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# Malignant Purkinje ectopy induced by sodium channel blockers

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**BACKGROUND** Sodium channel blocker (SCB) infusion is used to unmask the electrocardiographic pattern of Brugada syndrome. The test may also induce premature ventricular complexes (PVCs) in individuals without Brugada pattern, the clinical relevance of which is little known.

**OBJECTIVE** The purpose of this study was to describe the prevalence of short-coupled (Sc) PVCs induced by ajmaline or flecainide in patients with suspected or documented severe ventricular arrhythmias.

**METHODS** We reviewed the SCB tests performed in 335 patients with suspected ventricular arrhythmias and structurally normal hearts in 9 centers. ScPVCs were defined as frequent and repetitive

PVCs with an R-on-T pattern on SCB tests. Repeated SCB tests were performed in 7 patients and electrophysiological mapping of ScPVCs in 9.

**RESULTS** Sixteen patients (8 men; mean age  $36 \pm 11$  years) showed ScPVCs and were included. ScPVCs appeared  $229 \pm 118$  seconds after the initiation of infusion and displayed coupling intervals of  $288 \pm 28$  ms. ScPVC patterns were monomorphic in 12 patients, originating from the Purkinje system in mapped patients. Repetitive PVCs were induced in 15 patients (94%) including polymorphic ventricular tachycardias in 9 (56%). SCB infusion was repeated 45 (interquartile range 0.6–46) months later and induced identical ScPVC in all. SCB test was the only mean to reveal the malignant arrhythmia in 6 patients. Catheter ablation was performed in

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9 patients, resulting in arrhythmia elimination in 8 with a follow-up of 6 (interquartile range 2–9) years.

**CONCLUSION** SCB can induce ScPVC, mostly from Purkinje tissue, in a small subset of patients with idiopathic ventricular arrhythmias. Its high reproducibility suggests a distinct individual mechanism.

Introduction

Sudden cardiac death (SCD) accounts for >350,000 deaths per year in the United States and Europe. Although most cases are related to coronary artery disease, the incidence of unexplained SCD with negative autopsy exceeds 20%. In patients younger than 45 years, this prevalence is even higher with most cases of SCD remaining unexplained.<sup>1–6</sup> In a subset of patients with unexplained SCD, the use of comprehensive clinical and genetic investigations, including screening of first-degree relatives, allows the diagnosis of inherited arrhythmias such as long QT syndrome or Brugada syndrome (BrS).<sup>7,8</sup> The remaining subjects, who survived an unexplained episode of ventricular fibrillation (VF) with no specific disease identified after comprehensive investigations, are labeled as having idiopathic VF (IVF).<sup>9–11</sup> IVF accounts for ~10% of the mortality in the global context of SCD but accounts for up to one-third of SCD in young adults.<sup>5</sup>

Over the past decade, specific subtypes of IVF have been described. These were based on phenotypic characterization of the arrhythmia itself, for example, VF initiated by short-coupled premature ventricular complexes (ScPVCs)<sup>12–16</sup> or based on the presence of subclinical myocardial alterations.<sup>17</sup> ScPVCs originating from the Purkinje system are the most common triggers of IVF and an effective ablation target for preventing VF recurrence.<sup>18–21</sup> However, such PVCs are intermittent so that their documentation may be challenging.

**KEYWORDS** Idiopathic ventricular fibrillation; Ajmaline; Flecainide; Premature ventricular complex; Purkinje system

Pharmacological testing with infusion of a sodium channel blocker (SCB) is usually performed to exclude BrS according to the current guidelines to define IVF.<sup>22,23</sup> In a subset of patients without Brugada pattern, SCB may still be proarrhythmic with a reported incidence of PVCs of 1.8%–2.4%.<sup>24,25</sup>

The aim of this study was to assess the prevalence and clinical relevance of ScPVCs in patients presenting with unexplained severe syncope or IVF undergoing SCB infusion.

Methods  
Study patients

We retrospectively reviewed data from all patients referred to centers involved in a national cardiogenetics network for documented IVF or malignant syncope without electrocardiographic (ECG) documentation. IVF was diagnosed in the absence of other documented causes<sup>9–11</sup>; No identifiable structural heart disease had to be demonstrated by echocardiography and delayed gadolinium-enhanced magnetic resonance imaging and no detectable coronary artery disease upon coronary angiography or exercise testing, as appropriate. Prolonged ECG monitoring, pharmacological testing, and genetic testing of IVF patients were additionally performed to exclude inherited arrhythmia disease.

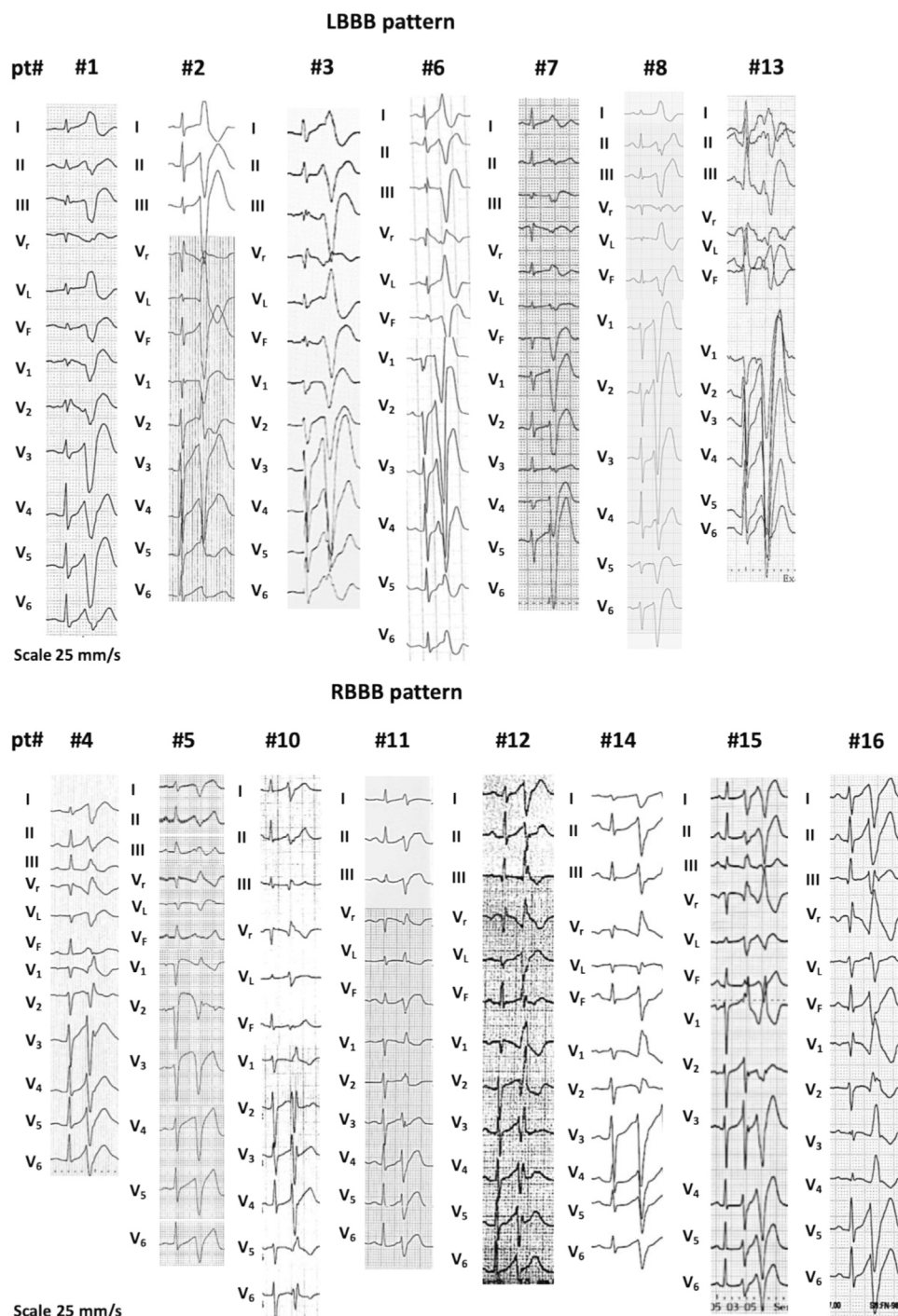
The study was approved by the local ethics committee according to the European guidelines for clinical and genetic research. Informed written consent was obtained from

Table 1 Clinical and ECG characteristics

Patient no.	Age (y)	Sex	Family history of SCD	Presentation	AF	Spontaneous ScPVC	ICD	Genetics
1	34	M	No	VF	No	No	TV-ICD	Negative
2	25	F	Yes	Syncope	No	Yes	TV-ICD	Negative
3	52	M	No	VF	No	Yes	TV-ICD	Negative
4	30	M	No	VF	No	Yes	TV-ICD	Negative
5	29	M	No	VF	No	No	TV-ICD	Negative
6	34	M	No	VF	No	Yes	TV-ICD	DPP6 haplotype
7	45	M	No	VF	No	Yes	TV-ICD	Negative
8	41	M	Yes	VF	No	No	TV-ICD	Negative
9	63	F	No	Syncope	No	Yes	TV-ICD	Negative
10	34	F	Yes	Syncope	No	Yes	TV-ICD	Negative
11	45	F	No	VF	No	No	TV-ICD	Unknown
12	27	F	Yes	VF*	No	No	No	Negative
13	36	M	No	VF*	Yes	No	No	Negative
14	23	F	No	VF	No	Yes	TV-ICD	Negative
15	24	F	No	VF	No	Yes	TV-ICD	Negative
16	24	F	No	VF	No	Yes	S-ICD	Unknown
Mean ± SD	35 ± 11							

AF = atrial fibrillation; ECG = electrocardiographic; F = female; M = male; ICD = implantable cardioverter-defibrillator; S = subcutaneous; SCD = sudden cardiac death; ScPVC = short-coupled premature ventricular complex; TV = transvenous; VF = ventricular fibrillation.

\*Induced during the medical procedure.



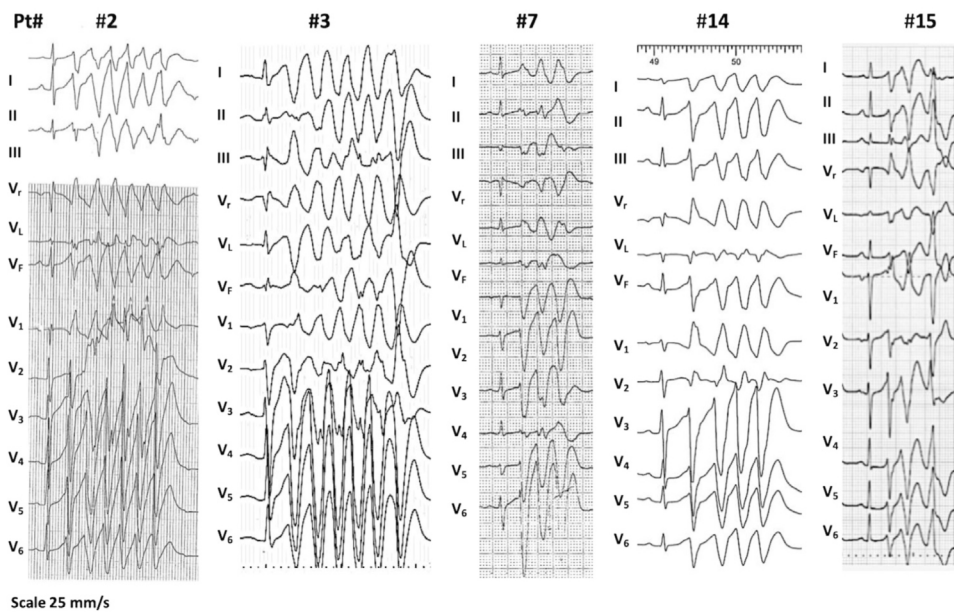
**Figure 1** Twelve-lead ECG morphologies of PVCs induced during SCB tests. Image represents all induced ScPVCs during SCB tests according to morphology and patient number. ECG speed was 25 mm/s. ECG = electrocardiographic; LBBB = left bundle branch block; Pt# = patient number; PVC = premature ventricular complex; RBBB = right bundle branch block; SCB = sodium channel blocker; ScPVC = short-coupled premature ventricular complex.

each patient who agreed to participate in the clinical and genetic studies.

### SCB challenge

SCB tests were performed according to the recommendations from the second consensus conference on BrS (ajmaline: 1 mg/kg perfused in 10 minutes; flecainide: 2 mg/kg perfused

in 10 minutes).<sup>25</sup> A continuous ECG monitoring was performed during the test. All patients without spontaneous PVC during the 10 minutes before drug infusion (baseline) and who presented frequent ScPVCs (>10 per minute) and/or repetitive forms during the test were included in the present study. None of these patients had induced Brugada type 1 ECG or J point elevation in the inferior leads. PVCs were defined as short coupled if they had a coupling interval/QT



**Figure 2** Twelve-lead ECGs of repetitive PVCs during SCB tests. Examples of induced repetitive ScPVCs during SCB tests according to patient number. Refer to [Online Supplemental Figure 1](#) for all ECGs. ECG speed was 25 mm/s. ECG = electrocardiographic; Pt# = patient number; PVC = premature ventricular complex; SCB = sodium channel blocker; ScPVC = short-coupled premature ventricular complex.

interval of  $<1$  (ie, an R-on-T pattern), as previously described.<sup>15,16</sup> Provocation of PVCs did not lead to premature discontinuation of the drug challenge, unless induction of VF or polymorphic ventricular tachycardia (VT). An absolute value of the coupling interval (such as 350 ms) was deemed inappropriate when using drug infusion with a significant impact on conduction properties, as such a threshold has been mainly reported in patients before drug intake.

Repetitive arrhythmias were distinguished into couplets, triplets, and VTs of  $>3$  beats. SCB tests were repeated in 7 patients, in 6 of those during another hospitalization. ECG parameter measurements were performed at baseline and during the test, including heart rate, QRS duration, corrected QT interval, and PVC coupling interval.

### Electrophysiology study

Electrophysiology study and ablation procedure were performed in patients with recurrent VF. Two to 4 multielectrode catheters were placed percutaneously through the femoral vessels. Surface electrocardiogram leads and bipolar intracardiac electrograms filtered at 30–500 Hz were recorded simultaneously. Three-dimensional electroanatomic mapping was performed using the CARTO system (Biosense Webster, Inc, Diamond Bar, CA).

The origin of PVCs was localized by the earliest intracardiac electrogram relative to the onset of the QRS complex. An initial high frequency short duration ( $<10$  ms) potential preceding a larger and slower ventricular electrogram during sinus rhythm and before PVC was defined as a Purkinje component. Its absence at the site of earliest activation indicated a PVC origin from the ventricular muscle.<sup>18,19</sup>

Catheter ablation was performed as described previously, targeting the optimal site and surrounding sites showing Purkinje potentials.<sup>18</sup>

### Genetic analysis

Patients were screened for mutations in 63 genes previously described in cardiomyopathy and inherited arrhythmia using Haloplex technology (Agilent, Santa Clara, CA).<sup>8</sup> One patient with a family history of SCD was known to be affected with a pathogenic *DPP6* mutation.<sup>26</sup>

### Statistical analysis

Variables are expressed as mean  $\pm$  SD in cases of normal distribution or median and interquartile range otherwise. Proportions are expressed as count (percentages). The paired Student *t* test or Wilcoxon signed rank test was used to compare paired variables. The  $\chi^2$  test was used to compare proportions. Tests were considered to be significant for  $P < .05$ . Statistical analysis was performed with SPSS version 17 (SPSS Inc., Chicago, IL).

## Results

### Clinical and genetic characteristics

Of 335 patients, 16 (4.7%) presented ScPVC during SCB tests. The clinical and ECG characteristics of this group are presented in [Table 1](#). Thirteen of these patients were studied after an event of cardiac arrest with documented VF, and 3 patients were investigated for syncope. Interestingly, 2 patients had VF during a medical procedure: 1 during general anesthesia using propofol and 1 during pharmacological cardioversion of atrial fibrillation with intravenous flecainide.

During hospital monitoring, spontaneous ScPVCs were observed in 10 patients (62%). They could be documented on a 12-lead ECG in 8 and on single-lead monitoring in the remaining 2.

Genetic testing in 14 patients showed no genetic variation likely to be pathogenic in the 63 genes screened. One patient



**Table 2** Characteristics of induced ScPVCs during SCB tests

Patient no.	Initial SCB test		ScPVC coupling interval (ms)	Repetitive monomorphic ScPVCs	ScPVC morphologies	Polymorphic VT	VF	Second SCB test	
	Drug	Time to first ScPVC (s)						Delay (mo)	ScPVC morphologies
1	Ajmaline	240	280	VT then VF	LBBB sup axis	Yes	Yes	–	–
2	Ajmaline	–	280	Bigeminy, triplets, NSVT	LBBB sup axis; RBBB sup axis	Yes	No	1	Similar
3	Ajmaline	210	300	Bigeminy, doublets, triplets	LBBB sup axis; RBBB sup axis	Yes	Yes	0.25	Similar
4	Ajmaline	300	285	Frequent isolated, doublets	RBBB sup right axis	No	No	54	RBBB inf right axis + LBBB sup axis
5	Ajmaline	–	370	Rare isolated	RBBB right axis	No	No	–	–
6	Ajmaline	180	240	Frequent bigeminy	LBBB sup axis	Yes	Yes	38	Similar
7	Ajmaline	120	280	Frequent trigeminy, triplets	LBBB sup left axis	No	No	–	–
8	Flecainide	180	270	Rare bigeminy	LBBB sup axis	Yes	No	72	Similar
9	Ajmaline	–	–	–	Unknown	No	No	–	–
10	Ajmaline	480	280	Isolated	RBBB right axis	No	No	–	–
11	Ajmaline	–	280	Isolated	7 Morphologies w/RBBB pattern	No	No	–	–
12	Ajmaline	300	320	Isolated	RBBB inf right axis	No	No	–	–
13	Flecainide	300	280	Frequent, bigeminy, NSVT	LBBB superior left axis	Yes	Yes	0.06	Similar
14	Flecainide	–	300	Frequent isolated, NSVT	RBBB sup right axis	Yes	No	–	–
15	Ajmaline	27	280	Frequent bigeminy, doublets	RBBB right axis	Yes	No	1	Similar
16	Ajmaline	180	280	Isolated, NSVT	RBBB right axis	Yes	Yes	–	–
Mean $\pm$ SD		229 $\pm$ 118	288 $\pm$ 28					Median 45.4 (IQR 0.625–46)	

inf = inferior; IQR = interquartile range; LBBB = left bundle branch block; NSVT = nonsustained ventricular tachycardia; RBBB = right bundle branch block; SCB = sodium channel blocker; ScPVC = short-coupled premature ventricular complex; sup = superior; VF = ventricular fibrillation; VT = ventricular tachycardia.

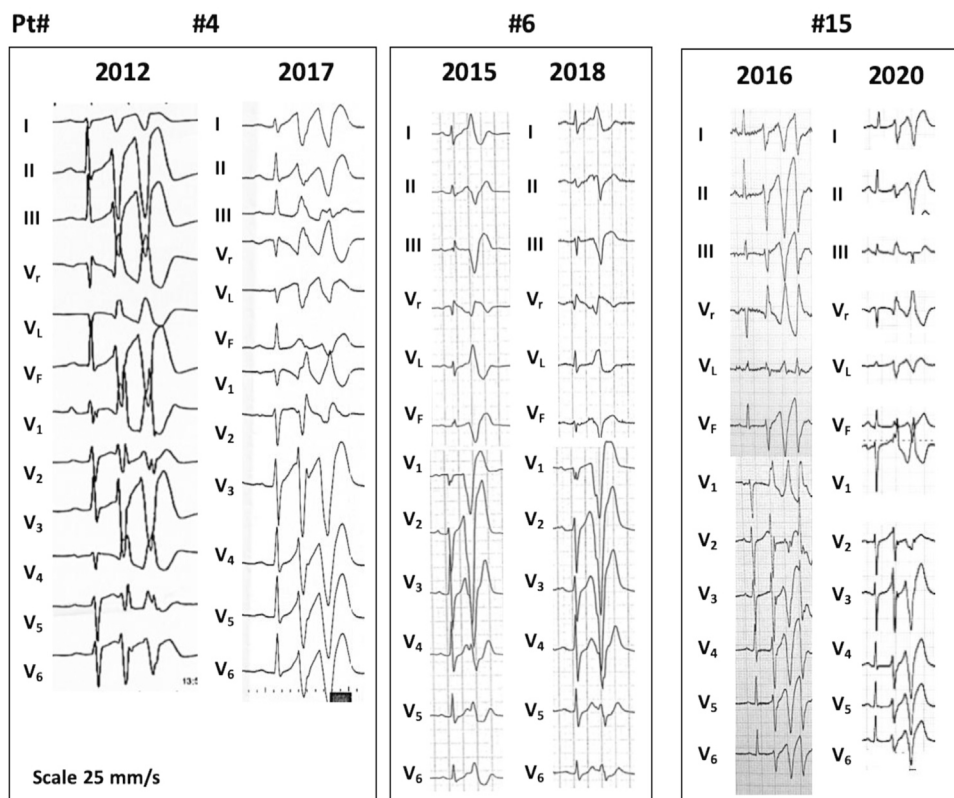
presented with a family history of SCD and pathogenic *DPP6* mutation.

### ECG characteristics of ScPVCs during SCB tests

SCB tests were performed using ajmaline infusion in 13 (81%) and flecainide infusion in 3 (19%). We observed induced ScPVCs in all patients (Figure 1), repetitive beats in 9, and polymorphic VT or VF in 9 (Figure 2 and Online Supplemental Figure 1). The first ScPVC was recorded 229  $\pm$  118 seconds after the initiation of injection, occurring during sinus rhythm at 85  $\pm$  11 beats/min. Their mean coupling interval was 288  $\pm$  28 ms. The characteristics of ventricular arrhythmias induced during SCB infusion are detailed in Table 2.

### ScPVC morphology

In the 10 patients who had a prior documented morphology of spontaneous ScPVCs on the 12-lead ECG, the ScPVC morphology induced during SCB infusion was identical to that of spontaneous ScPVCs (Online Supplemental Figure 2). Overall, ScPVC occurring during SCB tests displayed a single morphology in 12 patients (75%), 2 morphologies (12.5%) in 2, multiple morphologies (all with a right bundle branch block pattern) in 1 (6.5%), and was unknown in 1. All documented ScPVCs had a limited number of morphologies (3 predominantly), compatible with origins from the 3 main fascicles of the Purkinje system (Figure 1).



**Figure 3** Similarity of PVCs induced in SCB tests years apart. Characteristic examples of similar ScPVC morphologies induced during 2 SCB tests performed years apart in 3 patients. ECG speed was 25 mm/s. ECG = electrocardiographic; Pt# = patient number; PVC = premature ventricular complex; SCB = sodium channel blocker; ScPVC = short-coupled premature ventricular complex.

### *Repetitive arrhythmias*

Repetitive ScPVCs were observed in 9 patients (56%) during the test. Nine patients (56%) presented polymorphic ventricular tachycardia (Figure 2), with 5 of them degenerating in VF. Monomorphic doublets and triplets were observed in 5 patients (31%) (Figure 2 and Online Supplemental Figure 1).

### *Reproducibility*

Seven patients (44%) had a second SCB test performed 45.4 (interquartile range 0.6–46) months after the initial test. The second test was performed to help mapping during the electrophysiology study in 5, while it was performed for diagnostic confirmation in 2. In all 7 patients, the second test induced the same morphologies of ScPVCs with a similar coupling interval (Figure 3); in 1, the test induced an additional ScPVC morphology. Polymorphic VT occurred in 3 patients, including 2 who had presented polymorphic VT at the first test.

## **Electrophysiology study and ablation**

Nine patients underwent an invasive electrophysiology study and ablation of VF triggers. In all of them, clinical ectopic beats were scarce during the procedure, and pace mapping was first used to approach the area of interest in the Purkinje network. Ajmaline infusion was used in 5 patients to elicit ScPVCs and allow activation mapping (Table 3). Activation

mapping identified Purkinje potentials preceding local ventricular activation of PVCs by 20–72 ms (Figure 4).

Radiofrequency applications were performed in these 9 patients. SCB infusion was performed in 5 patients after the ablation procedure. It did not reinduce any ScPVCs in 3, while ScPVCs were still provokable in the patient with a *DPP6* mutation and ultimately induced VF.

## **Follow-up**

Fourteen of 16 patients received an implantable cardioverter-defibrillator. The remaining 2 patients were those who had VF occurring during a medical procedure (anesthesia and drug cardioversion for atrial fibrillation); they received a list of medications to avoid and recommendations in case of future anesthesia.

The follow-up duration was 6 (interquartile range 2–8) years. Three patients (19%) presented VF recurrence treated by the implantable cardioverter-defibrillator: 2 who did not have an ablation procedure and the patient with a *DPP6* mutation.

## **Discussion**

This study reports a novel malignant arrhythmogenic response induced during SCB infusion in patients with suspected or documented ventricular arrhythmias and structurally normal hearts.



**Table 3** Characteristics of the ablation procedure and events at follow-up

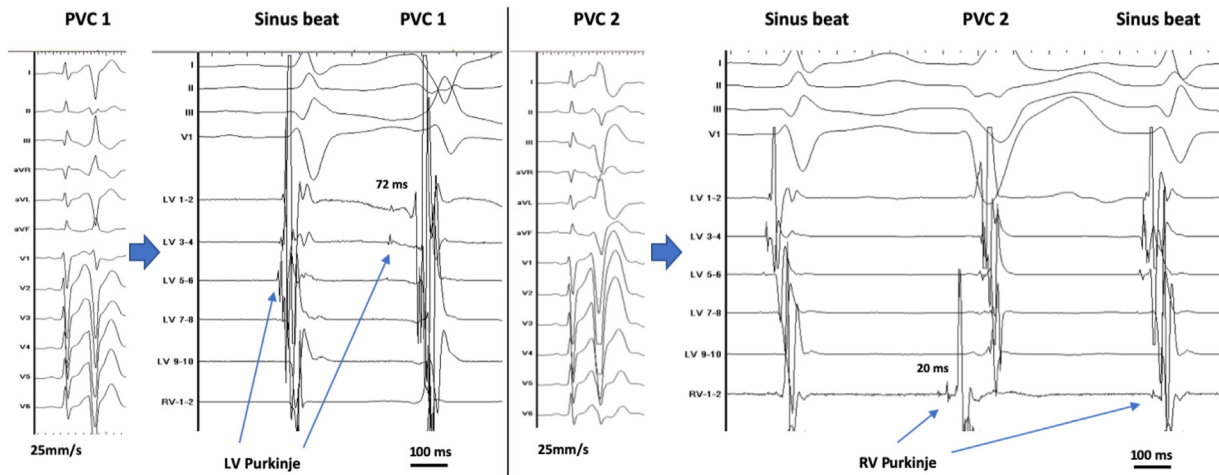
Patient no.	Ablation	Indication	Spontaneous ScPVC	SCBt before ablation	Comments	SCBt after ablation	Results	Follow-up	
								Delay (y)	Results
1	No	–	–	–	–	–	–	3	No recurrence
2	Yes	Recurrent VF	No	No	Ablation at Purkinje sites in the LV with pace mapping	Yes	Negativation	7	No recurrence
3	Yes	Recurrent VF	No	Yes	Ablation at Purkinje sites in the RV with pace mapping	Yes	Positive (similar)	4	No recurrence
4	Yes	Recurrent VF	No	Yes	Mapping and ablation of left Purkinje PVC triggers, normal substrate	No	–	2	No recurrence after the second procedure
5	Yes	Recurrent VF	No	Yes	Ablation of left Purkinje PVC triggers with PVC mapping	No	–	5	No recurrence
6	Yes	Recurrent VF	No	Yes with VF	Ablation at Purkinje sites in the RV with pace mapping	Yes	Positive with VF	2	Recurrences
7	No	–	–	–	–	–	–	2	No recurrence
8	No	–	–	–	–	–	–	10	Recurrences
9	No	–	–	–	–	–	–	9	Arrhythmic storm
10	Yes	Recurrent VF	No	No	Scarce PVC under isoprenaline ablation at Purkinje sites with pace mapping	No	–	8	No recurrence
11	Yes	Recurrent VF	Yes	No	Ablation at LV Purkinje ant and post sites with PVC mapping	Yes	Negativation	–	No recurrence
12	No	–	–	–	–	–	–	2	No recurrence
13	No	–	–	–	–	–	–	–	Unknown
14	Yes	Recurrent VF	–	–	–	–	–	11	No recurrence
15	Yes	Recurrent VF	No	Yes	Ablation at LV Purkinje post site with PVC mapping	Yes	Negativation	0.5	No recurrence
16	No	–	–	–	–	–	–	–	–
								Median 6 (IQR 2–8)	

ant = anterior; IQR = interquartile range; LV = left ventricle; post = posterior; PVC = premature ventricular complex; RV = right ventricle; SCBt = sodium channel blocker test; ScPVC = short-coupled premature ventricular complex; VF = ventricular fibrillation.

### Short-coupled ectopy and SCBs

Our patients presented with severe symptoms or SCD due to documented VF. The documentation of ScPVCs was established before the SCB test in 10 patients, whereas in 6 patients, only the SCB infusion revealed the diagnosis. In addition to the occurrence of ScPVCs, repetitive PVCs were the

most concerning events since the majority of patients presented malignant polymorphic VT or VF. In all mapped patients, ScPVCs originated from the Purkinje system and their morphologies were similar to those previously described from the right or left Purkinje system.<sup>18,19</sup> No ScPVC showed a right ventricular outflow tract morphology.<sup>21</sup>



**Figure 4** PVCs during ajmaline testing mapped from the distal Purkinje system. Origin of PVCs in the distal Purkinje system in patient 3. Two PVC morphologies are shown on the 12-lead ECG with associated endocardial recordings from a decapolar catheter positioned on the LV and RV septum. The numbers indicate the Purkinje to myocardium activation time. Catheter ablation has not been performed in the LV Purkinje system as very few PVCs were induced during ajmaline infusion. ECG speed was 25 mm/s. EGM speed was 200 mm/s. ECG = electrocardiographic; EGM = electrogram; LV = left ventricular; PVC = premature ventricular complex; RV = right ventricular.

ScPVCs were previously reported as an R-on-T phenomenon often initiating VF and described with different names in patients with apparently normal hearts.<sup>12–16</sup> The role of ScPVCs as a specific subset of IVF has been reported with an incidence varying from 6.6%<sup>16</sup> to 20%,<sup>27</sup> depending on the respective inclusion criteria. This arrhythmia was demonstrated to be responsive to quinidine.<sup>9,14,16</sup> Invasive mapping studies have shown that the main origin of ScPVCs is the Purkinje system and confirmed that such Purkinje excitability could be the unique abnormality without associated myocardial alteration on endo-epicardial mapping in patients with IVF.<sup>17,27</sup> Other manifestations of Purkinje abnormality with the normal myocardium have been reported as reentrant fascicular VT or MEPPC channelopathy.<sup>28–30</sup> However, identical ScPVCs can also be seen in a variety of structural heart diseases, particularly in VF storms occurring in acute coronary event or stable coronary artery disease, and they are also sensitive to quinidine.<sup>31–33</sup>

In our patients, ScPVCs appeared and were exacerbated by ajmaline or flecainide infusion. The phenomenon was consistently reproducible on repeated testing, including tests performed years apart. This clearly indicates an individual arrhythmogenic susceptibility. SCB may influence the complex elements of intracellular calcium handling, a key to the genesis of spontaneous ectopy by triggered activity. In a simulation study, Campos et al<sup>34</sup> showed that  $\text{Na}^+$  current loss of function in structurally normal ventricles provided conditions under which spontaneous calcium release occurred in Purkinje cells. Azithromycin and flecainide have been described to impact calcium handling through various mechanisms including loss of function of the ryanodine channel.<sup>35,36</sup> In our study, most patients were tested with ajmaline. This drug has no known effect on the ryanodine channel but produce inhibition of rapid delayed rectifier potassium current (human ether-a-go-go-related gene), which may increase action potential duration, favoring early afterdepolarizations

in Purkinje cells.<sup>37</sup> Finally, the repetitiveness (polymorphic VT) of Purkinje activity may also be reentrant, facilitated by altered conduction properties related to  $\text{Na}^+$  current inhibition of the Purkinje network.<sup>38</sup>

No common rare genetic variant was identified in our patients, which could underlie their response to SCB. However, a genetic polymorphism could not be demonstrated because of the limited number of patients. Of note, 1 patient was a carrier of a rare genetic variation in *DPP6* gene. *DPP6* is a regulatory protein involved in the magnitude of the transient outward potassium current outward repolarizing current, strongly expressed in Purkinje cells. The ajmaline effect on transient outward potassium current may explain such malignant response to SCB in *DPP6* haplotype carriers.<sup>26</sup>

## Clinical implications

The present study expands our knowledge of IVF associated with ScPVCs. We could show in a significant number of patients that class 1 antiarrhythmic drugs can induce malignant arrhythmias initiated by ScPVCs and Purkinje PVCs. This pro-arrhythmogenic effect may be a unique diagnostic opportunity in patients referred for evaluation of unexplained syncope or SCD. This is particularly important as the diagnosis in this specific mechanism of SCD is based only on documented arrhythmia and not on distinct ECG characteristics under baseline conditions as in other primary electrical diseases such as BrS or long QT syndrome.

Finally, this study shows that the high reproducibility of SCB tests was also of clinical interest during the ablation procedures to increase PVC load, allowing for detailed electroanatomic mapping, and to provide a procedural end point.

## Limitations

This study had limitations because of its small population and observational nature. Such results have to be confirmed by further studies.

The population included here was recruited from a wide range of patients undergoing SCB infusion to exclude BrS. The incidence of ScPVCs in the specific subset of Purkinje-related IVF is unknown and should be evaluated given its high potential clinical interest.

We were unable to provide a detailed characterization of Purkinje activity and the specific pathophysiological action of SCB, as major limitations are present in the clinical capabilities to investigate Purkinje function and structure.

We have used only ajmaline or flecainide for pharmacological testing. Procainamide is the only SCB drug available in parenteral form in some countries and has not been tested. It has a lower potency in provoking a Brugada pattern and may thus have a different sensitivity in inducing ScPVCs.<sup>39</sup>

## Conclusion

This study reports a novel malignant arrhythmogenic response induced during sodium blocker infusion in patients with suspected or documented ventricular arrhythmias and structurally normal hearts. The test could be the only way to show susceptibility to arrhythmia in these patients. Its high reproducibility may indicate a distinct pathophysiological mechanism.

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