High Prevalence of Catecholamine-facilitated Focal Ventricular Tachycardia in Patients With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Background—Exercise-related ventricular tachycardia (VT) and high burden of premature ventricular contractions (PVCs) are common in arrhythmogenic right ventricular dysplasia/cardio-myopathy. We hypothesized that VT in arrhythmogenic right ventricular dysplasia/cardio-myopathy shows a high degree of association with the PVC at baseline.

Methods and Results—The study population included 16 consecutive arrhythmogenic right ventricular dysplasia/cardio-myopathy patients with recurrent VT who underwent catheter ablation. Median age of the patients was 27 years (range, 18–66) and 50% were men. All patients had frequent ectopy at baseline with a median PVC count of 7275 (range, 1353–19084). During EP study, a total of 27 VTs were induced, of which 16 (59%) occurred during high-dose isoproterenol infusion. VT morphology was identical to the baseline PVCs in all the VTs induced during high-dose isoproterenol infusion. Focal ablation at the site of earliest activation and 12/12 pace map of the PVC eliminated the VT in all cases. Target site for focal ablation localized to scar border. Cumulative freedom from VT after ablation was 85.2% and 74.5% at 1 and 2 years, respectively, which was associated with a reduction in PVC count.

Conclusions—We report a high degree of association between PVCs at baseline and the VTs induced during catecholamine infusion. These VTs originated from the border region of scar most commonly in the right ventricular outflow tract and right ventricle basal regions. These findings highlight the importance of catecholamine challenge and PVC mapping, which can in turn facilitate ablation of the VT in arrhythmogenic right ventricular dysplasia/cardio-myopathy. (Circ Arrhythm Electrophysiol. 2013;6:160-166.)

Key Words: arrhythmia (mechanisms) ◼ arrhythmogenic right ventricular dysplasia ◼ catheter ablation ◼ ventricular tachycardia

Arrhythmogenic right ventricular dysplasia/cardio-myopathy (ARVD/C) is an inherited desmosomal cardiomyopathy characterized by a high burden of ventricular arrhythmias and increased risk for sudden death. Fibro fatty replacement of the right ventricle (RV) is thought to result in regions of slow conduction, which form the substrate for reentrant ventricular tachycardia (VT). Several studies have published on the prevalence of reentrant VT and on the role of radiofrequency catheter ablation (RFA) in reducing VT recurrence in ARVD/C.1,2

Methods

Study Population

The study population included 16 consecutive patients with definite ARVD/C diagnosed according to the 2010 Revised Task Force Criteria, who underwent radiofrequency catheter ablation for VT. All patients demonstrated frequent VE (Holter monitoring with >1000 premature ventricular contractions [PVCs]/d) and history of exercise-induced VT. All patients provided written informed consent for the study, which was approved by the Johns Hopkins School of Medicine Institutional Review Board.

One of the characteristics of ARVD/C is the high burden of ventricular ectopy (VE).3 Frequently, these are of left bundle-branch block morphology, suggesting RV origin consistent with the RV structural involvement. In contrast to idiopathic VT, VE in the setting of ARVD/C often do not resolve during exercise and in fact, exercise-induced VT is common in ARVD/C.4,5 The burden of VE is also associated with an increased risk of appropriate implantable cardioverter-defibrillator (ICD) interventions4 and increased likelihood of VT recurrence after catheter ablation, suggesting a causal relation between the VE and the VT. We hypothesized that VT in ARVD/C shows a high degree of association with the VE at baseline. A secondary aim was to test the effect of high-dose isoproterenol on inducing sustained VT in ARVD/C.
Cardiac Imaging
All patients who had an ablation underwent a contrast-enhanced high-resolution computed tomographic scan before the procedure. Radiologists experienced in evaluating ARVD/C interpreted the computed tomographic scans and the presence of regional fat infiltration was recorded.

Electrophysiology Study and Mapping
All antiarrhythmic medications were discontinued for at least 5 half-lives before the procedure. After obtaining informed consent, baseline recordings were made in the nonseated state before induction of anesthesia and the different morphology of PVCs were carefully recorded and labeled. Subsequently, patients were sedated, intubated, and quadripolar electrode catheters were advanced under fluoroscopic guidance to the high right atrium, His bundle, coronary sinus, and RV apex. A detailed electroanatomic map of the endocardial RV was created during sinus rhythm using a 3.5-mm open-irrigated tip catheter (Thermacool, Biosense Webster, Diamond Bar, CA).

The decision to proceed with epicardial mapping and ablation was based on findings from prior EP study, in which endocardial mapping suggested an epicardial VT circuit and endocardial ablation was unsuccessful, ECG characteristics suggestive of epicardial site of origin, such as slurred upstroke of the QRS complex, were present, or endocardial mapping during the procedure suggested an epicardial site of origin. In a subset of patients, the pericardium was accessed via a percutaneous subxiphoid puncture, as previously described.8 An anterior approach was used to access the pericardial sac to avoid puncture of coronary vessels or the left ventricle. A 3.5-mm open-tip-irrigated catheter (Thermacool, Biosense Webster, Diamond Bar, CA) was advanced into the pericardial space under fluoroscopic guidance. A detailed electroanatomic map of the epicardial RV was created during sinus rhythm. Reference values for identifying abnormal bipolar electrogram signals have been previously described.9 The standard protocol for initiation of tachycardia included programmed stimulation with up to 3 ventricular extrastimuli delivered from 2 different RV sites. Additionally, all patients underwent aggressive stimulation protocols for VT induction.

Isoproterenol Infusion
At baseline state, each patient underwent infusion of isoproterenol at a rate of 5 µg/min, which was incrementally increased to a rate of 30 µg/min at 2-minute intervals. The infusion was continued until either sustained VT was induced or significant hypotension ensued with mean arterial pressure of <40 mm Hg. At the peak tolerated dose, rapid burst pacing was performed to provoke VT as previously described.10

Ablation Strategy
For patients with persistent PVCs and sustained VT of similar morphology induced during isoproterenol infusion, the site of earliest activation was targeted by activation and pace mapping of the PVCs. Sustained VT was reinduced with high-dose isoproterenol and RFA was performed during stable monomorphic VT whenever possible. For reentrant VT, focal radiofrequency lesions were applied to sites with concealed entrainment, long stimulus to QRS interval, and a post-pacing interval within 30 ms of the tachycardia cycle length using a 3.5-mm open-irrigated catheter. For unappable VTs, focal radiofrequency lesions were applied to sites that demonstrated good or perfect pace map match and presystolic activation (10–20 ms presystolic) during brief periods of VT induction. After ablation of the clinical VT, additional radiofrequency lesions were applied to all the sites with isolated delayed potentials over the endocardial and epicardial surface as previously described.11,12 Radiofrequency energy output with a 3.5-mm open-irrigated catheter was set to 20 to 30 W, targeting a maximum temperature of 50°C in the epicardium. For the endocardial ablations, the target temperature was 60°C and the power was set to 40 to 50 W.

After catheter ablation, during a 30- to 60-minute waiting period, programmed stimulation with up to 3 ventricular extrastimuli was delivered from 2 different RV sites. Additionally, each patient underwent repeat infusion of isoproterenol at a rate of 5 µg/min, which was incrementally increased to a rate of 20 to 30 µg/min at 2-minute intervals. At the peak tolerated dose, rapid burst pacing was performed to provoke VT.

Follow-up
All patients were followed routinely in our electrophysiology clinic or by their treating electrophysiologist. ICD interrogation reports were reviewed by an experienced electrophysiologist (H.T.) for appropriateness of ICD therapy. VT recurrence was determined by review of documented sustained VT on 12-lead ECG, stored ICD electrocardiograms, or event monitoring.

Survival Data and Statistical Analysis
Continuous variables are expressed as mean±SD and categorical variables as frequency (%). Follow-up time was determined from the time of procedure until the occurrence of a VT event, loss of follow-up, heart transplant, or death. Kaplan–Meier survival analysis was used to determine the cumulative VT recurrence free survival in the study population.

All data analyses for research aims were performed using Statistical Analysis Software version 9.2 (SAS Cary, NC). A P value of <0.05 was considered to be significant.

Results
Patient Characteristics
The patient population consisted of 16 patients who underwent RFA procedures for recurrent VT. Four patients had failed prior endocardial RFA procedures (mean, 2; range, 1–3). Baseline characteristics of the study population are listed in Table 1. The median age was 27 years (range, 18–66) and 8 (50%) patients were male. All patients had an ICD implanted at the time of the RFA. Seven (44%) of the 16 patients had a history of multiple ICD shocks for VT storm related to physical exercise. Genetic testing identified pathogenic desmosomal mutations in 10 (63%) patients. Twenty-four-hour holter monitoring revealed the median PVC count to be 7275 (range, 500–20030).

Table 1. Clinical Patient Characteristics

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Overall Population (n=16)</th>
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<tr>
<td>Age at time of first procedure, y*</td>
<td>27 (18–66)</td>
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<tr>
<td>Sex, male</td>
<td>8 (50)</td>
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<tr>
<td>ICD implantation</td>
<td>16 (100)</td>
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<tr>
<td>Pathogenic desmosomal mutations</td>
<td>10 (63)</td>
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<td>Holter PVC count, baseline†/follow up‡</td>
<td>7275 (1353–19084)/985 (293–5679)</td>
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<td>VT storm</td>
<td>7 (44)</td>
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<td>RV function</td>
<td>Normal 5 (31)</td>
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<td></td>
<td>Mild-moderate dysfunction 11 (63)</td>
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<td></td>
<td>Severe dysfunction 0 (0)</td>
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<td>LV involvement</td>
<td>2 (13)</td>
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<td>β-Blockers, baseline†/follow up‡ 9 (60)/9 (60)</td>
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<td>AAD, baseline†/follow up‡</td>
<td>5 (33)/2 (13)</td>
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*Median with range in brackets.
†Baseline represents the interval before catheter ablation procedure.
‡Follow-up represents the interval after catheter ablation procedure.

Discrete data shown with percentages in parenthesis. AAD indicates antiarrhythmic drugs; ICD, implantable cardioverter-defibrillator; LV, left ventricle; PVC, premature ventricular contractions; RV, right ventricle; and VT, ventricular tachycardia.
Electrophysiological Characteristics

Detailed endocardial voltage maps were generated in all patients. Eight patients had additional epicardial mapping as the VT morphology was consistent with epicardial origin. Endocardial voltage map revealed normal voltage in 2 patients, and low voltage indicative of scar predominantly in the RV outflow tract (RVOT) or RV mid-lateral region in the remaining patients (Table 2). Three patients had extensive confluent scar involving the RV free wall and the RVOT extending toward the apex. None of the patients had scar on the RV septum. Epicardial mapping revealed larger scars involving the

<table>
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<th>Table 2. Electrophysiological Characteristics</th>
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CL indicates cycle length; LBBB, left bundle-branch block pattern; LV, left ventricle; PVC, premature ventricular contraction; RBBB, right bundle-branch block pattern; RFA, radiofrequency catheter ablation; RV, right ventricle; RVOT, right ventricle outflow tract; and VT, ventricular tachycardia.
RV basal free wall and RVOT in all 8 patients, including those with normal endocardial maps.

**Effect of High-Dose Isoproterenol**

The mean dose of isoproterenol was ≈20 μg/min, and only 2 patients tolerated the high dose of 30 μg/min. As shown in Table 2, a total of 27 different VTs were induced in the 16 patients with a mean of 1.9±0.8 (range, 1–3) VTs per patient. The mean cycle length of the induced VT was 289±53.9 ms (range, 420–220). Eleven of 16 patients had sustained VT induced either spontaneously during high-dose isoproterenol infusion or by burst pacing during high-dose isoproterenol. Of the 27 total sustained VTs, 16 were induced using high-dose isoproterenol ± burst pacing, whereas the remainder of the VTs (11) were induced by extrastimuli after the washout of isoproterenol. One VT was induced during catheter ablation targeting a PVC. The clinical VT was induced in 9 (56%) patients during high-dose isoproterenol infusion ± burst pacing and was identical to the baseline PVC (Figure 1A and 1B). The clinical VT was induced with extrastimuli after the washout of isoproterenol in 6 (38%) patients, and 1 patient had no inducible VT (6%). As illustrated, complex VE and cycle length variation during tachycardia were common during the catecholamine-facilitated induction protocol.

During high-dose isoproterenol infusion ± burst pacing, 2 distinct patterns were observed: (1) sudden onset of sustained VT with identical morphology to the clinical PVC (Figure 2), or (2) progression from PVC, to salvos of nonsustained VT, and finally to sustained VT with identical morphology (Figure 3).

Majority of the catecholamine-mediated VTs were unstable requiring aspiration of the isoproterenol and spontaneous termination or termination by overdrive pacing. Direct current cardioversion was required when pace termination failed in 6 patients. Adenosine at 18 mg given centrally was ineffective at terminating any of the induced sustained VTs.

**Mapping and Ablation**

Frequent PVCs persisted after discontinuation of the isoproterenol. Pace mapping identified sites with good or perfect match in all 16 sustained, catecholamine-induced VTs. All of the VTs localized to the border regions of scar defined by voltage mapping during sinus rhythm (Figure 4). After identification of the site of origin, the non-sustained ventricular tachycardias and VTs were easily reinduced. Five of the 16 sustained catecholamine-facilitated VTs were hemodynamically stable and repeated attempts to entrain the tachycardia at sites with good or perfect pace-maps and earliest activation consistently demonstrated lack of progressive fusion. RFA at the site of best pace map and/or earliest activation terminated the VT during RFA within 10 seconds.

The site of origin of the 16 catecholamine-mediated sustained VTs was always the border zone of scar tissue. Of the

![Figure 1. Comparison of ECG morphologies of clinical premature ventricular contractions (PVCs) and induced sustained ventricular tachycardia (VT) from a representative arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) patients. A, 12-lead ECG in a representative patient with T wave inversions across leads V1-V3 which are characteristic of ARVD/C and frequent PVCs and nonsustained VT with the same QRS morphology. B, Intracardiac ECG (electrogram) illustrating complex ventricular ectopy and progression to sustained VT with the same morphology as the clinical PVC and VT with incremental isoproterenol infusion. NSVT indicates non-sustained ventricular tachycardia.](http://circep.ahajournals.org/doi/fig/10.1161/CIRCULATIONAHA.112.153550)
16 catecholamine-mediated sustained VTs, 44% originated from the RVOT region with the majority coming from the anteroseptal region. Forty-four % originated from the basal RV region, whereas 12% were from the mid-RV region. The critical site was epicardial in location for 7 (44%) of the 16 catecholamine-facilitated sustained VTs.

The median number of radiofrequency lesions during catheter ablation was 19 (range, 5–85). The mean duration of radiofrequency catheter ablation for all the procedures was 22:07±13:01 (mm:ss; range, 4:19–49:02). The clinical VT was successfully ablated in 95% of the procedures.

**Follow-up**

The median follow-up duration was 15 months (range, 7–30). Figure 5 shows cumulative freedom from VT after a RFA procedure, which was 85.2% (95% confidence interval, 61.8–98.4) and 74.5% (95% confidence interval, 46.0–94.7) at 1 and 2 years, respectively. There were no procedure-related complications in this cohort.

**Main Findings**

This study is the first to report a high degree of association between VE at baseline and induced sustained VT among ARVD/C patients. This study also reports on the use of high-dose isoproterenol in inducing the clinical VT in ARVD/C. The VTs induced during isoproterenol uniformly originated from the border zone surrounding scar tissue with the most common locations being the RVOT and RV basal regions. Although the VTs were often clinically unstable, pace mapping and activation mapping of the frequent PVCs led to sites where successful RFA was performed after reinduction of the VT. Our study highlights the importance of defining the morphology of the PVCs at baseline in ARVD/C, which can in turn facilitate mapping and ablation of the culprit VT.

Commonly, ARVD/C patients experience life-threatening arrhythmias during exertion. In our prior report, we found that 63% of ARVD/C patients were engaged in physical activity at the time of their first appropriate ICD discharge. All of these patients also had >1000 PVCs per 24 hours with probability of ICD shock increasing with PVC burden. Furthermore, Bai et al recently showed that patients with ARVD/C with frequent PVCs after RFA of VT were more likely to have VT recurrence.

Although frequent VE and exercise-induced VT are common findings among ARVD/C patients, there is little information on the role of catecholamines in inducing sustained nonreentrant ventricular arrhythmias. Lerman et al have published extensively about stimulation protocols to induce catecholamine-mediated triggered VTs. In our cohort, the majority of sustained VTs were induced using a similar stimulation protocol with high dose of isoproterenol, and it often resembled the clinical VT. These VTs were often clinically unstable but pace mapping and activation mapping of the PVCs often led to successful sites for RFA. The critical sites were uniformly from border regions of scar tissue.
One could argue that the mechanism of VT induced by isoproterenol could be scar-mediated macro- or microreentry. Bogun et al14 have shown that PVCs in postinfarction patients are associated with reentrant VTs and often arise from the exit site of the circuit. However, several observations make this assumption less likely. The salvos of nonsustained and sustained VT of similar morphology but varying rates during incremental isoproterenol dosing argue for a triggered mechanism rather than macro- or microreentry. Additionally, the VTs initiated spontaneously during high-dose isoproterenol infusion ± burst pacing rather than with extrastimuli, which further suggest a mechanism due to triggered activity rather than reentry or increased automaticity. The stable VTs that were induced using high-dose isoproterenol ± burst pacing could not be entrained and showed no evidence of progressive fusion. Finally, RFA at the earliest site of the PVC identified by activation mapping frequently rendered the VT noninducible.

Taken together, these results suggest that the arrhythmias we observed are likely mediated by triggered activity. Normally, in well-coupled myocardium, cells prone to triggered activity are electrically loaded by neighboring cells that are less prone, which act to suppress focal activity. However, in the setting of ARVD/C, fibro fatty replacement may electrically isolate cells and promote focal activity. This is akin to Purkinje fibers that are normally less well coupled to the myocardium and are a common source of arrhythmia.

Last, ARVD/C in its early stages may be indistinguishable from idiopathic VT. In these instances, the features of the VT are occasionally used to differentiate ARVD/C and idiopathic VT. Characteristics such as VT induction with extrastimuli are suggestive of reentrant scar-related VTs, whereas induction with isoproterenol infusion and burst pacing are more consistent with idiopathic VT due to cAMP-dependent triggered activity. However, the majority of VTs in this cohort were induced with isoproterenol infusion and burst pacing. Criteria diagnostic of reentry such as entrainment or resetting with fusion were not present. Furthermore, the most common location of the site of origin of the focal VTs in ARVD/C were the RVOT and RV basal region which, similar to idiopathic VT, result in left bundle-branch block morphology VT with an inferior axis. The findings of this study show that focal VTs in ARVD/C can mimic RVOT VTs and highlight the importance of not relying solely on VT characteristics to discriminate ARVD/C and idiopathic VT.

Limitations
This study has several limitations. First, this study used a strategy of high-dose isoproterenol infusion to induce arrhythmias...
followed by an ablation specifically targeting all PVCs that were similar to the induced VT. We did not have a control group and so it is unclear whether this approach is superior to the conventional substrate-based ablation strategy targeting all late potentials. This can only be resolved with a randomized, prospective study. Second, no attempt was made to specifically determine the cellular mechanism of VT in these patients. Future cellular studies will be required to elucidate precisely the mechanism of these catecholamine-induced VTs. The focus of this article was to highlight the association between the PVC and sustained VT in this cohort of patients.

Conclusions

We report a high degree of association between monomorphic PVCs at baseline and induced sustained VT among ARVD/C patients. This study brings to light the high prevalence of catecholamine-facilitated focal VTs, which might explain the high incidence of VT during exercise. The site of origin of the focal VTs was uniformly the border region of scar with the most common location being the RVOT and RV basal regions. These findings highlight the importance of defining the morphology of the PVCs at baseline, which can in turn facilitate mapping and ablation of the culprit VT in ARVD/C. Last, this study emphasizes that focal VTs in ARVD/C can mimic RVOT VTs, and therefore VT characteristics should not be used to discriminate ARVD/C and idiopathic VT.

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Disclosures

None.

References

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