Indian Pacing and Electrophysiology Journal 20 (2020) 231–236

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Prognostic significance of accelerated ventricular response during radiofrequency ablation of premature ventricular complexes

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ARTICLE INFO

Article history:
Received 15 December 2019
Received in revised form
26 April 2020
Accepted 8 May 2020
Available online 16 May 2020

Keywords:
Premature ventricular complexes
Radiofrequency ablation
Accelerated ventricular response
Repetitive ventricular response

ABSTRACT

Background: Accelerated ventricular response is frequently observed during radiofrequency ablation (RFA) of premature ventricular complexes (PVCs). We hypothesized that acceleration indicates an appropriate site and adequate injury to the arrhythmogenic tissue, and sought to investigate its value in predicting the outcome.

Methods: We retrospectively analyzed RFA procedures performed for PVCs in our institution from 2011 to 2019.

Results: Fifty-eight patients (29 male; age 42.7 ± 15.6 years) underwent 62 RFA procedures. The most common site was the right ventricular outflow tract (67.7%). Acute success was seen in 88.7%. Accelerated ventricular response was observed in 60.0% of the successful procedures. After a median follow-up of 14.0 months (IQR: 6.0–26.6 months), 16 patients had a recurrence. Recurrence was significantly lower in the group with acceleration than in the group without acceleration (12.5% vs. 57.1%; log-rank $P < 0.001$). The 1-year recurrence rate was 6.5% in the acceleration group and 41.6% in the group without acceleration. On multivariable analysis the adjusted hazard ratio was 0.17 (95% CI, 0.04–0.64; Cox regression $P = 0.009$). The sensitivity, specificity, positive predictive, and negative predictive values of accelerated response to predict long-term success were 75.7%, 75.0%, 87.5%, and 57.2%, respectively.

Conclusions: The recurrence after PVC ablation is significantly lower when an accelerated response was observed at the successful location during RFA. This can be an additional useful marker of long-term success.

1. Introduction

Treatment of premature ventricular complexes (PVCs) is warranted if they produce symptoms, cause heart failure, or trigger malignant ventricular arrhythmias [1–4]. Due to the variable efficacy and adverse effects of antiarrhythmic drugs, catheter ablation has emerged as a relatively safe alternative to treat these arrhythmias with a good success rate [5–8]. Accelerated or repetitive ventricular response ("automaticity") is often observed during radiofrequency ablation (RFA) of PVCs [9]. Accelerated rhythm is also frequently seen during RFA of atrioventricular (AV) junction, "slow" AV nodal pathway, atriofascicular pathway, and focal atrial arrhythmias [9–11]. In the case of AV nodal reentrant tachycardia (AVNRT), accelerated junctional rhythm during RFA is a sensitive marker of success [12–14]. It is unclear whether acceleration seen during PVC ablation has any similar significance.

We hypothesized that if an accelerated response is observed, it indicates an appropriate site and adequate injury to the cells causing the arrhythmia. On the other hand, when PVCs disappear without acceleration during RFA, edema formation or reversible injury can be responsible for the suppression of the PVC. In some cases, this may mimic acute success but cause recurrence [15]. So, the accelerated response can give a sense of reassurance that the PVC focus was affected and not a chance phenomenon. We sought to investigate if this phenomenon had any prognostic significance after the radiofrequency ablation of PVCs.

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Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2020.05.001

2. Methods

2.1. Study population

We retrospectively analyzed 62 PVC ablation procedures done between January 2011 to May 2019. Patients who underwent ablation during sustained ventricular tachycardia and patients with structural heart disease were excluded. All patients underwent a standard pre-procedure evaluation which included ECG, Holter, and echocardiography. Beta-blockers and/or calcium channel blockers were tried before RFA in all patients. None of the patients received membrane active antiarrhythmic agents before the procedure.

2.2. Electrophysiology study and ablation

Electrophysiology study (EPS) was performed after stopping cardioactive drugs for at least 3 half-lives. Activation mapping guided by bipolar and unipolar electrograms (EGMs) was the usual method with pace mapping used as required. Ablation catheter choice and the use of electroanatomical mapping were based on operator preference. All procedures were done with either a 4-mm tip non-irrigated (Navistar®, Biosense Webster, Irvine, CA, USA), or a 3.5 mm (Thermocool®, Biosense Webster) to 4-mm tip (FlexAbility™, St.Jude Medical, St. Paul, MN, USA) open-irrigated ablation catheter. The temperature setting was 55–65 °C when a non-irrigated catheter was used and 42–48 °C for irrigated catheters. The starting power setting was 30–50 W for non-irrigated catheters and 20–30 W for irrigated catheters. Either temperature-feedback power control or manual titration of power was used according to operator preference. The decision about the duration of each radiofrequency (RF) lesion was operator dependent. The procedure was considered successful in the absence of spontaneous or inducible clinical PVCs on waiting for 30 min after successful RFA, during which time isoprenaline infusion and ventricular burst pacing were used.

Procedural data, which was recorded and stored on optical discs, was reviewed on commercially available EP systems (EP- tracer, Cardiotek B.V, Maastricht, Netherlands; WorkMate Claris™, St.Jude Medical; Lab System™ PRO, Bard Electrophysiology, Lowell, MA, USA). Procedures where ablation was performed during sustained ventricular tachycardia, were excluded.

We defined *accelerated ventricular response ("Automaticity" or "Acceleration")* as 3 or more consecutive ventricular beats induced during RF application with the QRS morphology similar to clinical PVC (>10/12 lead match). Radiofrequency applications delivered for short durations (<30 s) were not considered. If ablation was performed at more than one anatomical location for the same PVC, the site where the final successful lesion was delivered was considered as the site of PVC origin and only the lesions at that location were considered for analysis for the presence of acceleration. The procedure where an accelerated response was seen in any of the RF lesions at the successful site was adjudicated to the 'accelerated ventricular response' group. Catheter-induced artifacts were excluded as the cause for acceleration by taking into account only those episodes which started after initiation of RF energy and stopped with the termination of energy delivery.

2.3. Follow-up and outcome

Patient follow-up details were obtained from hospital electronic medical records. During the review, 24-h Holter was done as per the clinical discretion of the treating physician. If the patient had symptoms with obvious clinical and ECG evidence of PVCs before the procedure and the symptoms had subsided with no clinical and ECG evidence of PVCs, the treating physician sometimes chose not to do a Holter. Two patients were lost to follow-up and 41 patients underwent Holter monitoring.

Long-term failure or recurrence was defined as either the presence of the targeted PVC burden more than 10% of the pre-ablation PVC burden on 24-h Holter monitoring (Objective follow-up) *or* recurrence of symptoms with ECG evidence of PVCs (Clinical follow-up). This cut-off of 10% was chosen based on the observation that among twenty-three patients in this cohort who had more than one Holter monitoring (at least one month apart) prior to RFA, the median relative variability in the pre-ablation PVC burden was 16.2% (range 0–80.9%). To take the outliers into account, we have considered 'success' as a decrease in the PVC burden by at least 90% in patients who had Holter follow-up. As a corollary, we defined recurrence as the presence of >10% of the initial burden. In patients who had another non-dominant PVC before ablation, only the recurrence of targeted PVC was considered as failure.

2.4. Statistical analysis

Continuous variable distributions are expressed as means ± standard deviation and median with interquartile range (IQR) and compared with Student's t-test or Mann-Whitney *U* test. Categorical variables are summarized as frequency and percentage and compared with the Chi-square test or Fisher's exact test. Patients lost to follow-up and missing values were excluded from the analysis. Kaplan-Meier analysis was used to estimate time-to-event and comparison between two groups was done using the log-rank test. Multivariable analysis was performed using Cox proportional hazards regression analysis. Hazard ratios with 95% confidence intervals (CI) and P values from Cox regression analyses are provided. A two-sided P value of less than 0.05 was considered statistically significant. Statistical analysis was done with SPSS (Ver. 21.0, IBM, USA) and STATA/IC software (version 15.0; StataCorp LLC., USA).

3. Results

3.1. PVC and ablation characteristics

The patient, PVC, and procedure characteristics are summarized in Table 1. There were 58 patients (29 Male; age 42.7 ± 15.6 years) - one patient underwent RFA for 2 different PVCs and three patients underwent two procedures each. Indication for RFA was drug-refractory palpitations and/or dizziness in 51 patients. Three patients had recurrent unexplained syncope where a short-coupled PVC was implicated. The most common location for PVC was the right ventricular outflow tract (RVOT) which was followed by aortic sinuses of Valsalva (ASOV). In addition to PVCs, 15 patients had non-sustained ventricular tachycardia (NSVT) on Holter and 3 patients had documented sustained VT prior to the procedure. However, in all 3 cases sustained tachycardia was not inducible in the lab and so mapping and ablation were guided by PVCs.

3.2. Comparison between procedures with and without acceleration

An accelerated response was seen in 33/62 (53.2%) of overall procedures and 33/55 (60.0%) of the successful procedures. Patient and procedural characteristics were compared between procedures with and without accelerated response (Table 2). Patients in the acceleration group were significantly younger (38.7 ± 15.0 vs. 47.2 ± 15.2; P = 0.032). The accelerated response was less frequently seen in ASOV than other sites (11.1% vs. 60.4%; P = 0.009) and less frequently observed in patients with multiple PVC

Table 1
Patient and procedure characteristics.

Number of patients	58
Number of procedures	62
Age, yrs	42.7 ± 15.6
Male	29 (50.0)
Indication for the procedure	
Palpitations and/or dizziness	51 (87.9)
LV dysfunction	4 (6.9)
Syncope	3 (5.2)
Pre-ablation PVC burden, %	26.4 ± 12.5
Multiple PVC morphologies	12 (19.4)
PVC location	
RVOT	42 (67.7)
ASOV	9 (14.5)
Infravalvular LVOT / AMC	3 (4.8)
Mitral annulus	3 (4.8)
Tricuspid annulus	3 (4.8)
Anterior papillary muscle	3 (4.8)
Electroanatomical mapping	56 (90.3)
Irrigated-tip ablation catheter	58 (93.5)
Procedure time, hrs	3.0 (2.5 - 4.0)
Fluoroscopy time, min	36 (18 - 55)
Radiofrequency duration, min	17.7 (10.2 - 25.8)

Note: Data are mean ± standard deviation, number (%) or median (25th percentile - 75th percentile); **RVOT** - Right Ventricular Outflow Tract; **ASOV** - Aortic Sinuses of Valsalva; LVOT - Left Ventricular Outflow Tract; **AMC** - Aortomitral Continuity.

morphologies as compared to patients with single PVC morphology (25.0% vs. 65.0%; P = 0.029). Patient characteristics, pre-ablation PVC burden, presence of NSVT, irrigated-tip catheter use, and other ablation characteristics did not significantly differ between both the groups (Table 2).

3.3. Long term procedural outcome

Fifty-five (88.7%) procedures were acutely successful. Only procedures with acute success were included for analysis of long-term results (Table 3). Two patients were lost to follow-up and the remaining 53 patients were followed up for a median 14.0 months (IQR: 6.0–26.6 months). There were a total of 16/53 (30.2%) recurrences and the recurrence rate at 12 months was 20.3% (95% CI, 8.9–31.7%).

Recurrence occurred in significantly fewer patients in the group with acceleration than in the group without acceleration (4/32 patients [12.5%] vs. 12/21 patients (57.1%); log-rank P < 0.001). The unadjusted hazard ratio for recurrence was 0.16 (95% CI 0.05–0.50; Cox regression P = 0.002). The Kaplan-Meier recurrence rate estimates at 12 months were 6.5% (95% CI, 0–15.1%) in the acceleration group and 41.6% (95% CI, 19.4–63.8%) in the group without acceleration (Fig. 1.a.). Multivariable Cox regression was done by adjusting for age, sex, pre-ablation PVC burden, RVOT site, and multiple PVC morphologies. After adjustment for the other factors, the recurrence rate was significantly lower in patients with acceleration compared to those without (adjusted HR 0.17; 95% CI, 0.04–0.64; Cox regression P = 0.009).

The sensitivity and specificity of the presence of accelerated ventricular response to predict durable long-term success were 75.7% and 75.0%, respectively. Positive and negative predictive values were 87.5% and 57.2%, respectively. The overall accuracy was 75.5%.

Forty-one of the 53 patients who had an objective follow-up with 24-h Holter were analyzed separately (Table 4). In this subgroup, there were a total of 14 (34.2%) recurrences over a median follow-up of 13.4 (IQR: 5.5–26.4) months. Recurrence occurred in significantly fewer patients in the acceleration group than in the group without acceleration (4/25 patients [16.0%] vs. 10/16 patients [62.5%]; log-rank P = 0.002) and the unadjusted hazard ratio for recurrence was 0.19 (95% CI, 0.06–0.62; Cox regression P = 0.006). The recurrence rate at 12 months was 8.3% (95% CI, 0–19.3%) in the acceleration group and 46.2% (95% CI, 20.9–71.5%) in the group without acceleration (Fig. 1b). On multivariable Cox regression analysis, after adjustment for the same factors as above, the recurrence rate was significantly lower in patients with acceleration compared to those without (adjusted HR 0.13; 95% CI, 0.03–0.54; Cox regression P = 0.005).

4. Discussion

The main findings of our study are 1) accelerated response during RFA of PVCs was seen at the successful site in 60.0% of procedures, 2) the recurrence was significantly lower in patients who had accelerated response at the successful site compared to those without, and 3) the sensitivity and specificity of accelerated response to predict long-term success are reasonable.

Table 2
Characteristics of procedures with accelerated response and without accelerated response.

	No Accelerated Ventricular Response (n=29)	Accelerated Ventricular Response (n=33)	P value[a]
Age, yrs	47.2 ± 15.2	38.7 ± 15.0	0.032
Male	17 (58.6)	15 (45.5)	0.301
Pre-ablation PVC burden, %	28.7 ± 12.9	24.4 ± 12.0	0.188
Multiple PVC morphologies	9 (31.0)	3 (9.1)	0.029
Presence of NSVT on pre-ablation Holter	5 (17.2)	10 (30.3)	0.231
PVC location			
RVOT	17 (58.6)	25 (75.8)	0.150
ASOV	8 (27.6)	1 (3.0)	0.009
Infravalvular LVOT / AMC	0 (0)	3 (9.1)	0.241
Mitral annulus	2 (6.9)	1 (3.0)	0.595
Tricuspid annulus	2 (6.9)	1 (3.0)	0.595
Anterior papillary muscle	0 (0)	2 (6.1)	0.494
Irrigated-tip catheter	27 (93.1)	31 (93.9)	0.894
RF duration , min	19.1 (12.3 - 32.4)	16.6 (8.6 - 21.6)	0.117
Average power, Watts	33.1 ± 7.1	34.7 ± 8.4	0.453
Local EGM to QRS time, msec	31 ± 11	32 ± 8	0.874
Procedure time, hrs	3.0 (2.5 - 4.1)	3.0 (2.0 - 4.0)	0.300
Fluoroscopy time, min	35.5 (23.0 - 58.8)	36.0 (8.0 - 55.0)	0.954
Acute procedural success	22 (75.9)	33 (100.0)	0.003

Note: Data are mean ± standard deviation, number (%) or median (25th percentile - 75th percentile); **RVOT** - Right Ventricular Outflow Tract; **ASOV** - Aortic Sinuses of Valsalva; **LVOT** - Left Ventricular Outflow Tract; **AMC** - Aortomitral Continuity.

[a] P value for 'PVC location' was analyzed for that site vs. other sites.

Table 3
Long-term outcome analysis of patients with acute success (n = 53).

	Recurrence/ No Recurrence	Mean Time To Recurrence, Months (95 % CI)	Log-rank P Value	Univariate Analysis			Multivariable Cox Regression Analysis		
				HR	95% CI	P Value	HR	95% CI	P Value
Total Cohort	16/37	49.9 (37.1 - 62.8)	-	-	-	-	-	-	-
Sex									
Female	7/20	38.5 (28.9 - 48.1)		-	-	-	-	-	-
Male	9/17	48.8 (31.1 - 66.5)	0.638	1.27	0.47 - 3.41	0.639	0.59	0.18 - 1.96	0.387
Age	-	-	-	1.00	0.97 - 1.03	0.993	0.97	0.94 - 1.01	0.181
Pre-ablation PVC Burden, %	-	-	-	1.01	0.97 - 1.05	0.536	1.01	0.97 - 1.06	0.484
No. of PVC morphologies									
Single PVC morphology	9/34	57.8 (43.4 - 72.1)		-	-	-	-	-	-
Multiple PVC morphologies	7/3	17.2 (5.8 - 28.5)	0.002	4.28	1.57 - 11.63	0.004	3.15	0.84 - 11.75	0.088
Location									
Other locations	5/10	47.0 (21.5 - 72.6)		-	-	-	-	-	-
RVOT location	11/27	48.6 (35.5 - 61.6)	0.562	0.73	0.25 - 2.12	0.563	0.95	0.27 - 3.43	0.943
Acceleration									
No acceleration	12/9	22.4 (13.4 - 31.5)		-	-	-	-	-	-
Acceleration present	4/28	66.1 (50.8 - 81.4)	< 0.001	0.16	0.05 - 0.50	0.002	0.17	0.04 - 0.64	0.009

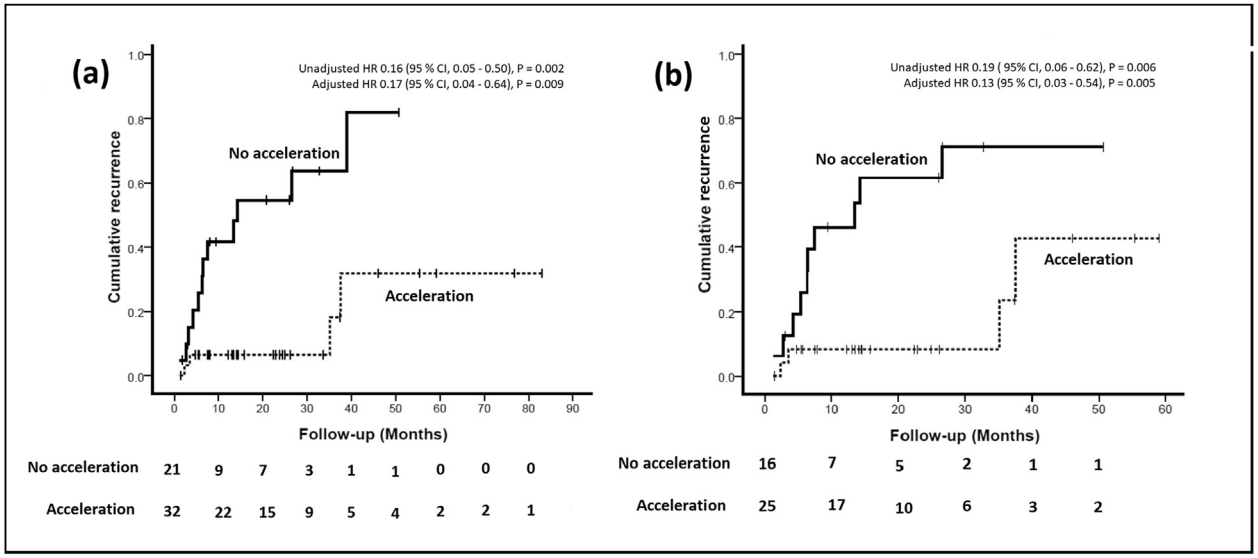

Fig. 1. Kaplan–Meier curves comparing recurrence in the groups with and without acceleration - **(a)** in all patients who had follow-up (n = 53), and **(b)** among patients who underwent Holter on follow-up (n = 41).

Table 4
Long-term outcome analysis of patients with ambulatory ECG monitoring (n = 41).

	Recurrence/ No recurrence	Mean Time To Recurrence, months (95 % CI)	Log-rank P Value	Univariate Analysis			Multivariable Cox Regression Analysis		
				HR	95% CI	P Value	HR	95% CI	P Value
Total	14/27	36.2 (27.2 - 45.2)	-	-	-	-	-	-	-
Sex									
Female	7/15	36.8 (26.6 - 47.0)		-	-	-	-	-	-
Male	7/12	36.3 (23.3 - 49.3)	0.554	1.38	0.48 - 4.00	0.556	1.02	0.28 - 3.70	0.973
Age	-	-	-	0.98	0.95 - 1.02	0.383	0.96	0.92 - 1.00	0.054
Pre-ablation PVC burden, %	-	-	-	1.01	0.96 - 1.07	0.656	1.01	0.96 - 1.06	0.659
No. of PVC morphologies									
Single PVC morphology	9/25	40.1 (30.4 - 49.7)		-	-	-	-	-	-
Multiple PVC morphologies	5/2	13.0 (2.9 - 23.0)	0.008	4.17	1.34 - 13.01	0.014	3.44	0.69 - 17.11	0.131
Location									
Other locations	5/7	22.4 (13.5 - 31.4)		-	-	-	-	-	-
RVOT location	9/20	39.0 (28.9 - 49.1)	0.290	0.55	0.18 - 1.70	0.297	1.03	0.24 - 4.4	0.964
Acceleration									
No acceleration	10/6	21.6 (11.2 - 32.0)		-	-	-	-	-	-
Acceleration present	4/21	46.7 (36.5 - 56.8)	0.002	0.19	0.06 - 0.62	0.006	0.13	0.03 - 0.54	0.005

Radiofrequency ablation induced accelerated response was seen in about two-thirds of the successful locations in this study. This is comparable to what was reported previously for the RVOT [9]. Accelerated response during RFA is thought to be due to a heat-induced increase in the slope of phase 4 of the action potential in cells that exhibit intrinsic automaticity [16,17]. In animal models, even in cells that did not exhibit intrinsic automaticity, abnormal automaticity was observed at temperatures >45 °C probably due to the effect of heat on membrane fluidity [18]. Between 45 °C to 50 °C this effect was reversible before the irreversible injury occurred at > 50 °C. However, it is unclear why some sites without spontaneous automaticity show an acceleration in response to RFA while others do not. Acceleration was less frequent in ASOV foci compared to other sites in this study. We propose a few possibilities to explain the above findings. First, it is likely that all PVC inducing cells are not responsive to a thermal stimulus. Second, the mass of arrhythmic tissue in some cases may be small, leading to prompt disappearance of PVCs as soon as the RF energy delivery is started. Third, the depth of the focus may play a role. Cells that are immediately underneath the catheter may reach adequate temperatures very rapidly causing instantaneous injury. In deeper layers, the temperature rise can be more gradual producing automaticity before irreversible damage occurs. It is known that ventricular arrhythmias ablated in the aortic cusps arise from thin myocardial sleeves extending into great arteries [19–21]. So the lesser incidence of acceleration in ASV sites could be due to small mass and superficial location of arrhythmic tissue as opposed to larger and deeper foci at other endocardial sites [22].

Long-term recurrence occurred in about a third of the patients and recurrence was significantly lower in patients who had accelerated response at the successful site. This supports our hypothesis that acceleration is a marker of the catheter being in the “right place” and the arrhythmic tissue was targeted. This response had good positive predictive value for long-term success. However, the negative predictive value was low. Chinushi et al. observed that the repetitive ventricular response was frequently seen in RFA of ventricular arrhythmias from RVOT. In their study, they were more frequent in ventricular arrhythmias ablated from a wide area compared to VA from a narrow area [9]. They did not assess its prognostic value but they hypothesized that each RF application possibly diminishes the arrhythmogenic mass leading to slower and less frequent acceleration and finally eliminated the arrhythmogenic tissue. Our finding of less recurrence when acceleration was seen is consistent with that. However, we did not analyze the changing pattern of acceleration with successive ablations in this study.

To our knowledge, this phenomenon of accelerated response was not formally studied in the setting of PVC ablation. The sensitivity and specificity of accelerated response as a marker of long-term outcomes were reasonable. In this study, the response had good positive predictive value but low negative predictive value. So its clinical utility for targeting ablation or deciding on delivering further lesions, like it is used during ablation of slow-pathway in AVNRT, may be limited. Nevertheless, it gives a sense of “being in the right place” and can be a useful marker of long-term outcomes. If validated in a larger prospective cohort, its appearance can be useful in prompting the operator to alter factors that improve lesion formation at the same focus i.e. increasing power or temperature to target a better impedance drop or attaining better catheter stability, rather than changing the site.

4.1. Limitations

There are all the limitations inherent to a single-center retrospective study. The initial power selected, temperature cut-off, duration of the lesion, and power titration were operator dependent and the power titration was not standardized. The presence or absence of automaticity can be significantly affected by the rate of increase in temperature. Similarly, adequate lesion formation can be affected by catheter stability. All the above procedure-related factors could be potential confounders. This cohort consists predominantly of RVOT PVCs and other PVC sites are too few to draw meaningful conclusions about non-RVOT sites. The positive and negative predictive values of accelerated response to predict long-term outcomes should be interpreted with caution due to the small sample size and low recurrence rate.

5. Conclusions

Accelerated ventricular response during RFA of PVCs was seen at a successful site in about two-thirds of procedures. The recurrence after PVC ablation is significantly lower when an accelerated response was observed at a successful location. The presence of accelerated response can be an additional useful marker of long-term outcome after RFA for PVCs. The usefulness and the implications during catheter ablation need to be validated in a larger prospective cohort.

Declaration of competing interest

The authors declare no conflict of interest for this study.

Acknowledgments

The authors are grateful to Ms. Gowri for her role in statistical analysis and thank Ms.Rintu Tisho James and Ms.Suganya for their assistance in collecting patient follow-up data.

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