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ORIGINAL RESEARCH

Distinct Substrates of Idiopathic Ventricular Fibrillation Revealed by Arrhythmia Characteristics on Implantable Cardioverter-Defibrillator

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ABSTRACT

BACKGROUND Idiopathic ventricular fibrillation (IVF) can be associated with undetected distinct conditions such as microstructural cardiomyopathic alterations (MiCM) or Purkinje (Purk) activities with structurally normal hearts.

OBJECTIVE This study sought to evaluate the characteristics of recurrent VF recorded on implantable defibrillator electrograms, associated with these substrates.

METHODS This was a multicenter collaboration study. At 32 centers, we selected patients with an initial diagnosis of IVF and recurrent arrhythmia at follow-up without antiarrhythmic drugs, in whom mapping demonstrated Purk or MiCM substrate. We analyzed variables related to previous ectopy, sinus rate preceding VF, trigger, and initial VF cycle lengths. Logistic regression with cross validation was used to evaluate the performance of criteria to discriminate Purk or MiCM substrates.

RESULTS Among 95 patients (35 women, age 35 ± 11 years) meeting the inclusion criteria, IVF was associated with MiCM in 41 and Purk in 54 patients. A total of 117 arrhythmia recurrences including 91% VF were recorded on defibrillator. Three variables were mostly discriminant. Sinus tachycardia (≤570 ms) was more frequent in MiCM (35.9% vs 13.4%, $P = 0.014$) whereas short-coupled (<350 ms) triggers were most frequent in Purk-related VF (95.5% vs 23.1%, $P = 0.001$), which also had shorter VFCLs (182 ± 15 ms vs 215 ± 24 ms, $P < 0.001$).The multivariable combination provided the highest prediction (accuracy = 0.93 ± 0.05, range 0.833-1.000), discriminating 81% of IVF substrates with a high probability (>80%). Ectopy were inconsistently present before VF.

CONCLUSIONS Characteristics of arrhythmia recurrences on implantable cardioverter- defibrillator provide phenotypic markers of the distinct and hidden substrates underlying IVF. These findings have significant clinical and genetic implications. (J Am Coll Cardiol EP 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CPVT = catecholaminergic polymorphic ventricular tachycardia

ECG = electrocardiograph

ICD = implantable cardioverter-defibrillator

IVF = idiopathic ventricular fibrillation

MiCM = microstructural cardiomyopathic alteration

PVC = premature ventricular complexes

Purk = Purkinje

SCD = sudden cardiac death

VF = ventricular fibrillation

VT = ventricular tachycardia

Ventricular fibrillation (VF) is the most common arrhythmia in patients experiencing a cardiac arrest associated with a structurally normal heart.[1-3] Idiopathic VF (IVF) is a subgroup defined as unexplained VF established after comprehensive clinical, electrocardiographic, and genetic testing, thus excluding structural and inherited arrhythmia conditions.[3-6] In studies collecting sudden cardiac death (SCD) in large populations, IVF accounted for 6.8% to 38.0% of cases, with the highest incidence being observed in the young.[5,6] Recent studies have shown that IVF is associated with undetected substrates, owing to the limited resolution of current imaging, the random occurrence of electrical triggers (focal ectopic sources or transient repolarization changes), and the uncertain functional significance of variants revealed by genomic testing.[3-13] The causes of VF when identified, have been notably linked to microstructural myocardial alterations or random ectopy mostly from the Purkinje (Purk) network.[2,4,7-14] Other causes such as catecholaminergic polymorphic ventricular tachycardia (CPVT), J-wave and Brugada syndromes, and long/short QT syndromes are rarely missed, provided that the initial investigations and subsequent monitoring were comprehensive.[3,4,12,15,16]

Microstructural myocardial alterations or Purk sources associated with structurally normal myocardium constitute distinct substrates with different management in terms of genetics and treatments. Because the underlying tissues have different conduction properties, we hypothesized that they would display different characteristics during spontaneous VF, such as those recorded on an implantable cardioverter-defibrillator (ICD) during follow-up.

In this study, we analyzed the characteristics of VF measured by ICD stored electrograms during an arrhythmia recurrence, in patients with IVF with demonstrated Purk or microstructural myocardial abnormalities.

METHODS

STUDY POPULATION. Consecutive patients with IVF and recurrent arrhythmia observed at 32 arrhythmia referral centers between 2010 and 2022 were reviewed retrospectively. We included all patients over the age of 15 who had: 1) VF documented at the time of index SCD, and extensive negative investigations supporting the diagnosis of IVF; and 2) recurrent sustained arrhythmia documented on ICD recordings in the absence of antiarrhythmic drugs (except beta-blockers) and prior ablation. A minimum delay of 1 month after the index VF was required to minimize the role of acute factors affecting

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Clinical Characteristics

	Total Group (N = 95)	Purkinje-Related VF (n = 54)	Microstructural Cardiomyopathy (n = 41)	*P* Value
Clinical characteristics				
Age at first VF (y)	34.6 ± 11.1	34.6 ± 11.1	37.2 ± 14.1	0.317
Female	35 (36.8)	25 (46.2)	10 (24.3)	**0.028**
Family history of unexplained sudden cardiac death	17 (18.0), 1 unknown	10 (18.8)	7 (17.9)	0.823
Symptoms before cardiac arrest	31 (35.6), 8 unknown	16 (32.6)	15 (38.4)	0.510
Activity at index VF, no. of available data	88	50	38	
Sleep or rest	33 (37.5)	26 (52)	7 (18.4)	**0.001**
Effort	19 (21.6)	3 (6)	16 (42.1)	**<0.001**
Others	36 (40.9)	21 (42)	15 (39.4)	0.811
PVC documented on 12-lead ECG	59 (62)	47 (94)	12 (29)	<0.001
Initial diagnostic screening				
Magnetic resonance imaging	83 (87.3)	44 (81.5)	39 (95.5)	0.047
Sodium channel blocker	70 (73.6)	33 (61.1)	37 (90.2)	0.003
Arrhythmia recurrence on ICD				
Implanted ICD: T-ICD or S-ICD	61 T-ICD, 34 S-ICD	36 T-ICD, 18 S-ICD	25 T-ICD, 16 S-ICD	0.566
Timing of first recurrence (months)	12 (4-37)	7 (4-41)	13 (4-36)	0.883
No. of documented arrhythmia recurrences	117	69	48	0.33
Arrhythmia episodes on BB treatment	45 on BB (38.5), 69 off BB, 3 unknown	28 on BB (41.8)	17 on BB (36.1)	0.280

Values are mean ± SD, n (%), or median (IQR) unless otherwise indicated.

BB = beta-blocker; ECG = electrocardiograph; PVC = premature ventricular complex; S-ICD = subcutaneous implantable cardioverter-defibrillator; T-ICD = transvenous implantable cardioverter-defibrillator.

electrophysiological properties, such as medications and ischemic insult; 3) invasive mapping demonstrating Purk or myocardial abnormality associated with IVF.

Exclusion criteria were IVF with a specific etiological diagnosis revealed by genetic testing or late clinical result, IVF with unidentified cause after mapping, and inappropriate signal quality on ICD owing to erased or incomplete tracings.

Patients were diagnosed with IVF in accordance with published guidelines.[1,4] Structural heart disease was ruled out using echocardiography, coronary angiography, and cardiac magnetic resonance (Table 1). No patient had any electrocardiograph (ECG) showing Brugada or short/long QT syndrome, or inferolateral early repolarization with a J-wave of ≥0.2 mV amplitude. Exercise testing was used to unmask CPVT in patients with exercise-induced VF. Ajmaline or flecainide infusions were used to unmask Brugada syndrome. The presence of short-coupled premature ventricular complexes (PVCs) was defined with a coupling interval of <350 ms.[2,10,11,13] Genetic testing was performed by sequencing a set of 31 to 109 genes in a great majority of patients to exclude long QT, CPVT, and SCN5A gene mutations.[5,8] All patients provided informed consent to participate in the registry according to institutional guidelines at each center. The study was completed in accordance with the Helsinki Declaration as revised in 2013.

ELECTROPHYSIOLOGICAL STUDY. An electrophysiological study was performed to determine the origin of VF triggers in patients with sufficiently frequent PVCs and to search for an abnormal myocardial substrate. A trans-septal or retro-aortic approach was performed to access the endocardial left ventricle and a subxyphosternal approach to access into the pericardial space. A 20-pole catheter with a 2-mm interelectrode distances (Pentaray or Lasso, Biosense) was used for endocardial and epicardial measurements. Electro-anatomical mapping of the endocardium and epicardium was performed using magnetic localization (CARTO system, Biosense Webster; or Rhythmia, Boston Scientific).

Purk-related IVF. Purk triggers were defined on the presence of Purk potential preceding the myocardial activation during the triggering PVCs. An initial sharp potential (≤10 ms in duration) preceding the ventricular electrogram during sinus rhythm and during PVCs indicated the latter originated from the Purk system whereas its absence at the site of earliest

activation indicated an origin from ventricular muscle.[17] In 3 patients, although no trigger PVC was observed during mapping, VF was considered as Purk-related because the short-coupled PVCs had narrow QRS complexes indicating left ventricular fascicular origin.[10,11,14]

Microstructural cardiomyopathic alterations. Microstructural cardiomyopathic alteration (MiCM) were defined by the presence of areas of abnormal myocardial conduction demonstrated by mapping, in the absence of macroscopic structural heart disease on echocardiography and late enhancement cardiac magnetic resonance.[7] This generic term likely covers a variety of genetic or acquired affections such as cardiomyopathies or myocarditis. High-density mapping (>800 sites in the endocardium, >2,000 sites in the epicardium) was performed to identify electrogram characteristics of abnormal conduction, identical to those defining fibrotic and cardiomyopathic tissue.[18,19] They were defined as bipolar electrograms with low voltage (≤1 mV) and prolonged duration of >70 ms (onset to offset), with >3 components or split or late potentials. On the epicardium, because low voltage signals can be due to normal fat tissue, electrograms were considered abnormal on the basis of prolonged duration and fractionated or split components.[16,18,19]

CHARACTERISTICS OF THE VF ONSET ON ICD STORED ELECTROGRAMS. Follow-up was performed after ICD implantation by examining all tracings in the archives or remote monitoring documents. The ICD electrograms were reviewed to determine whether ICD therapies—shock therapy and antitachycardia pacing—were delivered appropriately. The type of arrhythmia associated with appropriate therapy was defined as either monomorphic VT or polymorphic VT or VF. Monomorphic VT was defined by monomorphic ventricular complex and electrogram pattern, regardless of ICD programming in VT or VF detection zones defined by arrhythmia frequency. Polymorphic VT and VF were considered together because they could not be distinguished reliably at the arrhythmia onset, owing to limited electrogram leads; they were defined by a varying QRS complex and electrogram morphology. As summarized in the **Central Illustration**, we analyzed: 1) the sinus beats preceding VF: the mean sinus rate (based on 3-10 consecutive beats without intervening PVCs), and presence of ≥1 isolated PVCs and its morphology; sinus tachycardia suggesting sympathetic hyperactivity was defined as a rate of >105 beats/min, for example, ≤570 ms; 2) the trigger (first VF beat): coupling interval with the previous sinus beat; short-coupled trigger was defined with a coupling interval of <350 ms;[3,14,15,17] and 3) the 10 subsequent R-R intervals of VF: individual and cumulative cycle length (CL), and variability (difference from the 1st to 10th VFCL). The analysis was limited to 10 cycles of initial VF (approximately 2 seconds), because this early stage is associated with nonfragmented electrograms and driver activities related to the substrate.[17] The CL measurements provided by the ICD were verified by examination of electrograms to ensure that no VF cycles had been omitted or overcounted. In subcutaneous ICD, electrograms and intracardiac measurements were not available. The parameters were measured manually using QRS complex peaks, and cumulative (not individual) CLs during VF.

STATISTICAL ANALYSIS. Categorical variables are reported as numbers and percentages. Continuous variables are presented as mean ± SD when normally distributed or median with IQR (25th and 75th percentiles) when not normally distributed. Continuous variables were tested for normal distribution using the D'Agostino-Pearson test. Continuous variables were compared with the Student *t*-test or the Mann-Whitney *U* test and categorical variables with chi-square or Fisher exact test when applicable. Paired variables were compared with a paired *t*-test or Wilcoxon test. A *P* value of <0.05 was considered statistically significant.

Logistic regression with cross-validation was used to evaluate the performance of criteria to predict substrate. Cross-validation was performed by dividing the dataset in random order into 6 parts using StratifiedKFold, each part serving as a test set in each iteration and the rest serving as training set. The performance measures from all iterations were then measured. Finally, we estimated the probability of substrate using different data scenarios based on binarized variables and logistic regression. Statistical analyses were performed using R (Version2023) and Python (version 4.1.0).

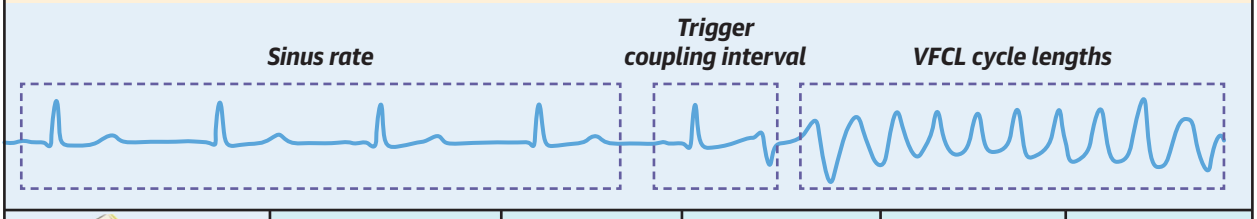
RESULTS

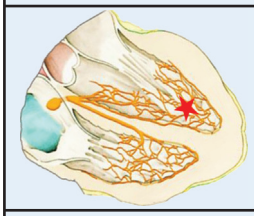
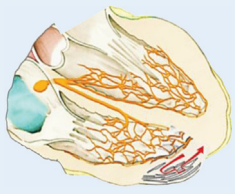
PATIENT CHARACTERISTICS. A total of 114 patients were enrolled initially. We excluded 19 patients because of specific late diagnosis (Brugada syndrome in 3, early repolarization in 3, CPVT in 2), an unidentified VF substrate (n = 7), ICD signal unsuitable for measurement (n = 3), or VT (instead of VF)

CENTRAL ILLUSTRATION Study Objective and Summary Results

ISSUE: Unexplained sudden cardiac death is associated with undetected or hidden substrates.

METHOD: In survivors of idiopathic ventricular fibrillation (VF), we evaluate the ability of defibrillator electrograms during recurrent arrhythmia to predict the underlying substrate.
The following characteristics were measured.



	Purkinje-related VF with normal myocardium, n = 69	Sinus rate >105 beats/min in 13%	Short-coupled trigger in 95% Short-Coupling	VFCL <195 ms in 89% Fastest VF	Monomorphic VT in 3%
	Myocardial structural abnormality, n = 48	Sinus rate >105 beats/min in 36% Sympathetic influence	Short-coupled trigger in 23%	VFCL <195 ms in 26%	Monomorphic VT in 19% Monomorphic tachycardia

FINDING: Combined characteristics of arrhythmia recurrences recorded on ICD, predict underlying substrate of unexplained sudden cardiac death with an accuracy of 0.93 ± 0.05

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ICD = implantable cardioverter-defibrillator; VF = ventricular fibrillation; VFCL = ventricular fibrillation cycle length; VT = ventricular tachycardia.

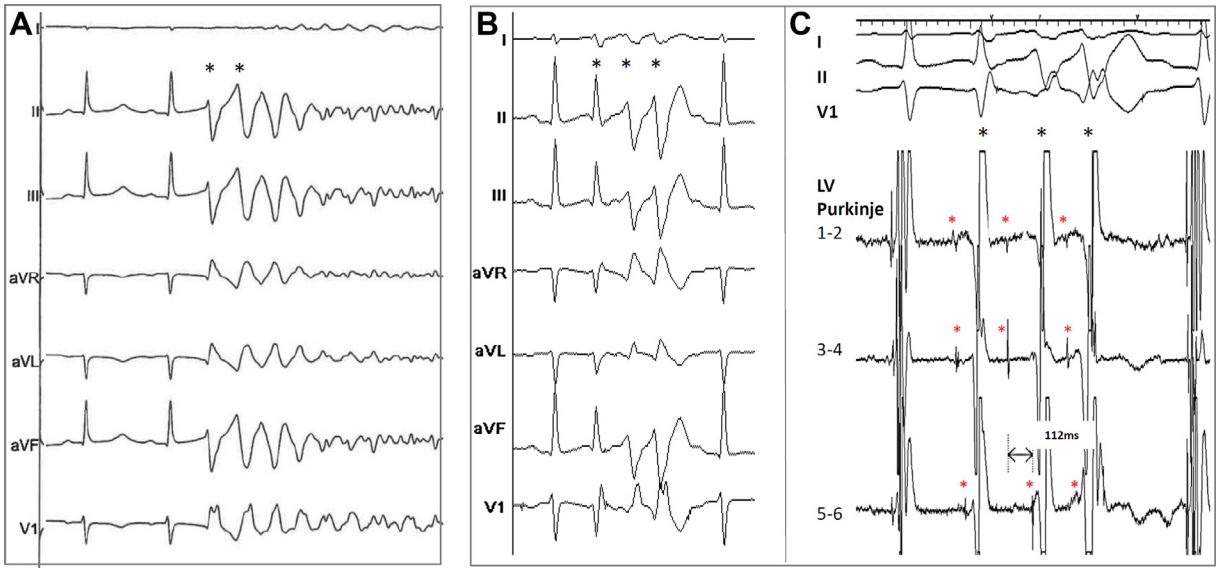
recorded at the time of index SCD (n = 1). The study population consisted of the 95 patients described in Table 1. The ECG baseline values were within normal ranges in all patients.

A total of 117 arrhythmia episodes (2 episodes in 22 patients) occurring in the absence of antiarrhythmic drug, were analyzed. Beta-blockers were taken at the time of 45 episodes with the medication prescribed according to the practices of each center to prevent VF occurrence or inappropriate shocks during coexisting atrial fibrillation.

ELECTROPHYSIOLOGICAL DATA. Purk triggers were confirmed in 54 patients, and originated from RV in 29, LV in 17 and both ventricles in 8 (Figure 1). Pharmacological infusions were required to induce Purk ectopy in 5 patients. Eighteen patients also underwent epicardial mapping, which showed no abnormal electrogram regions.

MiCM-VF was confirmed in 41 patients, by the presence of an abnormal region in the endocardium in 13 patients (RV in 5, LV in 8) and the epicardium in 28 (Figure 2). In 5 patients, the PVCs triggering VF (3 with short-coupled PVCs) was documented in 12-lead ECG and mapping showed its origin from the abnormal myocardial substrate. In 7 additional patients, spontaneous monomorphic PVCs were documented on 12-lead ECG without being able to define their role as VF trigger. Pace-mapping or catheter-induced PVCs in the substrate region matched their QRS morphologies in 6 patients, suggesting their origin from the same region (Supplemental Figure 2).

FIGURE 1 **Purkinje Mapping in a 23-Year-Old Patient**



Spontaneous VF (A) and triplet PVC (B, black asterisks) documented on ECG. Mapping shows the PVC origin in left ventricular Purkinje network (red asterisks). ECG = electrocardiograph; PVC = premature ventricular complex; VF = ventricular fibrillation.

ARRHYTHMIA CHARACTERISTICS ON DEFIBRILLATOR RECORDINGS. **Tables 1 and 2** show the clinical and arrhythmia characteristics depending on Purk or MiCM substrate. Clinically, male sex and the occurrence of SCD during exercise (mainly sport activities) were more frequent with MiCM, whereas Purk VF occurred at rest in most cases. From the time of ICD implantation, the first arrhythmia recurrence occurred at a similar timing in patients with Purk-VF and MiCM (median 7 and 13 months, respectively).

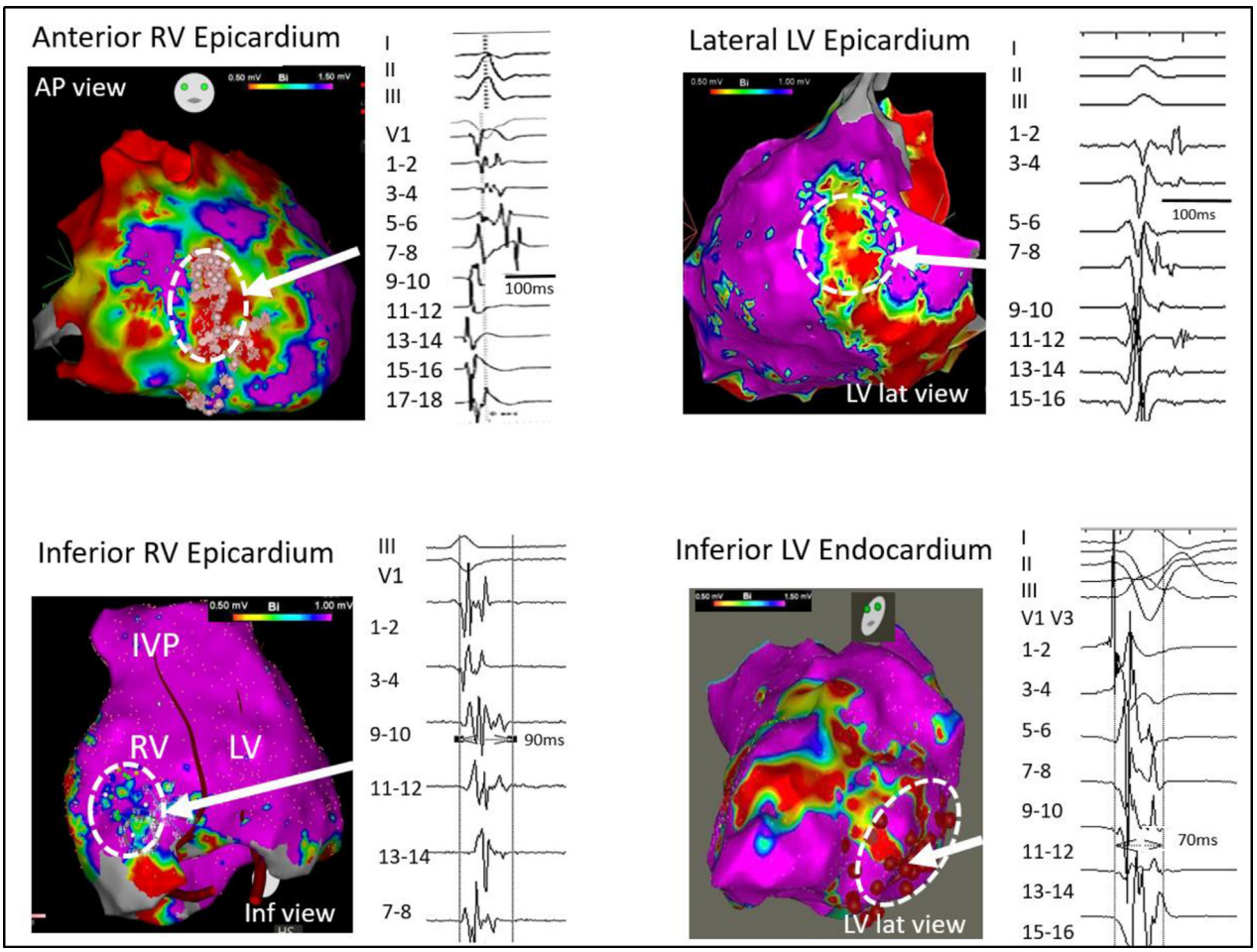
In Purk-VF, the recurrent arrhythmias (n = 69) were polymorphic VT/VF in 67 episodes and monomorphic VT in 2 episodes (2.9%). In MiCM-VF, the recurrent arrhythmia (n = 48) was VF in 39 episodes and a monomorphic VT (CL 256.2 ± 28.3 ms) in 9 episodes (18.7%, $P = 0.004$ vs Purk-VF) (Supplemental Figure 3). The mean sinus rate preceding the occurrence of VF/VT was similar in both groups. However a sinus tachycardia was more often observed in MiCM-VF/VT (20 of 48, 41.7%) in contrast with 10 of 69 (14.5%) Purk-VF/VT ($P = 0.002$). The characteristics of the VF episodes only (n = 106) are shown elsewhere in the text and in **Table 2**, and illustrated in **Figures 3 to 6** and Supplemental Figure 4.

The sinus rate preceding VF was similar in MiCM-VF and Purk-VF, but the larger SD for MiCM-VF indicated a broader spectrum of sinus rates preceding MiCM-VF (bradycardia or tachycardia) than Purk-VF (**Figure 3A**). Sinus tachycardia preceded 14 of 39 MiCM-VF (35.9%) and 9 of 67 Purk-VF (13.4%, $P = 0.014$). The presence of PVC was similar between subgroups with approximately one-half of the episodes preceded or not by a PVC.

The trigger initiating VF had a longer coupling interval in MiCM-VF than in Purk-VF (407 ± 78 ms vs 284 ± 45 ms, $P < 0.001$). Short-coupled triggers were observed in 64 of 67 Purk-VF episodes (95.5%), as well as in 9 of 39 MiCM-VF episodes (23%, $P < 0.001$). Importantly, short-coupled triggers were preceded by sinus tachycardia in most MiCM-VF cases (7/9, 78%) in contrast with a minority of Purk-VF (9/67, 13.4%) ($P < 0.001$). This finding suggested that greater sympathetic activity was necessary to induce short-coupled triggers in MiCM.

The 10 first VFCLs (after the trigger PVC) showed a marked acceleration from the first to tenth beats. The mean VFCL was significantly shorter in Purk-VF than in MiCM-VF (182 ± 15 ms vs 215 ± 25 ms, $P < 0.001$), corresponding with VF rates of 330 beats/min and 279 beats/min, respectively. Taking a threshold of 195 ms (308 beats/min) in line with the receiver-operating characteristic curve, VFCLs of <195 ms were observed in 89% Purk-VF and 26% in MiCM, respectively ($P < 0.001$) (**Table 2**). As with the trigger

FIGURE 2 Voltage Mapping and Representative Electrograms



Voltage mapping and representative electrograms from 4 patients with microstructural alteration of the myocardium. The areas of abnormal electrograms are shown in dotted circle. LV = left ventricle; RV = right ventricle.

coupling interval, short VFCLs in MiCM were associated with sinus tachycardia (6/10 VF) (**Figure 3E**), indicative of a greater sympathetic tone.

The characteristics of VF episodes according to the use of beta-blockers were not different. Patients on beta-blockers had similar sinus rate (with vs without beta-blocker, 743 ± 177 vs 737 ± 249, $P = 0.89$), similar trigger coupling interval (322 ± 71 vs 321 ± 78, $P = 0.88$), and similar VFCL (188.8 ± 198 vs 193.4 ± 204, $P = 0.27$). This similarity may be explained in part by the moderate dose of beta-blocker prescribed (mostly bisoprolol 5 mg/d).

Twenty-two patients had 2 VF episodes recorded on different time periods. Supplemental Table 1 and Supplemental Figures 1, 5, and 6 show that VF characteristics were consistent whereas the presence of PVCs was inconsistent in 13 of 22 cases (62%).

MULTIVARIABLE ANALYSIS. Because the presence of PVC or the VFCL variability were not discriminant, we used baseline sinus rate, trigger coupling interval, and VFCL in univariate and multivariate regression analyses. There was an increasing prediction accuracy of the model with 1, 2, and 3 parameters, resulting in 3 combined parameters providing a high accuracy, 0.93 ± 0.05, ranging from 0.83 to 1.00 between the iterations (**Figure 6**, Supplemental Table 3). ORs were as follows: sinus rate 1.01 (95% CI: 1.00-1.01, $P = 0.0024$), trigger coupling interval 0.951 (0.923-0.972, $P = 0.00012$), and VFCL0.99 (0.983-0.996,

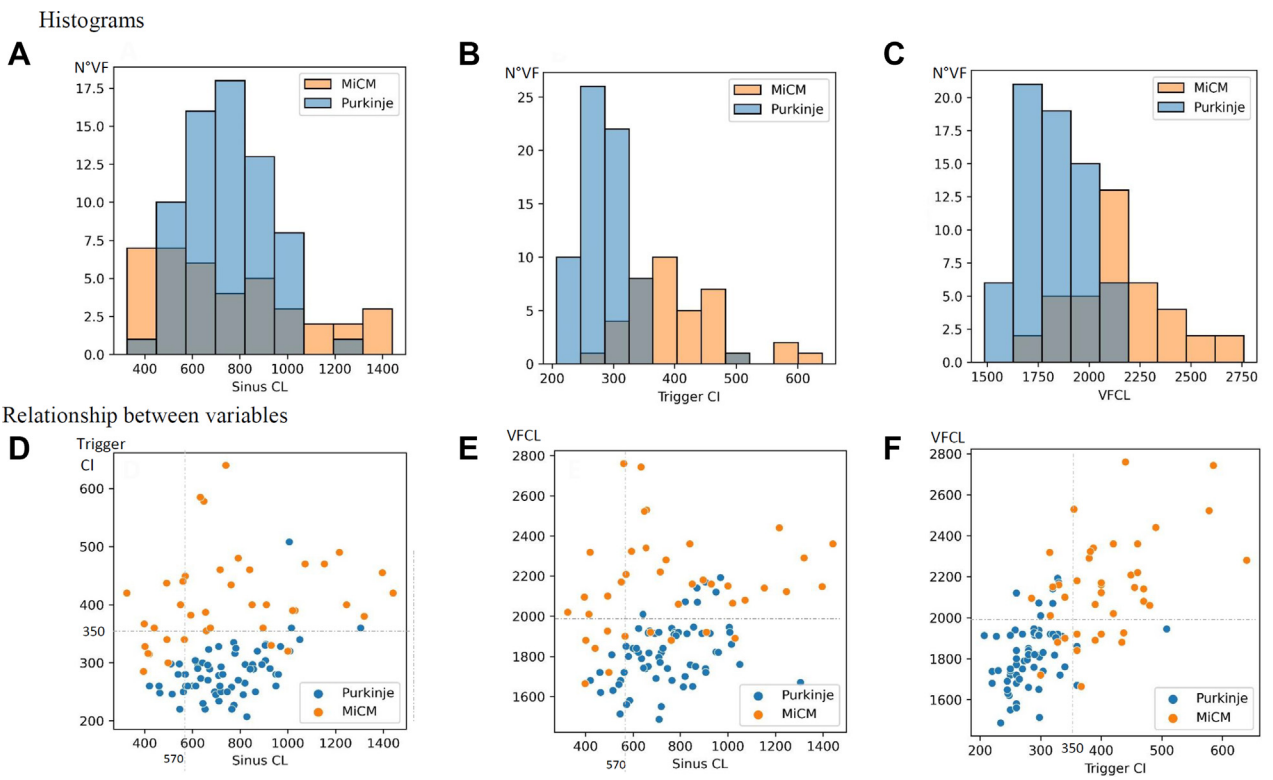
TABLE 2 Characteristics of Arrhythmia Initiation on ICD

	Total Group: 117 VF or VT Episodes	Purkinje 69 Episodes	Microstructural Cardiomyopathy 48 Episodes	*P* Value
Recurrent arrhythmia (VF and VT) on ICD				
Type of recurrent arrhythmia (VF or monomorphic VT)	106 VF, 11 VT (9.4)	67 VF, 2 VT (2.9)	39 VF, 9 VT (18.7)	0.004
Sinus rate preceding VT or VF, ms	742.8 ± 227	744 ± 164	733 ± 297	0.803
Sinus rate >105 beats/min	30 (25.6)	10 (14.5)	20 (41.7)	0.002
VT and VF trigger coupling interval, ms	331.8 ± 83.5	284.6 ± 44.4	399.6 ± 80.0	<0.001
VT CL of initial 10 cycles, ms	236.9 ± 40.1	180.5 ± 7.8		0.018
Recurrent VF on ICD	(N = 106)	(n = 67)	(n = 39)	
Preceding sinus rate, ms	751.5 ± 226.5	745.5 ± 167.1	761.9 ± 305.2	0.758
Sinus rate >105 beats/min	23 (22.6)	9 (13.4)	14 (35.9)	0.014
Presence of PVC before VF	56 (52.8)	34 (50.1)	22 (56)	0.573
VF Trigger coupling interval, ms	329.4 ± 84.1	283.9 ± 44.7	407.5 ± 78.4	<0.001
VF episodes with short-coupled (<350 ms) trigger	72 (67.9)	64 (95.5)	9 (23.1)	0.001
VFCL of initial 10 cycles (ms)	193.9 ± 25.1	181.6 ± 15.3	215.1 ± 24.8	<0.001
VF episodes with VFCL <195 ms	70 (66.0)	60 (89.6)	10 (25.6)	0.001

Values are n (%) or mean ± SD.

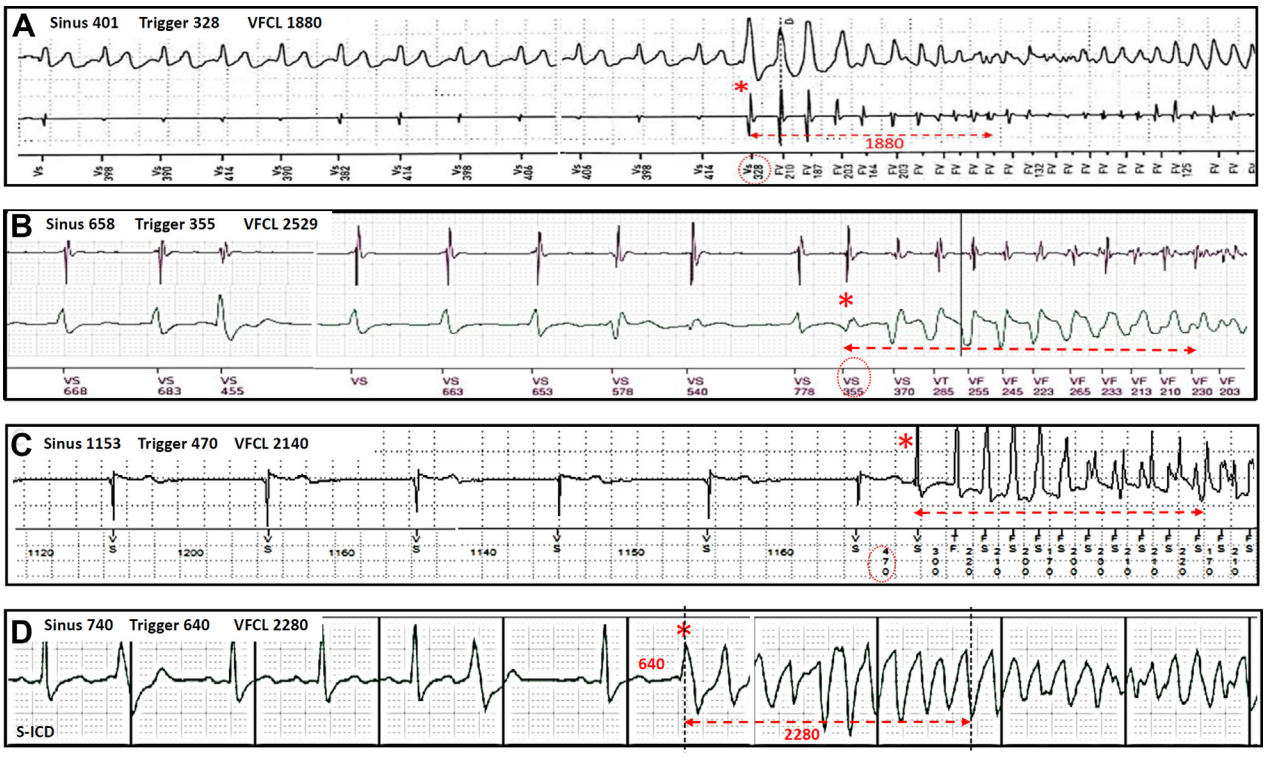
VFCL = ventricular fibrillation cycle length; VT = ventricular tachycardia; other abbreviations as in Table 1.

FIGURE 3 Distribution of VF Characteristics in Patients With IVF With MiCM or Purk



(A to C) The histograms show a more homogeneous distribution of data-points in Purkinje-related VF with clustering at sinus cycle lengths of 600 to 1,000 ms, trigger coupling intervals of 200 to 350 ms, and mean VFCL of <200 ms; in contrast with the wider distribution of MiCM characteristics. (D to F) Relationship between variables. VFCL = ventricular fibrillation cycle length; MiCM = microstructural myocardial substrate; Purk = Purkinje triggers with normal myocardium; other abbreviation as in Figure 1.

FIGURE 4 VF Episodes Associated With Microstructural Myocardial Alterations



Parameters quantifying VF initiation are shown in the top left, all in milliseconds, with VFCL being the sum of 10 cycles. VF triggering is indicated by an asterisk and its coupling interval by a dotted circle. In discontinuous tracings, we have restored continuity while making the reconnection visible. Three cases (B to D) show sinus frequencies between 658 and 1,153 ms (52-91 beats/min), a trigger coupling interval of >350 ms, and a mean VFCL of >195 ms. (A) VF occurring during sport activity (sinus rate of 150 beats/min) with short-coupled trigger and short VFCLs. (D) Subcutaneous ICD recording with manual measurements, the dotted lines indicating QRS peaks. ICD = implantable cardioverter-defibrillator; other abbreviations as in Figures 1 and 3.

$P = 0.0050$). The prediction model was also tested after removing the second VF (22 episodes) and was as accurate (area under the curve 0.95). Taking criteria in line with the receiver-operating characteristic curves, the substrate probabilities under different parameter scenarios are presented in Supplemental Table 4. Up to 81% of patients were predicted with high accuracy (probability score of >80%).

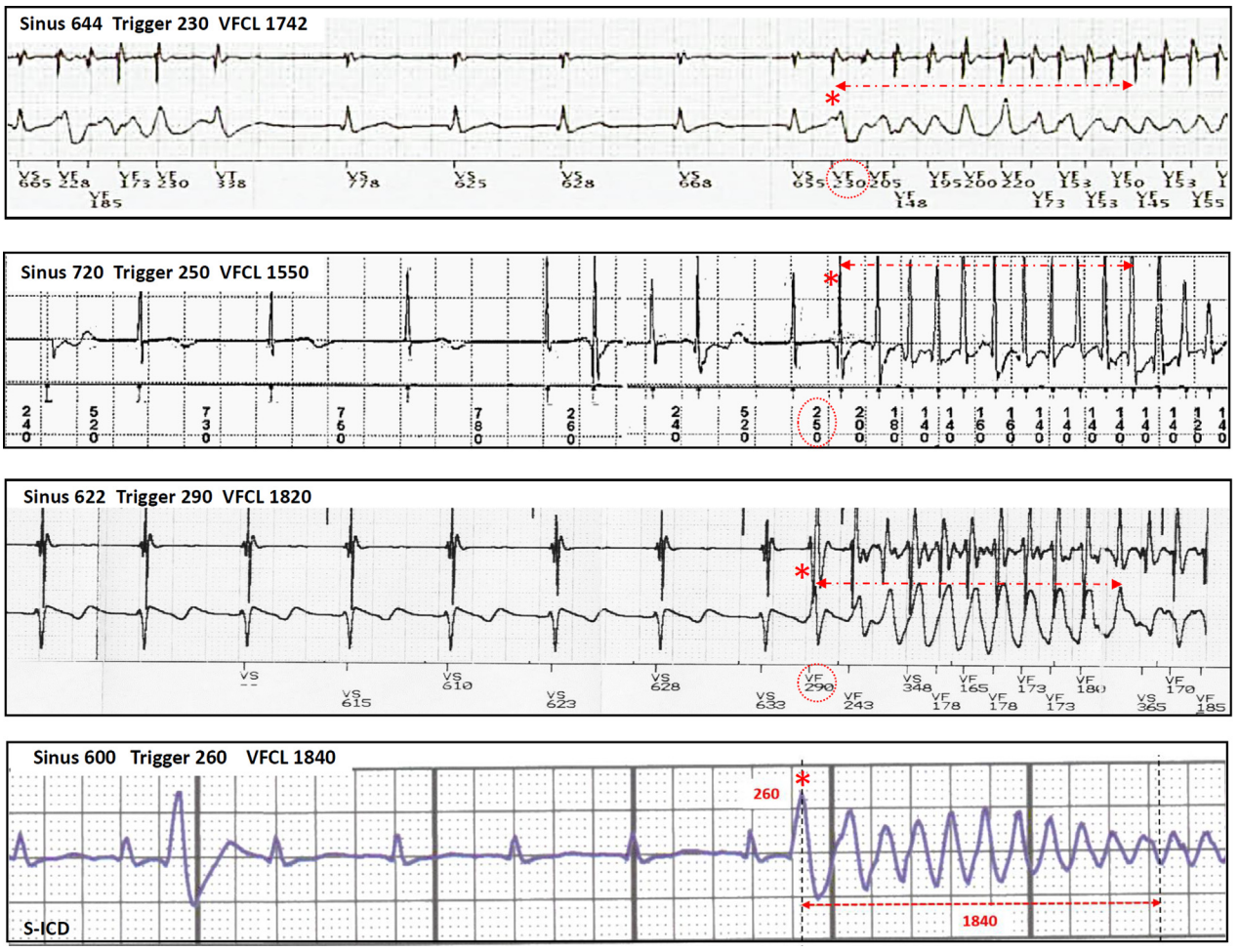
DISCUSSION

This multicenter collaborative study evaluated the characteristics of VF measured on ICD electrograms during a spontaneous arrhythmia recurrence, in patients with IVF with demonstrated Purk or microstructural myocardial abnormalities. It shows distinctive parameters between these substrates, with a combination of criteria allowing to discriminate a majority of patients.

IDIOPATHIC VF. The current diagnosis of unexplained or idiopathic VF is defined as a resuscitated cardiac arrest victim with documented VF, and negative extensive investigations.[1-6] IVF has considerable heterogeneity of presentation and is thought to be associated with undetected conditions, such as ephemeral short-coupled Purk PVCs or microstructural myocardial abnormalities. Purk-related IVF can be demonstrated by mapping the characteristic PVCs, most commonly documented in late recurrence.[10,13] Microstructural myocardial abnormalities can be demonstrated by electrogram mapping showing areas of altered conduction, or by the identification of pathogenic cardiomyopathy genes. The link of MiCM with VF pathogenesis has been established clinically by colocalization of VF activities with structural alterations.[7] or by genetic results using family segregation or functional studies.[4,8]

Arrhythmia recurrences in IVF. The arrhythmia recurrence on ICD recordings provides a remake of

FIGURE 5 **VF Episodes Associated With Purkinje Triggers and Normal Myocardium**



In all 4 patients, VF is preceded by a normal-range sinus rate, and initiated by short-coupling trigger and rapid VFCL. Note the variety of PVC patterns before VF. Abbreviations as in Figures 1 and 3.

the original SCD with the sequence of events leading to VF. We analyzed these recurrences in a large group of patients and observed several criteria predictive of underlying substrate. A short-coupled PVC trigger was a major characteristic of Purk-related VF, as shown previously in IVF and in other conditions, such as infarction, cardiomyopathies, or early repolarization.[14] However short-coupled PVCs could also originate from the myocardium as found here in 23% of MiCM and as reported previously.[20,21] An additional characteristic—preceding the sinus rate—was instrumental to differentiate the substrates, because the short-coupled triggers were associated consistently with sinus tachycardia in MiCM-VF, and rarely in Purk-VFs. In the total group, sinus tachycardia preceded arrhythmia (VF/VT) in 42% of MiCM vs 15% of Purk substrates. This result indicates a proarrhythmic role for sympathetic activity in a significant proportion of MiCM, similar to overt cardiomyopathies and myocarditis.[22]

The initial VF cycles were analyzed independently as an expression of the substrate's conduction properties. Slower VFCLs were observed in most MiCM, as opposed to few Purk-VF. We showed that VFCLs added independent information to trigger coupling interval and sinus rate, resulting in the 3 parameters providing the greatest discrimination. Thus, most Purk-VF occurred with normal sinus rate, short-coupling triggers, and fast VFCL, and vice versa for MiCM-VF. A small subset (9%) had recurrent

arrhythmia in the form of monomorphic VT, mainly associated with MiCM. This finding, previously reported in 23% to 46% IVF, suggests that initial VF resulted from VT degeneration.[23] Our lower incidence of VT is likely related to more systematic use of cardiac magnetic resonance, excluding more patients with structural heart disease.

Finally, the presence of PVCs preceding VF was inconsistent on ICD recordings. Moreover, the information available on spontaneous PVCs was incomplete, owing to limited documentation and provocative tests, whereas systematic collection could help to improve substrate prediction and localization. Besides narrow QRS PVCs of Purk origin, wide QRS PVCs with long coupling were observed originating from the MiCM substrate, a result also reported in other conditions.[24] Studies would be needed to assess their value as an indicator of MiCM, in the specific context of IVF.

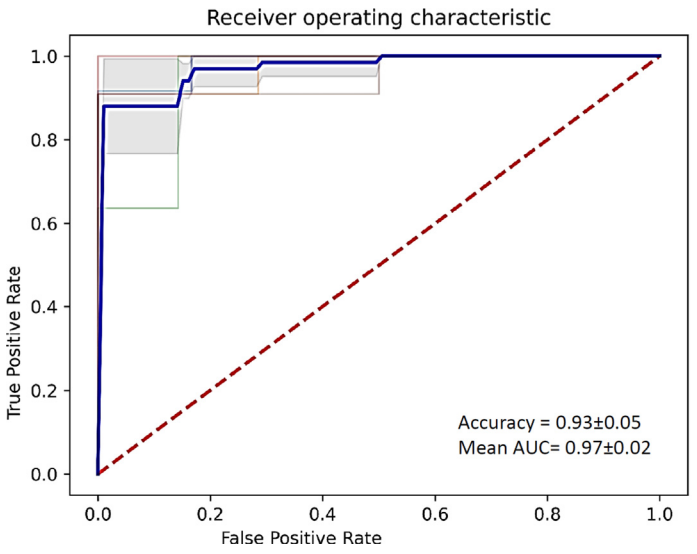
VF RECORDINGS ON ICD ELECTROGRAMS. The ICD electrograms have previously been used to evaluate VF mechanisms, particularly in patients with cardiomyopathies.[25] VFCL is a parameter of complex interpretation; it expresses the rate of focal and reentrant activities, and tissue properties (conduction and refractoriness), these parameters being undefined. VFCLs are reported with great variation among patients and pathologies, but remain consistent in an individual during separate events, suggesting reproducible VF mechanism. Comparisons of VFCLs between studies are difficult because of the diversity in initiation (spontaneous or induced), timing of recordings, or the use of drugs. VFCLs in the order of 220 to 250 ms are consistently reported in patients with structural heart disease, whereas few data are available in patients with apparently normal hearts. Our results showed average VFCLs of 180 and 215 ms in Purk-VF and MiCM-VF, respectively. Importantly, we excluded patients on antiarrhythmic drugs and those with specific causes in which particular mechanisms may be at play (phase 2 re-entry in J-wave syndromes, CPVT). As such, our results are only applicable to the conditions defining IVF.

CLINICAL IMPLICATIONS. The current study shows markers to estimate the probability of cardiomyopathic vs normal myocardium substrates. Subject to confirmation with a larger dataset, these results have implications for patients diagnosed with IVF in whom the cause of death is unknown. With a recurrence rate of ≤46%, electrograms on ICDs provide the opportunity to reanalyze the cause of unexplained SCD. Our results highlight criteria that distinguish Purk and MiCM substrates that can be confirmed by further investigations (long-term 12-lead ECG monitoring to identify PVC morphologies) or used to aid in procedural planning or drug therapy.

The results also may provide clues to investigate family members, and better estimate causes of unexplained SCD in large populations. It may have implications for the genetic analysis of variants of uncertain significance observed in a third of IVF, especially variants linked to cardiomyopathy.[8,26] Such variants may be more likely pathogenic if arrhythmia markers on defibrillator are suggestive of underlying abnormal myocardium.

STUDY LIMITATIONS. First, the results apply to limited dataset and 2 main substrates, whereas other transient or unknown causes (7%, excluded in the present study) may be involved in individuals. Further studies are needed to evaluate larger groups to further validate the prediction accuracy. Second, the mechanisms underlying individual VFs could not be defined, specifically Purk and myocardium refractoriness and conduction, and triggers in MiCM. There is some overlap of criteria between IVF subgroups, which may result from the diversity of

FIGURE 6 ROC Curve Discriminating Between MiCM-VF and Purkinje-VF Using Multivariable Logistic Regression With Cross-Validation



The blue dotted line shows the mean ROC of 6 iterations tested (gray areas representing the SD). ROC = receiver-operating characteristic; other abbreviations as in Figures 1 and 3.

individual myocardial and Purk properties, or from mixed substrates. Third, although a majority of cases were analyzed from intracardiac ICD leads, the current use of subcutaneous devices is associated with smoother signals that allow less accurate measurements. This factor can be improved by additional signal processing.

CONCLUSIONS

This study shows the ability of ICD electrograms to detect differences in VF signatures associated with MiCM or Purk substrates. Under study conditions, the results provide phenotypic markers to predict hidden causes of unexplained SCD.

DATA AVAILABILITY STATEMENT. Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The majority of patients with IVF investigated invasively have a hidden myocardial or Purk substrate. Defibrillator electrograms during arrhythmia recurrence show phenotypic markers expressing characteristics of underlying substrate. IVF related to myocardial microstructural alteration is often associated with sinus tachycardia, indicating higher sympathetic tone and slower VF frequencies, whereas Purk-related IVF is associated with short-coupled triggers and rapid VF frequencies. Combined markers identify substrates in most patients, which influences individual management and helps to interpret genetic variants of uncertain significance. The cardiomyopathy-related variants may be more likely pathogenic if arrhythmia markers on the ICD indicate abnormal myocardial substrate.

TRANSLATIONAL OUTLOOK: Unexplained SCD is a frequent cause of death in people <35 years of age. Further studies on a larger scale are warranted to optimize substrate prediction and estimate the underlying causes. The combination of genetic and phenotypic features of VF may influence the classification of uncertain variants in IVF population.

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KEY WORDS **idiopathic ventricular fibrillation, implantable cardioverter-defibrillator, Purkinje, sudden cardiac death, cardiomyopathy, ventricular fibrillation**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**