarala K, Atallah J. Efficacy of implantable cardioverter defibrillators in young patients with catecholaminergic polymorphic ventricular tachycardia: success depends on substrate. *Circ Arrhythm Electrophysiol*. 2013;6:579–587. doi: 10.1161/CIRCEP.113.000170
15. van der Werf C, Lieve KV, Bos JM, Lane CM, Denjoy I, Roses-Noguer F, Aiba T, Wada Y, Ingles J, Leren IS, et al. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J*. 2019;40:2953–2961. doi: 10.1093/eurheartj/ehz309
16. Roston TM, Jones K, Hawkins NM, Bos JM, Schwartz PJ, Perry F, Ackerman MJ, Laksman ZWM, Kaul P, Lieve KVV, et al. Implantable cardioverter-defibrillator use in catecholaminergic polymorphic ventricular tachycardia: a systematic review. *Heart Rhythm*. 2018;15:1791–1799. doi: 10.1016/j.hrthm.2018.06.046
17. Szumowski L, Walczak F, Przybylski A, Maryniak A, Szufladowicz E, Derejko P, Bieganowska K, Bodalski R, Orczykowski M, Sterliński M, et al. Ablation of a catecholaminergic polymorphic VT and VF originating from Purkinje fibers–a case report. Article in Polish. *Kardiol Pol*. 2007;65:319–326.
18. Kaneshiro T, Naruse Y, Nogami A, Tada H, Yoshida K, Sekiguchi Y, Murakoshi N, Kato Y, Horigome H, Kawamura M, et al. Successful catheter ablation of bidirectional ventricular premature contractions triggering ventricular fibrillation in catecholaminergic polymorphic ventricular tachycardia with RyR2 mutation. *Circ Arrhythm Electrophysiol*. 2012;5:e14–e17. doi: 10.1161/CIRCEP.111.966549
19. Rosso R, Kalman JM, Rogowski O, Diamant S, Birger A, Biner S, Belhassen B, Viskin S. Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:1149–1154. doi: 10.1016/j.hrthm.2007.05.017
20. Talib AK, Takagi M, Shimane A, Nakano M, Hayashi T, Okajima K, Kentaro M, Fukada K, Kowase S, Kurosaki K, et al. Efficacy of endocardial ablation of drug-resistant ventricular fibrillation in Brugada syndrome: long-term outcome. *Circ Arrhythm Electrophysiol*. 2018;11:e005631. doi: 10.1161/CIRCEP.117.005631
21. Haïssaguerre M, Extramiana F, Hocini M, Cauchemez B, Jaïs P, Cabrera JA, Farré J, Leenhardt A, Sanders P, Scavée C, et al. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. *Circulation*. 2003;108:925–928. doi: 10.1161/01.CIR.0000088781.99943.95
22. Kaneshiro T, Nogami A, Kato Y, Kuroki K, Komatsu Y, Tada H, Sekiguchi Y, Horigome H, Aonuma K. Effects of catheter ablation targeting the trigger beats in inherited catecholaminergic polymorphic ventricular tachycardia. *JACC Clin Electrophysiol*. 2017;3:1062–1063. doi: 10.1016/j.jacep.2017.04.017
23. Shirai Y, Goya M, Ohno S, Horie M, Doi S, Isobe M, Hirao K. Elimination of ventricular arrhythmia in catecholaminergic polymorphic ventricular tachycardia by targeting "catecholamine-sensitive area": a dominant-subordinate relationship between origin sites of bidirectional ventricular premature contractions. *Pacing Clin Electrophysiol*. 2017;40:600–604. doi: 10.1111/pace.13006
24. Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart*. 2003;89:66–70. doi: 10.1136/heart.89.1.66
25. Blich M, Marai I, Suleiman M, Lorber A, Gepstein L, Boulous M, Khoury A. Electrocardiographic comparison of ventricular premature complexes during exercise test in patients with CPVT and healthy subjects. *Pacing Clin Electrophysiol*. 2015;38:398–402. doi: 10.1111/pace.12574
26. Sy RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Gow RM, Green MS, Birnie DH, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2011;8:864–871. doi: 10.1016/j.hrthm.2011.01.038
27. Herron TJ, Milstein ML, Anumonwo J, Priori SG, Jalife J. Purkinje cell calcium dysregulation is the cellular mechanism that underlies catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2010;7:1122–1128. doi: 10.1016/j.hrthm.2010.06.010
28. Baher AA, Uy M, Xie F, Garfinkel A, Qu Z, Weiss JN. Bidirectional ventricular tachycardia: ping pong in the His-Purkinje system. *Heart Rhythm*. 2011;8:599–605. doi: 10.1016/j.hrthm.2010.11.038
29. Flores DJ, Duong T, Brandenberger LO, Mitra A, Shirali A, Johnson JC, Springer D, Noguchi A, Yu ZX, Ebert SN, et al. Conditional ablation and conditional rescue models for Casq2 elucidate the role of development and of cell-type specific expression of Casq2 in the CPVT2 phenotype. *Hum Mol Genet*. 2018;27:1533–1544. doi: 10.1093/hmg/ddy060
30. Blackwell DJ, Faggioni M, Wleklinski MJ, Gomez-Hurtado N, Venkataraman R, Gibbs CE, Baudenbacher FJ, Gong S, Fishman GI, Boyle PM, et al. The Purkinje-myocardial junction is the anatomic origin of ventricular arrhythmia in CPVT. *JCI Insight*. 2022;7:e151893. doi: 10.1172/jci.insight.151893
31. Liu N, Colombi B, Memmi M, Zissimopoulos S, Rizzi N, Negri S, Imbriani M, Napolitano C, Lai FA, Priori SG. Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia: insights from a RyR2 R4496C knock-in mouse model. *Circ Res*. 2006;99:292–298. doi: 10.1161/01.RES.0000235869.50747.e1
32. Novak A, Barad L, Lorber A, Gherghiceanu M, Reiter I, Eisen B, Eldor L, Itskovitz-Eldor J, Eldar M, Arad M, et al. Functional abnormalities in iPSC-derived cardiomyocytes generated from CPVT1 and CPVT2 patients carrying ryanodine or calsequestrin mutations. *J Cell Mol Med*. 2015;19:2006–2018. doi: 10.1111/jcmm.12581
33. Heidbüchel H, Corrado D, Biffi A, Hoffmann E, Panhuyzen-Goedkoop N, Hoogsteen J, Delise P, Hoff PI, Pelliccia A; Study Group on Sports Cardiology of the European Association for Cardiovascular Prevention and Rehabilitation. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. Part II: ventricular arrhythmias, channelopathies and implantable defibrillators. *Eur J Cardiovasc Prev Rehabil*. 2006;13:676–686. doi: 10.1097/01.hjr.0000239465.26132.29
34. Ackerman MJ, Zipes DP, Kovacs RJ, Maron BJ; American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in Young; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 10: the cardiac channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2015;132:e326–e329. doi: 10.1161/cir.0000000000000246
35. Hammond-Haley M, Patel RS, Providência R, Lambiase PD. Exercise restrictions for patients with inherited cardiac conditions: current guidelines, challenges and limitations. *Int J Cardiol*. 2016;209:234–241. doi: 10.1016/j.ijcard.2016.02.023
36. Christian S, Somerville M, Giuffre M, Atallah J. Physical activity restriction for children and adolescents diagnosed with an inherited arrhythmia or cardiomyopathy and its impact on body mass index. *J Cardiovasc Electrophysiol*. 2018;29:1648–1653. doi: 10.1111/jce.13713
37. Ostby SA, Bos JM, Owen HJ, Wackel PL, Cannon BC, Ackerman MJ. Competitive sports participation in patients with catecholaminergic polymorphic ventricular tachycardia: a single center's early experience. *JACC Clin Electrophysiol*. 2016;2:253–262. doi: 10.1016/j.jacep.2016.01.020
38. Peltenburg PJ, Pultoo SNJ, Tobert KE, Bos JM, Lieve KVV, Tanck M, Clur SB, Blom NA, Ackerman MJ, Wilde AAM, et al. Repeatability of ventricular arrhythmia characteristics on the exercise-stress test in RYR2-mediated catecholaminergic polymorphic ventricular tachycardia. *Europace*. 2023;25:619–626. doi: 10.1093/europace/euac177