ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Suppression of Recurrent Ventricular Fibrillation Associated with J-Wave Syndrome Using Cilostazol

Silostazol Kullanılarak J-Dalga Sendromuyla İlişkili Tekrarlayan Ventriküler Fibrilasyonun Baskılanması

ABSTRACT

Survivors of sudden cardiac death (SCD) should be thoroughly evaluated for primary electrical heart diseases, including early repolarization syndrome (ERS). In some patients, early repolarization patterns may be masked by depolarization abnormalities or may appear intermittently, making diagnosis difficult. In addition to implantable cardioverter-defibrillator (ICD) implantation for secondary prevention, pharmacological agents such as quinidine and phosphodiesterase III inhibitors (e.g., cilostazol) are recommended to prevent or reduce recurrent ventricular fibrillation (VF) episodes. We present the case of a young female SCD survivor with documented VF and ICD implantation, who was admitted after Home Monitoring detected multiple short-coupled premature ventricular contraction-induced (PVC-induced) VF episodes. She was successfully treated with cilostazol.

Keywords: Cilostazol, early repolarization syndrome, ventricular fibrillation

ÖZET

Ani kardiyak ölüm (AKÖ) yaşayanları, erken repolarizasyon sendromu (ERS) dâhil olmak üzere kalbin birincil elektriksel hastalıkları açısından dikkatlice değerlendirilmelidir. Bazı hastalarda erken repolarizasyon paterni depolarizasyon veya aralıklı olarak gizlenebilir ve bu da teşhisi zorlaştırır. İkincil önleme için implante edilebilir kardiyoverter defibrilatör (ICD) implantasyonunun yanı sıra, tekrarlayan VF ataklarını önlemek veya azaltmak için kinidin ve fosfodiesteraz-III inhibitörleri (örn. silostazol) gibi farmakolojik ajanlar önerilir. Bu olguda evden izlem cihazında semptom ile uyumlu çok sayıda kısa eşleşmiş PVC kaynaklı VF atağı tespit edilen ve silostazol ile başarılı bir şekilde tedavi edilen daha öncesinde belgelenmiş VF'ye bağlı AKÖ yaşayanı olan ve ICD implante edilmiş genç bir kadın hasta sunulmuştur.

Anahtar Kelimeler: Silostazol, erken repolarizasyon sendromu, ventriküler fibrilasyon

CASE REPORT
OLGU SUNUMU

Survivors of sudden cardiac death (SCD) with documented ventricular fibrillation (VF) should be evaluated for metabolic, toxicological, structural, and channelopathy causes. Idiopathic VF is a primary electrical disease of the heart and should only be diagnosed after a thorough evaluation excludes any underlying abnormalities.[1] However, in certain primary electrical disorders such as early repolarization syndrome (ERS), electrocardiographic (ECG) findings may be intermittent. As a result, idiopathic VF may be diagnosed when no abnormalities are detected during evaluation, especially if the ECG appears normal at the time of an index event. Intermittent and long-term ECGs monitoring is therefore essential for establishing a definitive diagnosis. Implantable cardioverter-defibrillator (ICD) implantation is indicated for SCD survivors and diagnosed with idiopathic VF or ERS. Although quinidine is an effective treatment for preventing and reducing recurrent VF in both idiopathic VF and ERS, alternative pharmacologic therapies may be considered based on the specific diagnosis and underlying mechanisms. Both preclinical and clinical studies have shown that phosphodiesterase-3 inhibitors, such as cilostazol and milrinone, can reduce VF recurrences in ERS when used alongside quinidine.[1-5]

ERS is classified as a subgroup of J-wave syndromes. The underlying mechanism involves an endo-epicardial transmural electrical gradient, primarily caused by regional differences in the distribution of the transient outward current (Ito). Known

Uğur Canpolat

Kudret Aytemir

Department of Cardiology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye

Corresponding author:
Uğur Canpolat
✉ dru_canpolat@yahoo.com

Received: October 31, 2024
Accepted: January 06, 2025

Cite this article as: Canpolat U, Aytemir K. Suppression of Recurrent Ventricular Fibrillation Associated with J-Wave Syndrome Using Cilostazol. *Turk Kardiyol Dern Ars.* 2025;53(0):000-000.

DOI: 10.5543/tkda.2025.48409

primarily as an antithrombotic agent, cilostazol increases intracellular cyclic adenosine monophosphate (cAMP) levels and enhances the inward calcium current (ICa). It also exerts a blocking effect on Ito. These combined effects have been shown to reduce the endo-epicardial transmural electrical gradient (dispersion) and suppress phase-2 reentry-related extrasystoles and ventricular arrhythmias.[1,2,4]

Herein, we present the case of a young female SCD survivor who was initially misdiagnosed with idiopathic VF and later correctly diagnosed with ERS. Her symptomatic, frequent premature ventricular complex (PVC)-initiated VF episodes, documented on ICD records, were successfully treated with cilostazol.

Case Report

A 41-year-old female patient presented to our center with a history of brief palpitations and fainting episodes dating back to the age of 18. In 2003, she underwent a neurological evaluation for similar symptoms. Her family history was unremarkable, and she reported no use of medications or illicit drugs. She was diagnosed with probable epilepsy following electroencephalography (EEG) and was treated with various antiepileptic medications. However, she continued to experience frequent fainting spells and intermittent syncopal episodes. In January 2006, she was brought to the emergency department after an episode of fainting and loss of consciousness and was evaluated for cardiac arrest. VF was detected and successfully defibrillated, and she was resuscitated after 35 minutes of cardiopulmonary resuscitation (CPR). During hospitalization, a cardiac evaluation, including laboratory tests (electrolytes and thyroid function), 12-lead ECG, echocardiography, 24-hour Holter ECG monitoring, exercise 12-lead ECG, pharmacologic provocation with ajmaline and epinephrine, coronary angiography (with cold pressor testing), and cardiac magnetic resonance imaging (MRI), revealed no abnormalities. Toxicology screening and brain/chest computed tomography were also unremarkable. Due to her history of cardiac arrest and a diagnosis of idiopathic VF, a single-chamber ICD (VVI-ICD, with Riata Defibrillator Electrode; St Jude Medical, Sylmar, CA) was implanted prior to discharge. In 2012, externalization of the Riata defibrillator electrode was detected during a fluoroscopic examination, and the lead was extracted using a hand-powered mechanical dilator sheath. A Biotronik Lumax 340 VR-T (XL) model VVI-ICD with Home Monitoring functionality was subsequently implanted at our center (settings: basal rate 40 bpm, impedance: 646/54 Ohm, R wave: 11.3 mV, VT zone: OFF, VF zone: 200 ms). The 12-lead ECG recorded during the second implantation procedure showed normal sinus rhythm with no abnormal findings (Figure 1A).

During follow-up, no symptoms or abnormalities were observed in the Home Monitoring data. However, in 2017, the Home Monitoring system issued an alert indicating the presence of PVCs and multiple short-duration VF episodes initiated by short-coupled PVCs. Upon calling the patient for an outpatient evaluation, she reported that the episodes of brief palpitations and fainting sensations, previously experienced, had reoccurred. A 12-lead ECG obtained during this visit revealed findings consistent with ERS, a form of J-wave syndrome, which had not been present on prior ECGs. The abnormalities included ST-segment elevation in the inferolateral leads, notching in leads V_{4-6} and slurring in lead I (Figure 1B). We confirmed multiple episodes of short-coupled, PVC-induced VF (Figure 2), although the overall PVC burden was less than 1% based on ICD interrogation. However, given that the VF episodes were initiated by PVCs, we proceeded with a diagnostic electrophysiological study. No tachycardia could be induced during the procedure, and neither spontaneous nor induced PVCs were observed. Since the patient had previously been intolerant to beta-blockers, and quinidine is unavailable in our country, we initiated treatment with cilostazol at 100 mg, based on evidence from the literature. Shortly after initiating therapy, we observed a reduction and eventual complete disappearance of both the PVC frequency and the short-term VF episodes triggered by PVCs, as documented in the Home Monitoring records and ICD interrogations (Figure 3). The patient, who continued clinical and device follow-up visits at six-month intervals, reported no symptoms, ECG findings of ERS, or arrhythmic episodes during the seven-year follow-up period.

ABBREVIATIONS

cAMP	Cyclic adenosine monophosphate
CPR	Cardiopulmonary resuscitation
ECG	Electrocardiography
EEG	Electroencephalography
ERP	Early repolarization pattern
ERS	Early repolarization syndrome
Ica	Inward calcium current
ICD	Implantable cardioverter-defibrillator
Ito	Transient outward current
MRI	Magnetic resonance imaging
PVC-induced	Premature ventricular contraction-induced
SCD	Sudden cardiac death
VF	Ventricular fibrillation

Discussion

Approximately half of all cardiovascular deaths occur as SCD, and nearly half of these patients have no prior history of cardiovascular disease.[1,6,7] In individuals under the age of 50, more than half of SCD cases are attributed to potentially hereditary electrical disorders or structural non-ischemic diseases.[8] Diagnostic tools, including a detailed personal or family history, laboratory tests, 12-lead resting or exercise ECG, Holter ECG monitoring, imaging studies (e.g., echocardiography, computed tomography, and cardiac magnetic resonance imaging), provocative testing, genetic analysis, and invasive electrophysiological studies, should be employed to investigate the underlying etiology of SCD.[1] Physicians should also review any ECG tracings from the emergency department, data from cardiovascular implantable electronic device (CIEDs) interrogation, and serial ECGs obtained during recovery to aid in the etiological evaluation of SCD survivors.[1] After the exclusion of all probable etiologies for documented VF in a SCD survivor, a diagnosis of idiopathic VF is made. In such cases, ICD implantation is recommended for secondary prevention when no reversible cause is identified.[1]

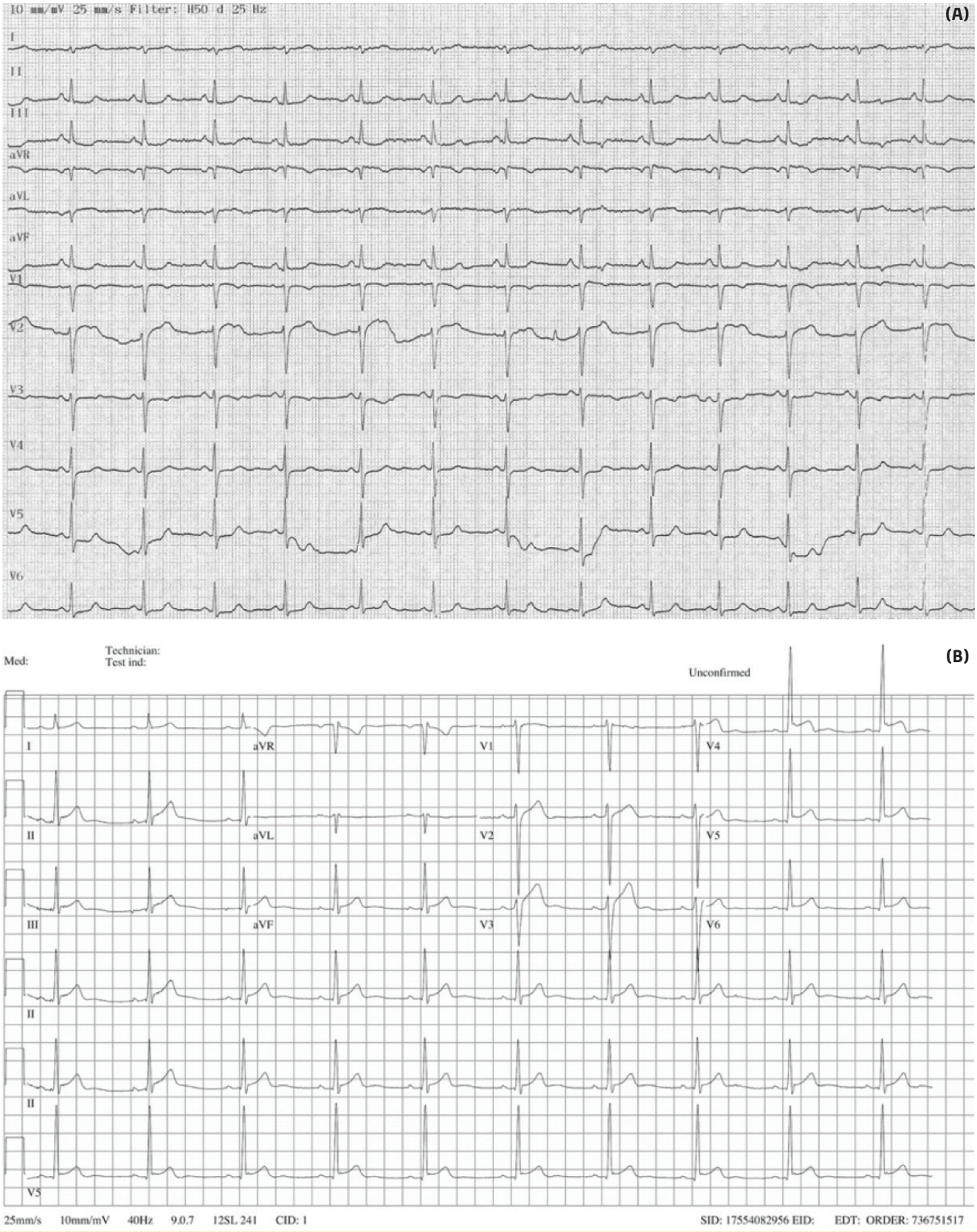

Figure 1. (A) The 12-lead electrocardiogram (ECG) obtained before implantable cardioverter-defibrillator (ICD) implantation showed normal sinus rhythm without any abnormalities suggestive of a channelopathy. (B) The 12-lead electrocardiogram (ECG) recorded during the time of ventricular fibrillation (VF) episodes, as detected by the Home Monitoring system, showed ST-segment elevations in all inferolateral leads, notching in leads V_{4-6}, and slurring in the lead I—findings consistent with early repolarization syndrome (ERS).

Guidelines also recommend the use of quinidine for long-term therapy to suppress electrical storms or recurrent ICD discharges in patients with idiopathic VF. Additionally, catheter ablation should be considered in idiopathic VF patients with recurrent episodes of VF triggered by similar PVCs, most commonly originating from the Purkinje system, especially when these episodes are resistant to antiarrhythmic medications.[1] ERS is diagnosed in patients resuscitated from VF without structural heart disease and is characterized by the presence of an early repolarization pattern (ERP), defined by:

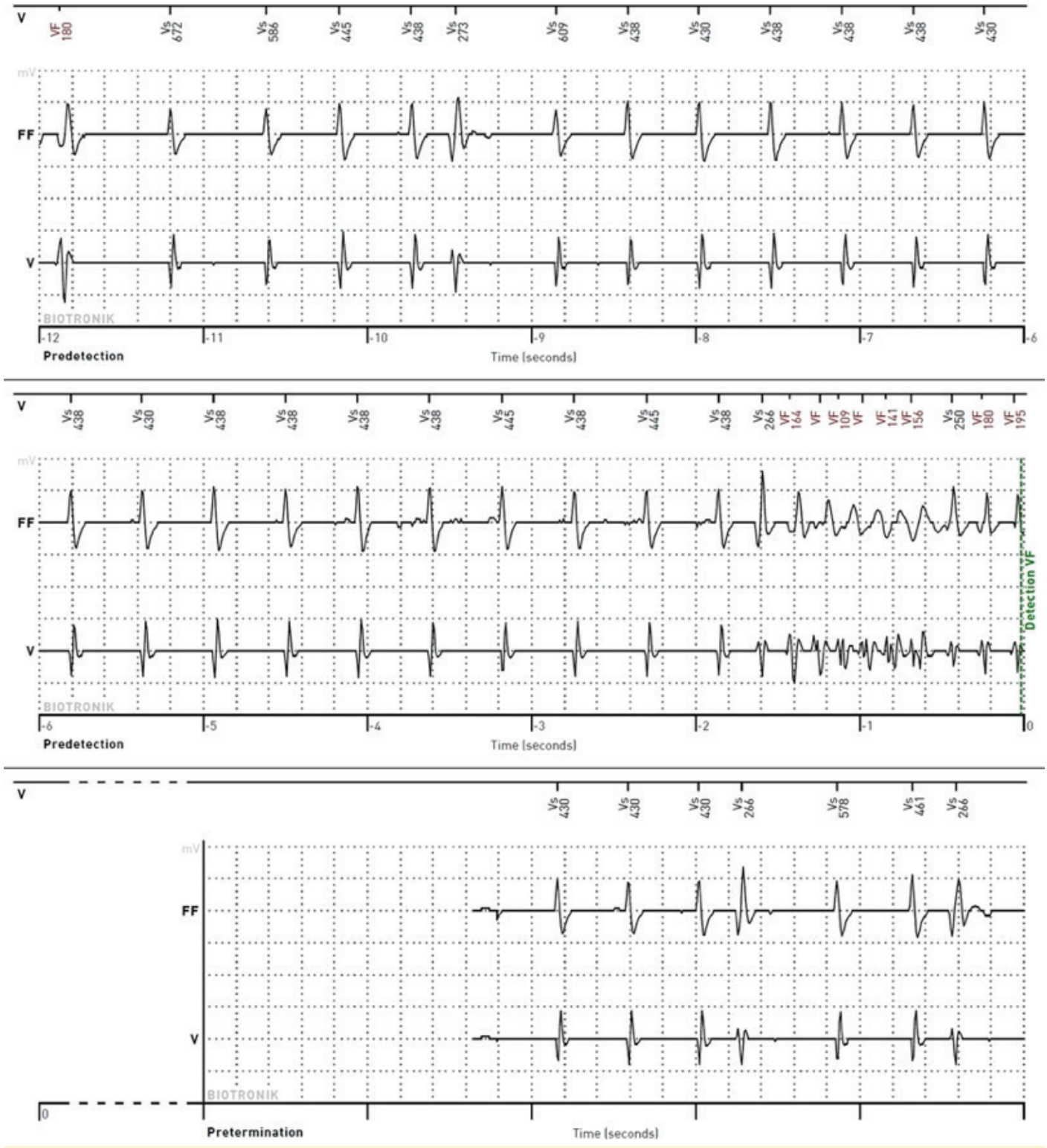

Figure 2. The Home Monitoring alert revealed multiple episodes of short-coupled premature ventricular contraction (PVC)-induced ventricular fibrillation (VF).

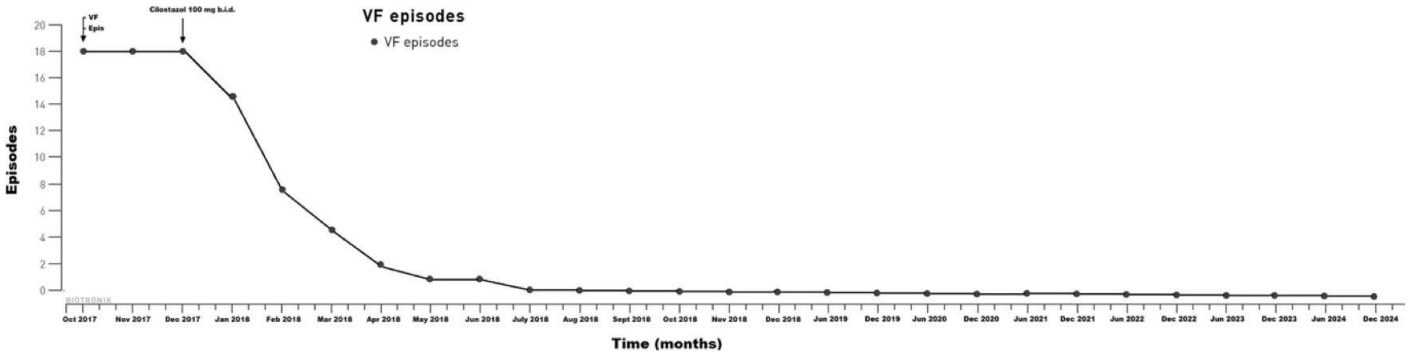

Figure 3. The short-coupled premature ventricular contraction (PVC)-induced ventricular fibrillation (VF) episodes decreased and ultimately disappeared, as shown in the Home Monitoring data and implantable cardioverter-defibrillator (ICD) interrogations, following the initiation of cilostazol 100 mg twice daily during follow-up.

1. An end QRS notch (J wave) or slur on the downslope of a prominent R wave, with or without ST-segment elevation;
2. A peak of the notch or J wave (Jp) ≥ 0.1 mV in ≥ 2 contiguous leads of the 12-lead ECG, excluding leads V1-3; and
3. A QRS duration (measured in leads without a notch or slur) of < 120 ms.[1,9]

The incidence of ERS is underestimated as a potential cause of VF and SCD due to spontaneous fluctuations in the J-wave pattern and the limited opportunity to capture arrhythmia initiation when repolarization abnormalities are at their peak. Additionally, early repolarization may be present but temporally suppressed within the depolarization phase.[10] Data on the pharmacological treatment of recurrent VF episodes in ERS are limited. In addition to quinidine and catheter ablation (in cases of PVC-induced VF), which are also used in idiopathic VF treatment, phosphodiesterase-3 inhibitors such as cilostazol and milrinone also reduce VF recurrence in ERS patients.[2] Cilostazol enhances the ICa by increasing cAMP, reverses repolarization abnormalities, and restores electrical homogeneity across the ventricular wall in ERS. It also blocks the Ito. Both of these mechanisms of cilostazol are effective in suppressing J-wave activity and reducing recurrent VF episodes.[3,9,11,12]

Although our patient had some suspicious cardiac symptoms prior to the episode of sudden cardiac arrest and VF, the condition was initially attributed to convulsions by a neurologist. As mentioned above, no abnormalities related to metabolic, toxicological, structural, or channelopathic etiologies were found in the evaluations performed after the sudden cardiac arrest and VF episode (although an ECG from that event was not available), so our initial diagnosis was idiopathic VF. Since the patient who experienced sudden cardiac arrest was diagnosed with idiopathic VF, an implantable ICD was implanted for secondary prevention. Thanks to the Home Monitoring feature of the device, we detected brief episodes of VF initiated by frequent PVCs. These episodes did not trigger therapy, as they were short in duration. This occurred during a period when the patient experienced a recurrence of symptoms similar to her previous episodes, prompting an early clinic visit. At that admission, the ECG revealed 1 mm ST-segment elevation with a slur on the downslope of the R wave in the lateral leads, and 1.5 mm ST-segment elevation in the inferior leads. Since this finding was not present on the patient's previous ECG, we considered that it was either intermittent or previously masked by depolarization abnormalities.[9,10] Furthermore, the PVCs triggering VF in our patient were short-coupled (< 350 ms), a feature reported in 6.6% of unexplained cardiac arrests in the CASPER registry (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry).[13] As a result, we revised the patient's diagnosis from idiopathic VF to ERS with short-coupled PVC-induced VF. Quinidine is the recommended pharmacological agent for reducing recurrent VF episodes in this setting. However, since quinidine was not available in our country, we initiated low-dose beta-blocker therapy, which the patient could not tolerate due to hypotension. Catheter ablation was not feasible, as no spontaneous or inducible PVCs were observed during the electrophysiological study. As an alternative, we started cilostazol at a dose of 100 mg twice daily, based on its reported effectiveness in case reports from the literature.[4,5] Shortly after initiation, the patient's symptoms resolved, and the short-term VF episodes recorded in the Home Monitoring data decreased and eventually disappeared. We have not observed any recurrence of early repolarization findings on the ECG in the patient, who has also continued regular clinic visits. She has been followed uneventfully for approximately seven years.

Conclusion

In conclusion, patients who present with sudden cardiac arrest and documented VF, and who survive as sudden cardiac death cases, should undergo comprehensive evaluation for underlying cardiac etiologies. Although a diagnosis of idiopathic VF may be made when no cause is identified, clinicians should be aware that some channelopathies may present with intermittent ECG findings and arrhythmic episodes, as observed in our patient. The Home Monitoring feature of ICD devices allows for close follow-up and facilitates early detection of previously unrecognized arrhythmic events. It also ensures timely clinical evaluation during symptomatic periods, enabling accurate diagnosis based on ECG findings. It is important to note that cilostazol, commonly used for its antithrombotic properties, may also be considered an alternative antiarrhythmic therapy to quinidine, as it effectively prevents short-term VF episodes triggered by short-coupled PVCs in patients with ERS, as seen in our patient.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient.

Conflict of Interest: U.C.: Proctoring for Biotronik & Medtronic & Boston Scientific; K.A.: Proctoring for Abbott, Medtronic, Boston Scientific, Biosense Webster, and LifeTech.

Funding: The authors declare that this study received no financial support.

Use of AI for Writing Assistance: This case report did not utilize artificial intelligence (AI)-assisted technologies.

Author Contributions: Concept – U.C., K.A.; Design – U.C., K.A.; Supervision – U.C., K.A.; Resource – U.C.; Materials – U.C.; Data Collection and/or Processing - U.C., K.A.; Analysis and/or Interpretation - U.C., K.A.; Literature Review – U.C.; Writing – U.C., K.A.; Critical Review – U.C., K.A.

Peer-review: Externally peer-reviewed.

References

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43(40):3997-4126. [CrossRef]
2. Patocskai B, Barajas-Martinez H, Hu D, Gurabi Z, Koncz I, Antzelevitch C. Cellular and ionic mechanisms underlying the effects of cilostazol, milrinone, and isoproterenol to suppress arrhythmogenesis in an experimental model of early repolarization syndrome. *Heart Rhythm*. 2016;13(6):1326-1334. [CrossRef]
3. Gurabi Z, Koncz I, Patocskai B, Nesterenko VV, Antzelevitch C. Cellular mechanism underlying hypothermia-induced ventricular tachycardia/ventricular fibrillation in the setting of early repolarization and the protective effect of quinidine, cilostazol, and milrinone. *Circ Arrhythm Electrophysiol*. 2014;7(1):134-142. [CrossRef]
4. Iguchi K, Noda T, Kamakura S, Shimizu W. Beneficial effects of cilostazol in a patient with recurrent ventricular fibrillation associated with early repolarization syndrome. *Heart Rhythm*. 2013;10(4):604-606. [CrossRef]
5. Shinohara T, Ebata Y, Ayabe R, et al. Combination therapy of cilostazol and bepridil suppresses recurrent ventricular fibrillation related to J-wave syndromes. *Heart Rhythm*. 2014;11(8):1441-1445. [CrossRef]
6. Stecker EC, Reinier K, Marijon E, et al. Public health burden of sudden cardiac death in the United States. *Circ Arrhythm Electrophysiol*. 2014;7(2):212-217. [CrossRef]
7. Lynge TH, Risgaard B, Banner J, et al. Nationwide burden of sudden cardiac death: A study of 54,028 deaths in Denmark. *Heart Rhythm*. 2021;18(10):1657-1665. [CrossRef]
8. Risgaard B, Winkel BG, Jabbari R, et al. Burden of sudden cardiac death in persons aged 1 to 49 years: Nationwide study in Denmark. *Circ Arrhythm Electrophysiol*. 2014;7(2):205-211. [CrossRef]
9. Antzelevitch C, Yan GX, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Europace*. 2017;19(4):665-694.
10. Haïssaguerre M, Sacher F, Nogami A, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol*. 2009;53(7):612-619. [CrossRef]
11. Kanlop N, Shinlapawittayatorn K, Sungnoon R, Weerateerangkul P, Chattipakorn S, Chattipakorn N. Cilostazol attenuates ventricular arrhythmia induction and improves defibrillation efficacy in swine. *Can J Physiol Pharmacol*. 2010;88(4):422-428. [CrossRef]
12. Kanlop N, Chattipakorn S, Chattipakorn N. Effects of cilostazol in the heart. J Cardiovasc Med (Hagerstown). 2011;12(2):88-95. [CrossRef]
13. Steinberg C, Davies B, Mellor G, et al. Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: A report from the CASPER registry. *Eur Heart J*. 2021;42(29):2827-2838. [CrossRef]