Circadian variability patterns predict and guide premature ventricular contraction ablation procedural inducibility and outcomes

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BACKGROUND Infrequent intraprocedural premature ventricular complexes (PVCs) may impede radiofrequency catheter ablation (RFA) outcome, and pharmacologic induction is unpredictable.

OBJECTIVE The purpose of this study was to determine whether PVC circadian variation could help predict drug response.

METHODS Consecutive patients referred for RFA with detailed Holter monitoring and frequent monomorphic PVCs were included. Patients were divided into 3 groups based on hourly PVC count relationship to corresponding mean heart rate (HR) during each of the 24 hours on Holter: fast-HR-dependent PVC (F-HR-PVC) type for a positive correlation (Pearson, $P < .05$), slow-HR-dependent PVC (S-HR-PVC) type for a negative correlation, and independent-HR-PVC (I-HR-PVC) when no correlation was found.

RESULTS Fifty-one of the 101 patients (50.5%) had F-HR-PVC, 39.6% I-HR-PVC, and 9.9% S-HR-PVC; 30.7% had infrequent intraprocedural PVC requiring drug infusion. The best predictor of infrequent PVC was number of hours with PVC count <120/h on Holter (area under the curve 0.80, sensitivity 83.9%, specificity 74.3%, for ≥2 h). Only F-HR-PVC patients responded to isoproterenol. Isoproterenol washout or phenylephrine infusion was successful for the 3 S-HR-PVC patients, and no drug could increase PVC frequency in the 12 I-HR-PVC patients. Long-term RFA success rate in patients with frequent PVCs at baseline (82.9%) was similar to those with infrequent PVC who responded to a drug (77.8%; $P = .732$) but significantly higher than for those who did not respond to any drug (15.4%; $P < .0001$).

CONCLUSION A simple analysis of Holter PVC circadian variability provides incremental value to guide pharmacologic induction of PVCs during RFA and predict outcome. Patients with infrequent I-HR-PVC had the least successful outcomes from RF ablation.

KEYWORDS Autonomic nervous system; Circadian profile; Isoproterenol; Premature ventricular complexes; Radiofrequency ablation

ABBREVIATIONS **AUC** = area under the curve; **EPS** = electrophysiological study; **F-HR-PVC** = fast-heart rate–dependent premature ventricular contraction; **HR** = heart rate; **I-HR-PVC** = independent-heart rate–premature ventricular contraction; **LVEF** = left ventricular ejection fraction; **PVC** = premature ventricular contraction; **RFA** = radiofrequency catheter ablation; **S-HR-PVC** = slow-heart rate–dependent premature ventricular contraction

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Introduction

Premature ventricular contractions (PVCs) are frequently encountered in clinical practice and may cause symptoms, lead to cardiomyopathy,[1,2] or even cause sudden cardiac death.[3,4] Radiofrequency catheter ablation (RFA) of PVCs is routinely performed, aiming to prevent these risks and manage drug-refractory symptoms.[5]

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However, infrequent intraprocedural PVCs make activation mapping difficult, impeding the ablation procedure and resulting in reduced short- and long-term ablation success rates.[6] Pace-mapping is of limited value as an alternative approach. Isoproterenol, sometimes in combination with pacing maneuvers, is used in such instances to increase intraprocedural PVC frequency. Successful induction of PVCs with isoproterenol has been reported in <50% of cases,[6] and no specific criteria have been developed to predict the likelihood of success. In addition to its unreliability in enhancing PVC frequency, isoproterenol is a very expensive drug in the United States (~$1,200 per dose) and in rare instances may lead to serious complications.[7,8]

Idiopathic PVCs are thought to be mainly sympathetically mediated, making the use of isoproterenol to increase intraprocedural PVC burden a rational strategy. However, the circadian distribution of PVCs is highly variable between patients, suggesting a more complex autonomic neural control. A subset of patients seems to have a preferentially higher burden during daytime as heart rate (HR) accelerates (eg, exercise, stress), whereas PVCs are suppressed at night or rest. However, some patients have the opposite distribution pattern, in which PVCs are mainly present at night or rest but are infrequent during the day or with activity. A third group of patients do not seem to have PVC frequency linked to any discernable circadian distribution or HR changes.

We hypothesized that PVC circadian variation could help predict (1) which patients may have infrequent intraprocedural PVCs; and (2) the likelihood of drug (ie, isoproterenol) response when used to increase PVC frequency to allow activation mapping. In addition, we sought to describe patient clinical characteristics associated with each PVC profile, to assess possible mechanistic and clinical implications.

Methods

Patient characteristics

Retrospective data collection was approved by the local institutional review boards at 5 international centers. Between December 2013 and May 2016, 101 consecutive patients with detailed 24-hour Holter monitoring and frequent idiopathic monomorphic PVCs referred for RFA were included in the study. Patients with cardiomyopathy were excluded if the PVCs were thought to be secondary to the underlying cardiomyopathy (ie, scar-related). Cases of cardiomyopathy due to a high burden of PVCs were included as long as alternative etiologies of cardiomyopathy, such as severe obstructive coronary artery or significant valvular disease, were ruled out.

Patient classification based on Holter PVC circadian distribution

Patients were divided into 3 groups based on their hourly PVC relationship to the corresponding mean HR during preprocedural Holter monitoring (Figure 1). When their hourly PVC number had a positive correlation with mean HR (Pearson, *P*

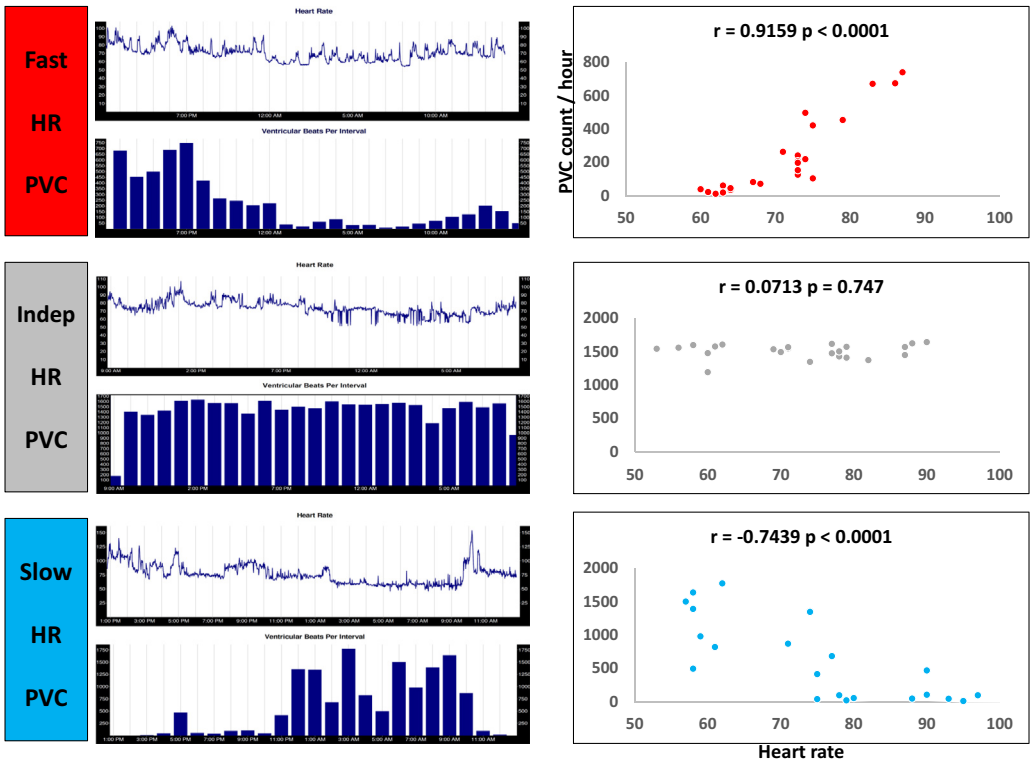

Figure 1 Holter example of the 3 PVC circadian profiles. **Left:** Panels generated by Holter software represent mean HR **(top)** and PVC count/hour **(bottom)** over 24 hours. **Right:** Panels represent PVC count (y) over mean HR (x) distribution (correlation) derived from Holter hourly summary raw data. HR = heart rate; PVC = premature ventricular contraction.

<.05), they were defined as fast HR-dependent PVC (F-HR-PVC) type. Those with a negative correlation were defined as slow HR-dependent PVC (S-HR-PVC) type. Patients with no statistical link between PVC number and mean HR were defined as independent-HR-PVC (I-HR-PVC).

Ablation procedure

Antiarrhythmic drugs other than amiodarone were discontinued at least 5 half-lives before ablation. Amiodarone was usually stopped approximately 6 weeks before ablation per institutional protocols. Intravenous sedation was minimized as tolerated to avoid anesthesia-related PVC suppression. Isoproterenol infusion was used as needed to induce PVCs when judged by the operator to be too infrequent for activation mapping, often after attempting burst pacing induction as well as decrease in intravenous sedation as tolerated. Mapping of the PVC origin was performed, targeting the earliest site of activation compared with the onset of the surface PVC QRS complex, after which RFA was attempted using standard or irrigated radiofrequency energy after excluding proximity to a major coronary artery or the conduction system. In most cases, ablation was facilitated by use of a 3-dimensional electroanatomic mapping systems (CARTO, Biosense Webster, Diamond Bar, CA; or Nav-X (St. Jude Medical, Minneapolis, MN). Acute procedural success was defined as the absence of spontaneous or inducible clinical PVCs after a waiting period of at least 30 minutes following the successful RF application, either at baseline or after isoproterenol infusion if required to induce PVCs prior to ablation.

Baseline evaluation and follow-up

The most recent detailed baseline Holter monitoring including hourly PVC count and mean HR was analyzed. Transthoracic echocardiography was also performed before ablation to assess left ventricular ejection fraction (LVEF), quantified by using the Simpson biplane formula in sinus rhythm after at least 3 consecutive sinus beats.

At least 1 postablation Holter recording was obtained at each institution to document intermediate- to long-term success, and echocardiography was commonly repeated once or twice per year for patients with initial impaired LVEF, until normalization or stabilization. Long-term ablation success was defined as >80% decrease in Holter PVC burden associated with symptom improvement at ≥3 months when available.[9] As previously described, a PVC-induced cardiomyopathy was defined as LVEF <50% that normalized after successful RFA.[10]

Data collection

Surface ECGs from the diagnostic electrophysiological study (EPS) were analyzed using electronic calipers at a sweep speed of 100 mm/s. Only the clinical PVC was studied. At baseline, PVC count per minute was averaged over 5 minutes before catheter insertion. Other measurements included PVC coupling (averaged 6 consecutive PVCs when possible), coupling variability (max–min), and sinus beat RR and QT intervals.

Infrequent intraprocedural PVCs was defined as a burden preventing adequate activation mapping (usually ≤1 or 2 PVC/min),[6] requiring isoproterenol infusion. When isoproterenol was used, the same parameters were collected at peak response. If isoproterenol could not increase PVC frequency, we again analyzed the same parameters during the washout period, which was defined as the time period when HR was decreasing, between isoproterenol cessation until return to baseline conditions. Finally, in 1 center (UCLA), when PVCs were not sustainably present at baseline or during isoproterenol infusion/washout, phenylephrine (repeated boluses) was used in order to obtain a 25% increase in systolic blood pressure (~30 mm Hg) triggering a vagal response decreasing HR (~10%). Again, PVC frequency, coupling, and RR and QT intervals were measured during maximal drug effect. A significant response to drug was defined as an increase in PVC frequency allowing comfortable mapping (≥5 PVC/min).

Statistical analysis

Normally distributed variables are expressed as mean ± SD and compared using the Student *t* test or Mann–Whitney's *U* test, as appropriate. Categorical variables are expressed as count and percentage and were compared using the χ^2 test or Fisher exact test as appropriate. Receiver operating characteristic (ROC) curves were constructed to determine the cutoff value, sensitivity (Se), and specificity (Spe) of variables associated with infrequent intraprocedural PVCs. The area under the curve (AUC) was measured to discriminate the power of each parameter. To test whether there was a linear correlation between the 24-hour Holter hourly mean HR and their corresponding PVC frequencies, the Pearson correlation test was used to assess the strength of this relationship and to classify patients into the F-HR-PVC, S-HR-PVC, or I-HR-PVC group given a positive (P <.05), negative (P <.05), or no correlation (P = NS) was found, respectively. PVC count/min values at baseline vs during drug infusions were compared using the paired *t* test or Wilcoxon test as appropriate. Analysis of variance model was used to compare patient characteristics among the 3 subgroups. P <.05 was considered significant. Analyses were performed using SPSS Version 16.0 (SPSS Inc, Chicago, IL).

Results

One hundred one consecutive patients were included in this study. Clinical characteristics are summarized in Table 1. Most patients referred for ablation were symptomatic (87.1%), with decreased LVEF (<50%) in 21.8% of cases. According to baseline Holter monitoring, the most common circadian PVC profile was an F-HR-PVC type, found in half (50.5%) of our patients (r = 0.68 ± 0.17), followed by I-HR-PVC (39.6%; r = 0.09 ± 0.21) and S-HR-PVC (9.9%; r = –0.56 ± 0.15) profiles. Pharmacologic therapy had been prescribed before the index ablation in 75.2%, mainly beta-blockers (66.3%), and 28.7% had undergone at least 1 previous ablation attempt before the index

Table 1 Baseline characteristics (n = 101)

Age (yrs)	49.9 ± 16.9
Male	57 (56.4)
LVEF (%)	55.5 ± 12.1
Symptoms	88 (87.1)
Palpitations	76 (75.2)
Dyspnea	23 (22.8)
Sustained ventricular tachycardia	1 (1.0)
Syncope	3 (2.9)
Nonsustained ventricular tachycardia	8 (7.9)
PVC burden (%)	19.7 ± 12.3
SDNN (ms)	145.2 ± 51.6
SDANN	113.2 ± 38.4
Fast-HR-PVC	51 (50.5)
Independent-HR-PVC	40 (39.6)
Slow-HR-PVC	10 (9.9)
Drug before ablation	76 (75.2)
Beta-blocker	67 (66.3)
CCB	12 (11.9
Class I AAD	17 (16.8)
Amiodarone	5 (4.9)
Other	5 (4.9)
PVC origin	
RVOT	44 (43.6)
Parahisian/intraseptal	9 (8.9)
Tricuspid annulus	2 (2.0)
Other RV endo	4 (4.0)
LVOT	18 (17.8)
Mitral annular	7 (6.9)
Papillary muscle	2 (2.0)
Other LV endo	6 (5.9)
Epicardial	7 (6.9)
Unknown	2 (2.0)

Values are given as n (%) or mean ± SD.

AAD = antiarrhythmic drug; CCB = calcium channel blocker; HR = heart rate; LV = left ventricle; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; PVC = premature ventricular contraction; RV = right ventricle; RVOT = right ventricular outflow tract; SDANN = standard deviation of the average NN interval; SDNN = standard deviation of the NN interval.

procedure; this subgroup had similar baseline characteristics. The right outflow tract (43.6%) and left outflow tract (17.8%) were the most common PVC origins (Table 1). We could not identify a significant relationship between the different circadian PVC profiles and the PVC origin.

Predictors of infrequent intraprocedural PVCs

Almost one-third of our patient population (30.7%) had infrequent intraprocedural clinical PVC requiring drug infusion for activation mapping. These patients had a dramatically lower PVC count at the beginning of EPS compared to those who did not require drug infusion (1.1 ± 1.9 PVC/min vs 16.4 ± 9.7 PVC/min; $P < .0001$). Of note, they also had a significantly lower baseline HR during EPS (68.4 ± 12.9 vs 77.7 ± 13.1; $P = .001$), even though mean HR was similar between the 2 groups on Holter recordings (74.3 ± 11.3 vs 74.8 ± 11.3; $P = .953$) and they had undergone similar anesthesia protocols.

Approximately one-third of patients with infrequent intraprocedural PVCs were present in each PVC profile group (31.4% of F-HR-PVC, 30% of I-HR-PVC, and 30% of S-HR-PVC types; $P = .989$). The best predictor of infrequent intraprocedural PVC was the number of hours with PVC count <120/h (AUC 0.80; $P < .0001$; Se 83.9%, Spe 74.3% for cutoff ≥2 hours) on Holter monitoring. The overall PVC burden (%) was the second most powerful but the most specific predictor (AUC 0.77; $P < .0001$; Se 67.7%; Spe 75.7% for cutoff ≤11.7%) (Table 2).

Impact of PVC circadian profile on intraprocedural drug response

Among patients with infrequent intraprocedural PVC (n = 31), 58.1% had a favorable response to at least 1 drug (Table 3). All patients who responded to isoproterenol (48.4%) (Figure 2) had an F-HR-PVC profile (r range 0.395–0.845; $P < .05$), and isoproterenol was successful in all but 1 patient in this group, in whom polymorphic nonclinical PVCs were induced. Of note, the magnitude of the PVC frequency response on isoproterenol in this group was not associated with the strength of the correlation coefficient (r) ($P = .489$) or to the intensity of the HR increase ($P = .545$). Isoproterenol washout or phenylephrine was successful for the 3 patients with an S-HR-PVC type (r range –0.350 to –0.480; $P < .05$), No drug could increase PVC frequency in the 12 patients with an I-HR-PVC profile (r range –0.315 to 0.359; P = NS). Of note, the minimum cycle length at the peak response of isoproterenol was similar in patients who responded and those who did not (545 ± 112 ms vs 486 ± 66 ms; $P = .153$). Examples of successful drug responses to isoproterenol and phenylephrine are shown in Figure 3.

PVC ablation outcome and impact of PVC frequency during EPS

After mean follow-up of 9 ± 7 months, ablation success was achieved in 73.3% of patients. Mean PVC burden in this group was 0.4% ± 1.4%, and none of these patients remained symptomatic. Intensification of medical therapy after failed ablation resulted in significant PVC suppression in 4

Table 2 Predictors of infrequent intraprocedural PVC during EPS requiring drug trial

	Patients with infrequent intraprocedural PVC (n = 31)	Patients without infrequent intraprocedural PVC (n = 70)	*P* value	AUC	Cutoff	Se	Spe
Holter-PVC burden (%)	12.2 ± 10.1	23.0 ± 11.8	<.001	0.77	≤11.7	67.7	75.7
Holter-lowest hourly PVC count (n/h)	120 ± 342	362 ± 462	<.001	0.74	≤88	82.8	65.2
Holter-hours (n) with PVC <120/h	7.4 ± 7.1	1.8 ± 3.3	<.001	0.80	≥2	83.9	74.3
EPS baseline mean heart rate	68.4 ± 12.9	77.7 ± 13.1	.001	0.69	≤78	86.7	49.3

Values are given as mean ± SD unless otherwise indicated.

AUC = area under the curve; EPS = electrophysiological study; PVC = premature ventricular contraction; Se = sensitivity; Spe = specificity.

Table 3 Response to different drugs during EPS in patients with infrequent intraprocedural PVC at baseline

Patients needing drug infusion	Isoproterenol infusion	Isoproterenol washout	Phenylephrine infusion	Epinephrine infusion
All n (% success)	15/31 (48.4)	3/16 (18.7)	1/9 (11.1)	0/6 (0)
Fast-HR-PVC	15/16 (93.7)	0/1 (0)	0/1 (0)	Ø
Independent-HR-PVC	0/12 (0)	0/12 (0)	0/7	0/6 (0)
Slow-HR-PVC	0/3 (0)	3/3 (100)	1/1 (100%)	Ø

Values are given as n/N (%). Ø = Drug not used. Abbreviations as in Table 1.

additional patients; therefore, overall clinical success in our patient cohort was 77.2%. The highest ablation success rate (82.9%) was obtained for patients with frequent PVCs at baseline (Figure 4). Importantly, ablation success was not significantly different in the group of patients with infrequent PVC at baseline who responded to a drug (77.8%; $P = .732$) but was dramatically lower in those who did not respond to any drug (15.4%; $P < .0001$). Therefore, PVC frequency during EPS (spontaneous or on drug) was an important determinant of ablation success (AUC 0.82; $P < .0001$; Se 83.8%; Spe 74.1% for cutoff >7 PVC/min). Lastly, PVC origin was also associated with procedural outcome, with mitral annulus, parahisian, papillary muscles, and epicardial foci displaying the poorest outcome. PVC-cardiomyopathy could be diagnosed with confidence (successful ablation, with mean LVEF recovering from 35% ± 9% to 53% ± 8%) in 13 patients (12.9%); 6 (11.8%) from the F-HR-PVC group, 6 (15%) from the I-HR-PVC group, and 1 (10%) from the S-HR-PVC group ($P = .868$).

Discussion

Main findings

This is the first study assessing the impact of PVC circadian variation on procedural outcome, including drug responses. Our main findings are as follows.

1. There are 3 distinct PVC profiles based on the correlation of hourly PVC frequency distribution to HR changes, and a significant positive correlation (F-HR-PVC) characterized 50% of cases.
2. Infrequent intraprocedural PVCs affected about one-third of patients and may reduce ablation success. PVC burden (≤11.7%) and at least 2 hours with <120 PVCs on a 24-hour ECG Holter recording best predicted patients for whom ablation was likely to be unsuccessful.
3. Infrequent intraprocedural F-HR-PVC types likely responded to isoproterenol and S-HR-PVC types to washout or phenylephrine, but no drug could increase PVCs in the I-HR-PVC type.

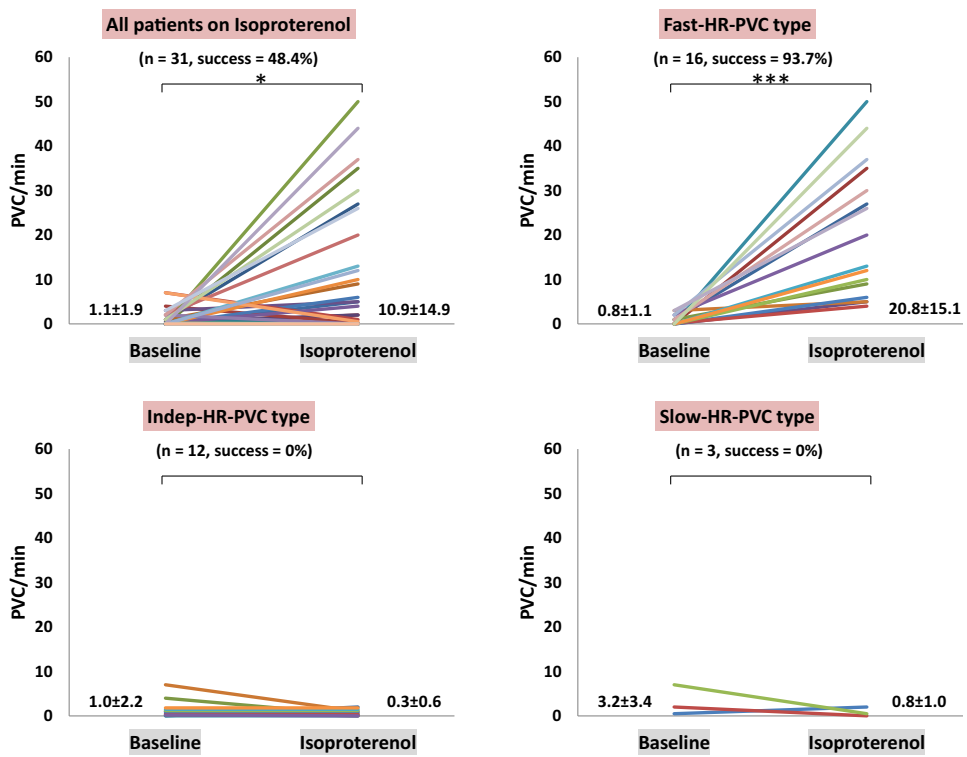

Figure 2 Isoproterenol response in patients with infrequent intraprocedural PVC. Representation of the PVC frequency (PVC/min) during electrophysiological study at baseline and during isoproterenol infusion in all patients with infrequent PVC and the subgroups of patients with infrequent intraprocedural PVC(Fast-HR; Indep-HR and Slow-HR PVC). Each line represents a different patient. HR = heart rate; PVC = premature ventricular contraction.

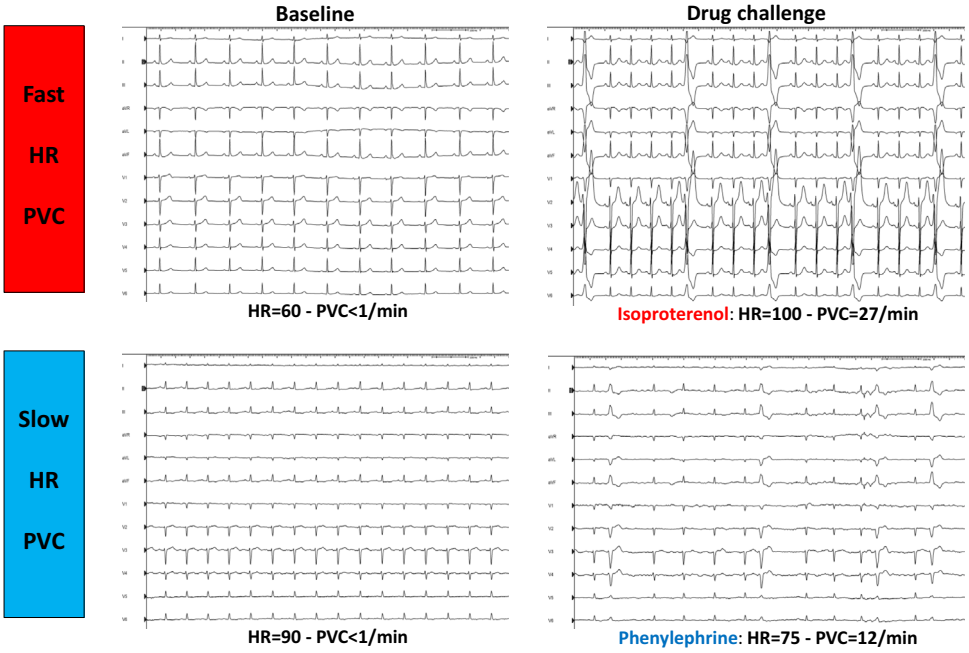

Figure 3 Example of drug response to isoproterenol for F-HR-PVC and to phenylephrine for S-HR-PVC. The first patient (F-HR-PVC) had no PVC spontaneously present at baseline, but PVC frequency increased dramatically during isoproterenol infusion, allowing mapping. Likewise, the second patient (S-HR-PVC) had very infrequent PVCs at baseline but also during isoproterenol infusion, and phenylephrine could successfully increase its frequency. Therefore, the 2 patients had successful ablations. F =fast; HR = heart rate; PVC = premature ventricular contraction; S = slow.

4. Patients with drug response had similar intermediate-term ablation success rates as patients with frequent PVCs at baseline, whereas patients in whom drugs failed to increase PVCs (ie, infrequent I-HR-PVC type) displayed a poor outcome.

PVC ablation has been used to manage drug-refractory symptoms and has become the preferred approach to treat and prevent PVC-induced cardiomyopathy.[5] Long-term PVC suppression is essential for total and durable recovery because a delayed recurrence of frequent PVCs has been reported to result in recurrence of PVC-induced cardiomyopathy.[11] A classically described cause of RFA failure is the inability to reach the site of origin for technical or anatomic reasons. However, another important cause, independent of PVC location, is insufficient intraprocedural PVCs for mapping,[6] which leads to the inability to precisely identify the site of origin. Some operators then use pace-mapping as a surrogate, which has poor spatial resolution and lacks a reliable procedural endpoint.

Baser et al[6] reported that patients with a PVC count <32 during the first 30 minutes of a procedure had lower success rates at 3 months. Similarly, they found that approximately one-third of their patients were affected by low burden at baseline and that most of those patients (59%) did not respond to isoproterenol. The current study provides data that will help predict which patients are at risk for infrequent intraprocedural PVCs and, more importantly, in which cases an increase in PVC frequency can be expected in response to drug (and to which drugs). In our study, patients who had a pharmacologic response had a better clinical outcome compared to those who did not (Figure 4).

Autonomic involvement in arrhythmogenesis is well established.[12] In this study we report distinct circadian PVC profiles. I-HR-PVC suggests a pathogenesis likely independent of autonomic variation, whereas the F-HR-PVC type

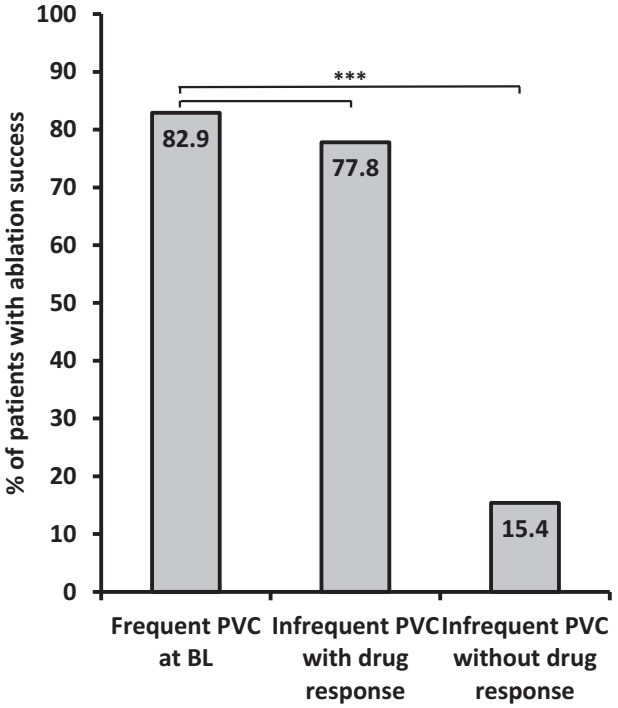

Figure 4 Impact of PVC frequency during electrophysiological study on ablation outcome. ***P <.0001. BL = baseline; PVC = premature ventricular contraction.

is evoked by adrenergic triggers and the S-HR-PVC type is evoked by vagal triggers. Increased sympathetic and parasympathetic activity estimated through HR variability parameters has been specifically described during the onset of PVCs displaying these respective profiles.[13] The fact that patients with F-HR-PVC responded with increased PVC frequency to isoproterenol, a $beta_2$-receptor agonist, which has been used for decades to reproduce sympathetically mediated arrhythmias, further supports this concept.

Phenylephrine, an α-adrenergic agonist, induces a vagal baroreflex activation, mediated through an acute rise in blood pressure following vasoconstriction.[14] Attempts to induce arrhythmias with this drug in patients with Brugada syndrome have been made in the past, because these patients are at risk for sudden cardiac death, specifically at rest.[15] Because only 3 patients with the S-HR-PVC type required drug infusion and phenylephrine was used in only 1 center, in this study we report only 1 attempt. Nonetheless, we believe it is a promising patient-customized approach for increasing PVC frequency during mapping in this subgroup that should be evaluated further. This specific patient had a mild (6/min) and temporary (≤1 min) increase of PVC during isoproterenol washout that was more intense and more sustained with phenylephrine infusion (12/min until RF delivery). Isoproterenol washout corresponds to a more complex situation mimicking exercise recovery, during which, while sympathetic drive is decreasing, parasympathetic drive is progressively increasing in healthy subjects.[16] Therefore, the suitable autonomic balance targeted to increase PVC frequency in the S-HR-PVC group may be achieved for only a brief period. Nonetheless, we could successfully use this technique for the 2 other patients requiring drug challenge is this subgroup.

There are several possible mechanistic explanations for how increased vagal tone could increase PVC frequency. In the setting of a normally automatic focus surrounded by a region of depressed excitability (ie, allows entrance block but not always exit block), a slower sinus rate may result in appearance of PVCs without any change in the underlying substrate (modulated parasystole). Furthermore, increased vagal activity has been shown to prolong ventricular action potential duration[17] and to transiently elicit inexcitable zones near an ectopic pacemaker in atrial tissue. Thus, it may protect it from conducted sinus impulses and, in the setting of slow HR, may result in spontaneous discharges likely manifested as late coupled PVCs.[18]

In this study, no differences in mean coupling interval, coupling interval variability, or PVC location between subgroups was found that could have helped decipher the plausible pathophysiology linked to each subtype (Table 4). It is noteworthy that although recent studies shed light on some of the pathophysiological aspects and consequences of the coupling interval and its variability, it remains a complex interaction not yet fully elucidated.[3,19] Nonetheless, similar to vagally mediated atrial fibrillation, patients in the S-HR-PVC subgroup were significantly younger; therefore, increased normal automaticity (of a focus) is a likely plausible mechanism (unlike reentry or afterdepolarizations) in this subgroup of "healthier" patients.

Clinical implications

This study, based on detailed analysis of PVC circadian variation on Holter monitoring allowing classification into 3 distinct subgroups, provides a simple clinical tool that may guide ablation management in patients with frequent PVCs. Furthermore, it may help inform patients about a more realistic and customized outcome estimation.

Mapping in F-HR-PVC (r ≥0.4) patients with a high likelihood of infrequent intraprocedural PVCs should be

Table 4 Patient/PVC characteristics in the 3 subgroups

	Fast-HR PVC [N (%)]	Independent-HR PVC [N (%)]	Slow-HR PVC [N (%)]	
	51 (50.5)	40 (39.6)	10 (9.9)	*P* value
Age	52.7 ± 17.4	50.1 ± 14.9	34.3 ± 12.8	.006
Male	28 (54.9)	24 (60)	5 (50)	.848
PVC burden (%)	20.4 ± 13.2	19.3 ± 11.6	18.0 ± 11.0	.820
LVEF (%)	55.2 ± 12.3	55.7 ± 12.2	56.5 ± 7.3	.946
PVC/min at baseline	10.5 ± 10.8	12.1 ± 10.5	13.5 ± 12.5	.484
Mean coupling	485.3 ± 69.3	478.4 ± 70.7	463.4 ± 83.8	.669
Coupling variability (max-min)	63.0 ± 70.9	63.3 ± 43.8	36.4 ± 42.0	.451
PVC localization				NS
RVOT	21 (41.2)	17 (42.5)	6 (60)	
Parahisian/intraseptal	4 (7.8)	4 (10.0)	0 (0)	
Tricuspid annulus	1 (2.0)	1 (2.5)	0 (0)	
Other RV endo	3 (5.9)	1 (2.5)	1 (10)	
LVOT	9 (17.6)	8 (20.0)	1 (10)	
Mitral annular	2 (3.9)	1 (2.5)	0 (0)	
Papillary muscle	1 (2.0)	1 (2.5)	0 (0)	
Other LV endo	6 (11.8)	2 (5.0)	2 (20.0)	
Epicardial	4 (7.8)	3 (7.5)	0 (0)	
Unknown	0 (0)	2 (5.0)	0 (0)	

Values are given as mean ± SD or n (%). Abbreviations as in Table 1.

managed with isoproterenol use. Likewise, for slow-HR-PVC ($r \leq -0.35$), phenylephrine may be useful, but further data are needed. However, I-HR-PVC patients with infrequent intraprocedural PVCs have a low likelihood of success, as our data demonstrate that no commonly used drug can induce PVCs in these cases. Therefore, when patients are known to have I-HR-PVCs, we believe PVC frequency should be monitored before EPS and the procedure potentially rescheduled when PVC burden is not sufficient at the time. In addition, we believe that these data can be made easily accessible to clinicians by having Holter software automatically generate the PVC/HR correlation coefficient and displaying it on reports.

An additional point can be made regarding procedural cost. In many centers after ablation of the targeted PVC, isoproterenol is used to test whether PVCs can be reinduced, regardless of whether the drug was needed to allow for mapping. Knowing that isoproterenol is effective in <50% of cases and only in the F-HR-PVC subgroup, it should not be used postablation, except in these specific cases. Knowing when isoproterenol can be useful ahead of time has the potential to save both time and procedural cost.

Study limitations

This is a retrospective study. Because isoproterenol always increased PVC frequency in the setting of infrequent F-HR-PVC, phenylephrine was not tested in the subgroup. Different drug administration approaches (bolus vs continuous infusions, maximal dose, etc) were used in the different centers in this study; nonetheless, the infusion protocol did not seem to interfere with drug responses, and this likely increases the applicability of our results to centers using different ablation protocols for management of PVCs. Predictors of infrequent intraprocedural PVCs as well as our circadian variation PVC classification were based a single Holter monitor recording before the ablation procedure, yet inter-Holter PVC burden variability has been described in patients with repeated Holter recordings. More specifically, whether the correlation between PVC frequency and HR could vary between different Holter monitoring sessions and whether a patient could have several PVCs displaying different circadian profiles remain unclear and should be the focus of further research. Our classification that was developed based on Pearson correlation to identify a linear correlation between the hourly mean HR and PVC frequency may not identify unusual associations such as PVC frequency concentrated during a very narrow range of HR or specific moments of the day and therefore classify them as I-HR-PVC. It is noteworthy that PVCs were not excluded from the mean HR count that is automatically generated by Holter software. Nonetheless, interpolated PVCs were not common; therefore, PVC presence did not affect the mean HR calculation.

Conclusion

A simple analysis of Holter PVC circadian variability may provide incremental value to predict infrequent intraprocedural PVCs, guide pharmacologic induction of PVCs during RFA, and predict outcome. Patients with infrequent F-HR-PVC or S-HR-PVCs have a high likelihood of successful ablation when PVC frequency can be pharmacologically enhanced, whereas those with infrequent I-HR-PVC have a low ablation success rate regardless of intervention when infrequent baseline PVCs are present.

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