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KEYWORDS

Early repolarization; J-wave; Syncope; Implantable, loop recorder; Ventricular fibrillation

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BACKGROUND

Syncope in patients with an early repolarization (ER) pattern presents a challenge for clinicians as it has been identified as an indicator of a higher risk of life-threatening ventricular arrhythmias (VAs).

OBJECTIVES

This study aimed to analyze the outcome of patients with an ER pattern and syncope and to evaluate the factors predictive of VAs.

METHODS

Over a period of 5 years, we enrolled 143 patients with an ER pattern and syncope in a multicenter prospective registry.

RESULTS

After the initial examinations, 97 patients (67.8%) were implanted with a device allowing electrocardiogram monitoring including 84 (58.7%) with an implantable loop recorder. During a mean follow-up period of 68 6 34 months, we documented 16 arrhythmias presumably responsible for syncope (5 VAs, 10 bradycardias, and 1 supraventricular tachycardia). Additionally, recurrent syncope not associated with electrocardiogram documentation occurred in 16 patients (11.2%). The cause of syncope was identified in 23 of 97 patients with a monitoring device (23.8%). The 5-year incidence of VAs and arrhythmic events presumably responsible for syncope was 4.9% and 11.0%, respectively. Patients who developed Vas showed no prodromes or specific triggers at the time of syncope. Neither the presence of a family history of sudden cardiac death nor the previously reported high-risk electrocardiographic parameters differed between patients with and without VAs.

CONCLUSION

VAs occurred in 4.9% of patients with an ER pattern and syncope. Device implantation based on detailed history taking seems to be a reasonable strategy. Previously reported high-risk electrocardiographic patterns did not identify patients with VAs.

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Introduction

The early repolarization (ER) pattern or inferolateral J wave is a common electrocardiographic feature that occurs in 2%–31%of individuals.[1,2] Controversial data have been published on the impact of these electrocardiographic findings. When present in >/=2 contiguous inferior and/or lateral leads, this pattern has been associated with a higher risk of death due to life-threatening ventricular arrhythmia.[3,4] In this context, distinguishing between arrhythmic and nonarrhythmic syncope in patients with ER remains a difficult challenge for clinicians.

According to the current expert consensus statement, implantable cardioverter-defibrillator (ICD) placement may be considered (class IIb indication) in patients with ER, a history of syncope of arrhythmic origin, and a strong family history of sudden death at a young age.5 Meticulous clinical follow-up or monitoring with implantable loop recorder (ILR) placement are strategies suggested for patients with syncope of an unknown origin. However, the long-term outcome of such patients is currently unknown and data supporting the optimal clinical strategy are scarce.5

Therefore, we performed a multicenter prospective study with the objectives of investigating the long-term outcome of patients with ER pattern and a history of syncope as well as of identifying predictive characteristics of arrhythmiarelated syncope to optimize the management of this condition.

Methods

Study population

This study included all patients with syncope from a French national prospective registry on ER. This registry was held from 2009 to 2014 and funded by a national grant (PHRC: DGOS 20-12). This study was conducted according to the European guidelines for clinical and genetic research and was performed in accordance with the Helsinki Declaration, as revised in 2013. The respective institutional ethics committees approved the use of the clinical and genetic databases. Written informed consent was obtained from each patient.

Patients underwent transthoracic echocardiography and had no apparent structural heart disease. Clinical examinations performed are listed in Online Supplemental Table 1.

Electrocardiographic analysis

Electrocardiograms (ECGs) were analyzed by 2 physicians (T.K. and F.S.) blinded to the clinical data. A third physician evaluation was conducted in cases of disagreement. The ER pattern was identified on the basis of the presence of a Jpoint elevation of >/=0.1 mV in>/=2 contiguous inferolateral leads in at least 1 ECG recording. The criteria for the identification of an ER pattern were as follows: an amplitude of the inferolateral J-point elevation of >/=0.1 mV above the baseline level, manifesting as either QRS slurring or notching in any of the inferior (II, III, and aVF) and lateral (I and aVL or V4–V6) leads. Slurring or notching had to occur in the final 50% of the R-wave downslope. The QRS interval in patients with an ER pattern had to be<120 ms. The amplitude of the J point was evaluated at the peak of the notch or at the onset of slurring.2 An ST segment with an amplitude exceeding 100 ms after the end of the ER pattern (ie, the end of the notch or slur) vs that observed at the end of the ER pattern indicated the ascending ST segment. An ST segment of an amplitude of >/=100 ms after the end of the ER pattern vs that observed at the end of the ER pattern indicated the horizontal or descending ST segment.6 The corrected QT (QTc) interval was evaluated using the Bazett formula, and an abnormal QTc interval was defined as <360 and >/=440 ms during sinus rhythm.

Pharmacological tests were performed in 70 patients (49.0%) using ajmaline (1 mg/kg body weight for 10 minutes) or flecainide (2 mg/kg body weight for 10 minutes) to rule out Brugada syndrome.

Clinical data

The clinical data including age at the time of diagnosis, sex, family history of sudden cardiac death at<45 years of age in a first- or second-degree relative, detailed personal history, and prognosis were collated for all patients.

According to the European Society of Cardiology guidelines, a presumed diagnosis of "arrhythmic syncope" was made in the event of sudden-onset syncope either without prodromes or without triggers for reflex or situational syncope or when syncope was associated with nocturnal agonal respiration.[7,8] A presumed diagnosis of "nonarrhythmic syncope" was made in the event of reflex syncope or orthostatic hypotension, which was associated with at least 1 typical prodrome or 1 trigger. The prodromes included nausea, vomiting, pallor, or yawning, and typical triggers were emotional distress, prolonged standing, or being in crowded or hot spaces. A syncope of an "unknown origin" was defined when distinctive elements of arrhythmic and nonarrhythmic syncope could not be established or detailed information about syncope was unavailable.

The head-up tilt test was performed in 74 patients (51.7%). A positive response to tilt testing was defined as the induction of syncope or presyncope in the presence of bradycardia, hypotension, or both. An electrophysiological test was performed in 39 patients (27.2%). At least 2 extrastimuli with a minimum coupling interval of 200 ms were delivered from at least 1 right ventricular site until ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) was induced.

Device implantation and follow-up

Device implantation was left to the discretion of each physician. Arrhythmic events presumably responsible for syncope included ventricular tachyarrhythmias, bradycardias, and supraventricular tachycardia when they were detected at the time of recurrent syncope. Ventricular tachyarrhythmias were defined as the occurrence of ILR-documented monomorphic or polymorphic VT or VF, appropriate ICD shock, or sudden death. Bradycardias were defined as symptomatic sinus bradycardia (heart rate less than 40 beats/min), sinus arrest >3 seconds, or high-degree atrioventricular block (AVB) (Mobitz II second-degree AVB or third-degree AVB).

Statistical analysis

Data were analyzed using JMP12 software (SAS Institute Inc., Cary, NC). Continuous variables are presented as mean +/- SD and analyzed using the independent Student t test or Mann-Whitney U test, wherever appropriate. Categorical variables are expressed as number and percentage and were analyzed using the Fisher exact test or χ^2 test. The Kaplan-Meier curve was used to assess the time to syncope or arrhythmic events and ventricular tachyarrhythmia. P values <.05 were considered statistically significant.

Table 1 Patient characteristics

Characteristic	Total (N = 143)	VA/SCD (+) (n = 6)	VA/SCD (−) (n = 137)	*P*
Clinical characteristics				
Age at diagnosis (y)	33.9 ± 15.3	27.8 ± 12.4	34.1 ± 15.4	.27
Male sex	124 (86.7)	6 (100)	118 (86.1)	1.0
Family history of SCD	17 (11.9)	1 (16.7)	16 (11.7)	.54
Positive head-up tilt testing	30/74 (40.5)	0/1 (0)	30/73 (41.1)	1.0
Induction of VT/VF by EPS	2/39 (5.1)	1/1 (100)	1/38 (2.6)	.051
Occurrence of syncope				
Prodromes or specific trigger	75/127 (59.1)	1/6 (16.7)	74/121 (61.2)	.042
Situation				
Exercise	22 (15.4)	0 (0)	22 (16.1)	.59
Rest or light movement	89 (62.2)	5 (83.3)	84 (61.3)	.41
Unknown	32 (22.4)	1 (16.7)	31 (22.6)	1.0
Convulsion	15 (10.5)	4 (66.7)	11 (8.0)	.0011
Agonal respiration	2 (1.4)	2 (33.3)	0 (0)	.0015
Injury after syncope	19 (13.3)	1 (16.7)	18 (13.1)	.58
Arrhythmic syncope	20 (14.0)	5 (83.3)	15 (11.0)	.0002
Nonarrhythmic syncope	48 (33.6)	0 (0)	48 (35.0)	.18
Syncope of unknown origin	75 (52.4)	1 (16.7)	74 (54.0)	.10
Electrocardiographic findings				
QRS interval (ms)	91.4 ± 12.0	91.7 ± 10.7	91.4 ± 12.1	.95
QTc interval (ms)	391.1 ± 27.5	375.8 ± 11.7	391.8 ± 27.8	.018
J-point elevation ≥ 0.2 mV	90 (62.9)	6 (100)	84 (61.3)	.085
Horizontal/descending ST segment	24 (16.8)	2 (33.3)	22 (16.1)	.26
Inferior ER pattern (II, III, aVF)	120 (83.9)	4 (66.7)	116 (84.7)	.25
Lateral ER pattern (I, aVL, V_4–V_6)	91 (63.6)	4 (66.7)	87 (63.5)	1.0
Inferior + lateral ER pattern	68 (47.6)	2 (33.3)	66 (48.2)	.68

Values are presented as mean ± SD, n (%), or n/total n (%).

EPS = electrophysiology study; ER = early repolarization; Family history of SCD = family history of sudden cardiac death before 45 y of age in a first-degree or second-degree relative; QTc = corrected QT; SCD = sudden cardiac death; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

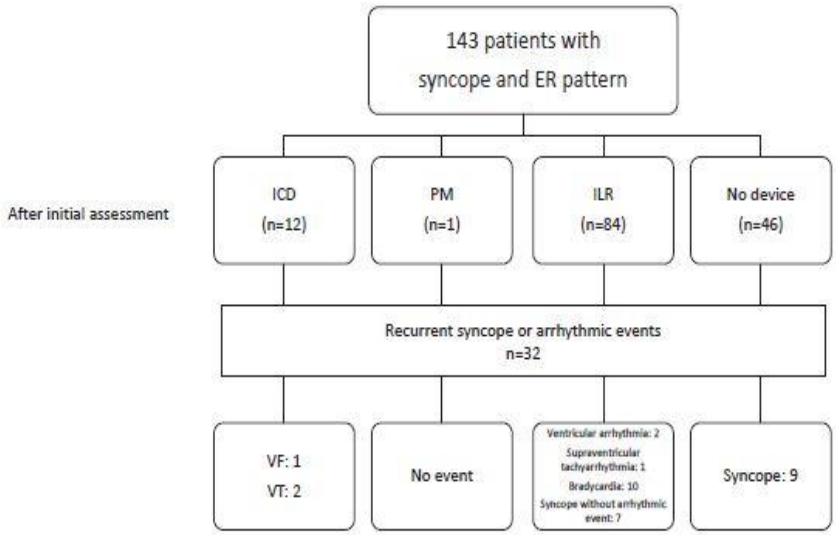


Figure 1 Flowchart of this study. After the initial assessment, 12, 1, and 84 patients were monitored using ICD, PM, and ILR placement, respectively. Forty-seven patients were monitored without device implantation. Recurrent syncope or arrhythmic events occurred in 32 patients during the follow-up period. ER = early repolarization; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; PM = pacemaker; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

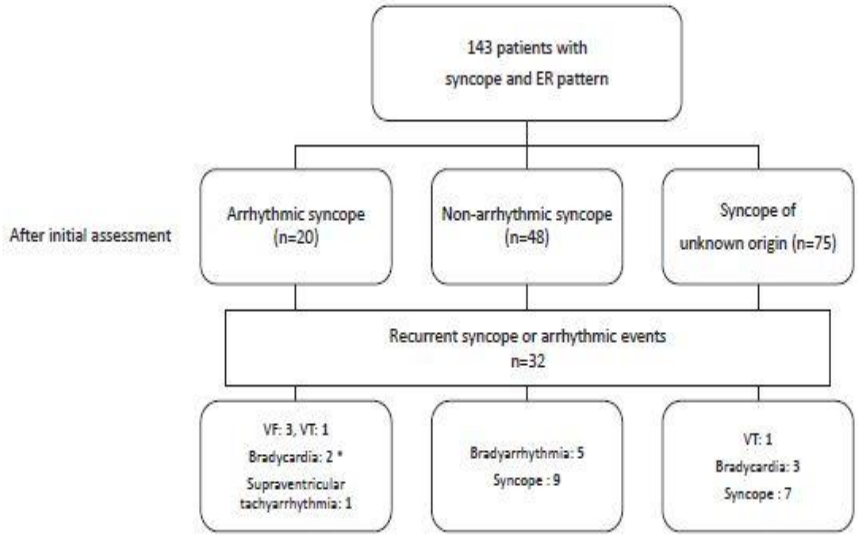


Figure 2 Clinical outcomes depending on the type of syncope. After the initial assessment, 20, 48, and 75 patients were deemed to have arrhythmic syncope, nonarrhythmic syncope, and syncope of unknown origin, respectively. Ventricular tachyarrhythmias or sudden cardiac death occurred in 6 patients: 5 diagnosed with arrhythmic syncope and 1 with syncope of unknown origin. Bradycardias occurred in 2 patients with arrhythmic syncope, 5 with nonarrhythmic syncope, and 3 with syncope of unknown origin. ER = early repolarization; VF = ventricular fibrillation; VT = ventricular tachycardia. *One of 2 patients with bradyarrhythmia died suddenly.

Results

General characteristics

A total of 143 patients were enrolled in this study (124 men; mean age 33.9 +/- 15.3 years). Their clinical characteristics are detailed in Table 1. Among them, 24 patients (16.8%) had a family history of sudden cardiac death before 45 years of age, including 17 (11.9%) in a first-degree or second degree relative. Prodromes or specific triggers were observed in 75 of 127 patients (59.1%). A type 1 Brugada pattern was not observed in any of the patients during the follow-up period. VF was induced in 2 of 39 patients (5.1%). On the basis of the proposed Shanghai score system,5 1 patient was diagnosed with probable/definite ER syndrome (ERS) (score >5), 31 with possible ERS (score 3–4.5), and 111 with nondiagnostic (score <3) at the time of admission.

After the initial assessment, 20 patients (14.0%) were deemed to have arrhythmic syncope, of whom 12 underwent ICD placement, 5 underwent ILR placement, and 1 underwent pacemaker placement owing to the detection of paroxysmal AVB. Forty-eight patients (33.6%) were diagnosed with nonarrhythmic syncope. Among them, 33 patients (23.1%) were then followed clinically whereas 15 (10.5%) underwent ILR placement. In the remaining 75 patients (52.4%), the cause of syncope was unknown; among them, 64 (44.8%) were monitored with ILR placement. Overall, 97 patients (67.8%) were monitored with a cardiac implantable device, including 84 with ILR, 12 with ICD, and 1 with pacemaker (Figure 1).

Long-term outcomes

Thirty-two patients (22.4%) experienced recurrent episodes of syncope or arrhythmias that were responsible for syncope during 68.4+/- 33.9 months of follow-up. Five patients (3.5%) had ventricular tachyarrhythmias (VF: 3 and VT: 2), 10 (7.0%) had bradycardias (sinus arrest: 7, sinus bradycardia: 1, and paroxysmal AVB: 2), and 1 (0.7%) had supraventricular tachycardia. One of 10 patients with bradycardia died suddenly at the age of 35 years. His initial syncope was suspected to be of arrhythmic origin, and an ILR was implanted. Although sinus arrest was detected by the ILR, he refused to undergo device implantation. Electrocardiograms at the time of sudden death could not be obtained. Sixteen patients (11.2%) (7 with ILR and 9 without ECG monitoring) experienced recurrent syncope without the documentation of arrhythmia. No arrhythmic events were observed during recurrent syncope in 7 patients with ILR; therefore, the cause of syncope was considered to be noncardiac. The cause of syncope in 9 patients without ECG monitoring is unknown; however, 8 of 9 patients were initially diagnosed with reflex syncope, which was also seemingly observed in most of their recurrent episodes. Finally, 4 patients were diagnosed with probable/definite ERS (3 with VF and 1 with bradycardia).

Overall, ventricular tachyarrhythmias or sudden cardiac death occurred in 6 patients: 5 diagnosed with arrhythmic syncope and 1 with syncope of unknown origin (Figures 2 and 3). Bradycardias occurred in 2 patients with arrhythmic syncope, 5 with nonarrhythmic syncope, and 3 with syncope of unknown origin. The incidence of a positive response to the head-up tilt test was not significantly different between patients with and without bradycardias (with vs without bradycardia: 42.9% vs 40.3%; P >.99).

The outcomes according to the type of implanted device are shown in Figure 1. The cause of syncope was identified in 23 of 97 patients with a monitoring device (23.8%). Eighteen patients with ILR experienced recurrent syncope or arrhythmias in their first implanted ILR, and 2 had bradycardias after the ILR exchange. After the documentation of arrhythmic events by the ILR, 9 patients underwent device implantation (ICD: 4 and pacemaker: 5). In addition to the 2 patients with ventricular arrhythmia, 2 with bradycardia underwent ICD implantation because of concerns regarding ventricular arrhythmic events due to the presence of the ER pattern. One patient with a pacemaker did not have recurrent syncope.

Nine of 46 patients without device implantation experienced a recurrent episode of syncope. All the 9 patients with recurrent syncope were deemed to have nonarrhythmic syncope, and none of them underwent device implantation.

Characteristics of patients with ventricular arrhythmias

The incidences of ventricular tachyarrhythmias including sudden death and arrhythmic events presumably related to syncope at 5 years were 4.9% and 11.0%, respectively (Figure 4). The clinical characteristics of the 6 patients with ventricular tachyarrhythmias are listed in Tables 1 and 2 and Figure 5. The incidence of prodromes or specific triggers before syncope was significantly lower in patients with ventricular tachyarrhythmias than in those without ventricular tachyarrhythmias. The QTc interval was significantly shorter in patients with ventricular arrhythmias than in those without ventricular tachyarrhythmias. Importantly, there were no significant differences in the previously reported high-risk ECG markers between patients with and without ventricular tachyarrhythmias in this study, such as large-amplitude

ER, presence of a broad ER pattern, and horizontal or descending ST segment after the ER pattern and other clinical characteristics, such as a family history of sudden cardiac death.

Among patients with ventricular tachyarrhythmias, 2 had monomorphic VT (cases 1 and 5) and 3 had nonsustained VF (cases 2, 3, and 4). The mean coupling interval of premature ventricular contraction, which initiated nonsustained VF, was 320.0 +/- 84.5 ms.

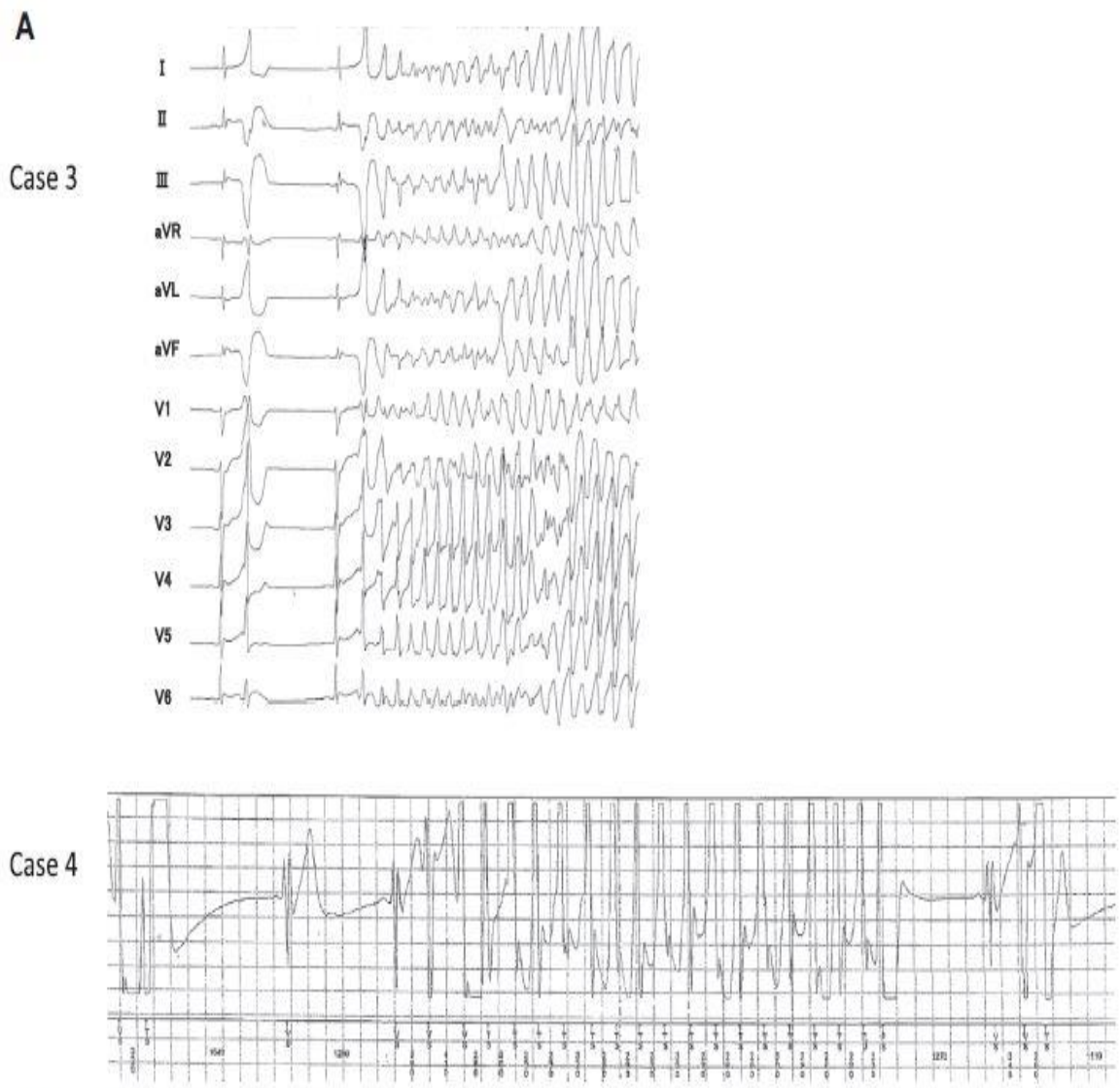
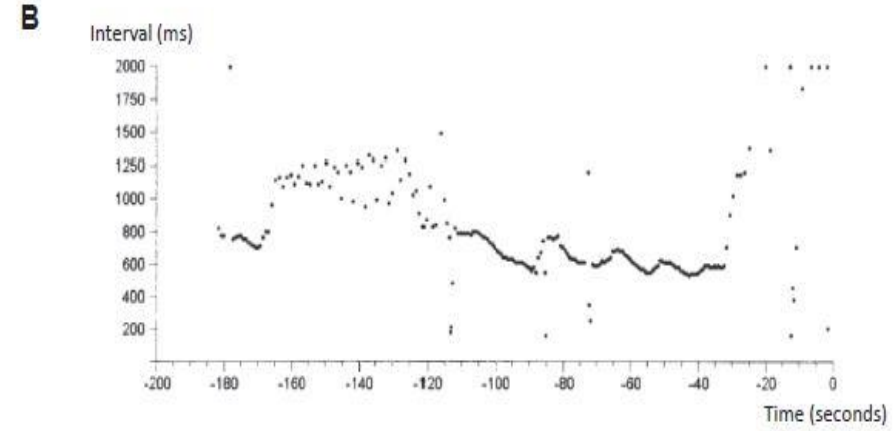


Figure 3 Arrhythmic events. **A:** Two cases of nonsustained VF. Nonsustained VF was detected by 12-lead ECG during hospitalization after recurrent episodes of syncope (case 3) (*upper figure*). Nonsustained VF was detected by an ILR during follow-up (case 4) (*lower figure*). **B:** Sinus arrest detected by an ILR. ECG = electrocardiogram; ILR = implantable loop recorder; VF = ventricular fibrillation.



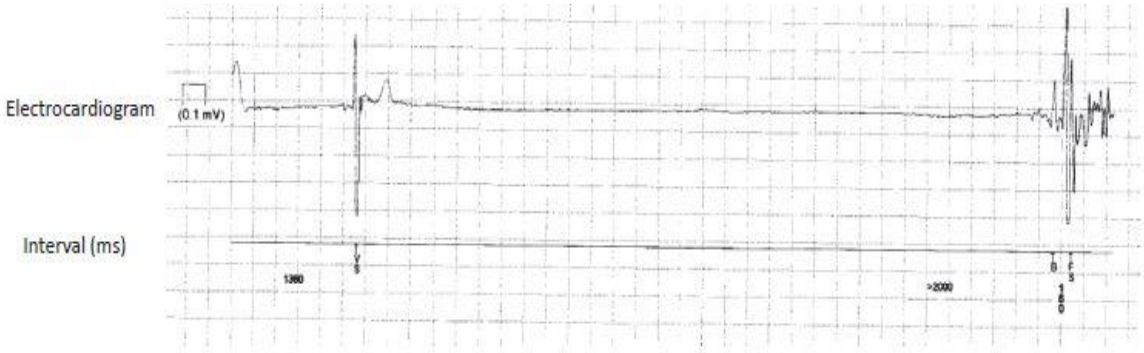


Figure 3 Continued.

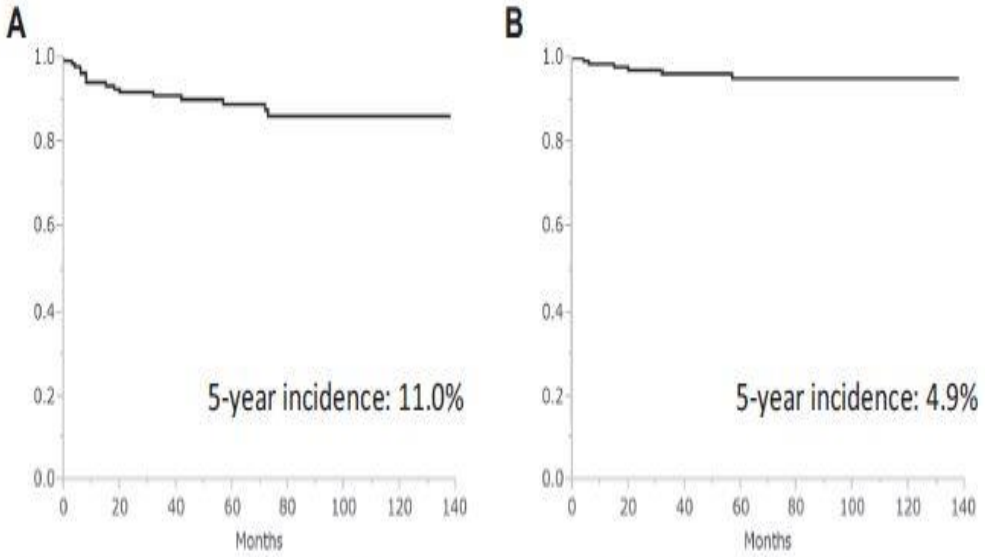


Figure 4 Kaplan-Meier analysis of freedom from arrhythmic events (panel A) and sudden cardiac death or ventricular tachyarrhythmia (panel B). **A:** The incidence of arrhythmic events presumably related to syncope at 5 years after diagnosis was 11.0%. Arrhythmic events included sudden cardiac death, ventricular tachyarrhythmias, supraventricular tachycardias, and bradycardias. **B:** The incidence of sudden cardiac death or ventricular tachyarrhythmia at 5 years after diagnosis was 4.9%.

Table 2 Clinical characteristics of patients with ventricular tachyarrhythmias or SCD during follow-up

Case no.	Age at diagnosis (y)	Situation at the time of syncope	Prodrome or specific trigger before syncope	Associated symptom	Family history of SCD	VA	ER location	J-point elevation (mV)	QTc interval (ms)	ST segment
1	27	Rest	Hot flush	–	–	VT	Lateral	2.5	378	Ascending
2	16	After exertion	–	Convulsion	–	VF	Inferior	2.5	367	Ascending/horizontal
3	13	Rest	–	Agonal respiration	–	VF	Inferolateral	2	393	Ascending/horizontal/descending
4	47	Sleep	–	Agonal respiration	–	VF	Lateral	2	380	Ascending
5	33	Rest	–	Convulsion	–	VT	Inferior	2	378	Ascending
6	31	Rest	–	Convulsion	Yes	SCD	Inferolateral	3	359	Ascending

ER = early repolarization; Family history of SCD = family history of sudden cardiac death before 45 y of age in a first-degree or second-degree relative; QTc = corrected QT; SCD = sudden cardiac death; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Discussion

To our knowledge, this is the largest study to describe the long-term prognosis of patients with ER pattern and a history of syncope. The salient findings of this study were as follows: first, 22.4% of patients with ER pattern and a history of syncope experienced recurrent episodes of syncope or arrhythmic event presumably related to syncope including ventricular tachyarrhythmias, supraventricular tachycardias, and bradycardias during the 5.7-year follow-up period; however, the association of these events with ER is yet to be elucidated; second, the 5-year incidence of ventricular arrhythmias or sudden cardiac death was 4.9%, which occurred mostly in patients with syncope of presumably arrhythmic origin. In contrast, bradycardias were detected irrespective of the type of syncope; third, the ILR helped to identify the cause of syncope in 23.8% of patients; fourth, device implantation based on a detailed patient history may be a rational option for the management of patients with ER pattern and a history of syncope, as neither a family history of sudden cardiac death nor the previously reported ECG parameters were predictive of future ventricular arrhythmic events in this study.

Syncope in patients with an ER pattern

Syncope in patients with an ER pattern presents a dilemma, ever since ER has been shown to be a possible indicator of ventricular tachyarrhythmias. The differentiation between syncope due to malignant and benign arrhythmias is often difficult, akin to Brugada syndrome.[8] Although several indicative ECG parameters have been proposed in patients with an ER pattern,[5,6] risk stratification remains a challenging task. The inducibility of VF during electrophysiology studies failed to predict arrhythmic events[9] and is not helpful in this situation. Several studies suggested a possible relationship between ER and reflex syncope.[10,11] Therefore, patients with an ER pattern may suffer from both arrhythmic and reflex syncope,[12] complicating the evaluation of syncope in such patients.

Significance of ILR monitoring

A previous study that included 13 patients with an ER pattern and a history of syncope reported that no ventricular arrhythmias occurred during the 22-month follow-up period.[13] However, 1 case report described spontaneous VF documentation by the ILR in a patient with ER and previous syncope.[12]

This present study included the largest number of patients with an ER pattern and a history of syncope. Moreover, most patients (67.8%) were followed up with a cardiac implantable electronic device, which provided accurate information on the association between syncope and arrhythmic events. The incidence of ventricular arrhythmias or sudden cardiac death at the 5-year follow-up period was 4.9%, which occurred mostly in patients with syncope suspected to be of arrhythmic origin. This study also shows that only a small number of typical patients with ERS and polymorphic VT, VF, or sudden cardiac death were found, even in those with ER and syncope. Furthermore, continuous ILR monitoring enabled the detection of bradycardias, considered as a possible cause of syncope in 7% of patients. Of note, the incidence of bradycardias was higher than the incidence of ventricular tachyarrhythmias. Similarly, continuous ILR monitoring revealed that bradycardias were detected more frequently than ventricular arrhythmias in patients with Brugada syndrome.14,15 This is consistent with previous studies that used ILRs for the diagnosis of unexplained syncope, in which the events were caused by bradycardias in the majority of patients.16

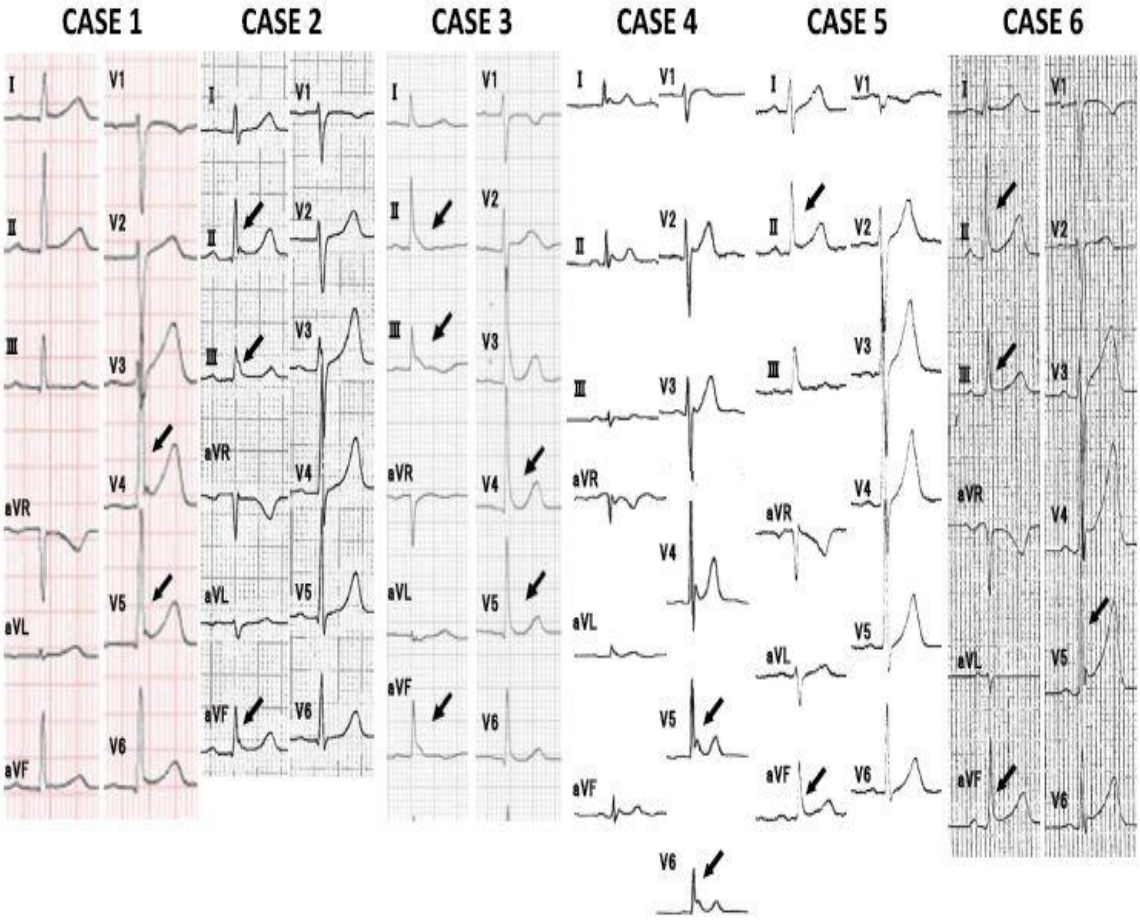


Figure 5 Twelve-lead electrocardiograms of the 6 patients with ventricular tachyarrhythmias or sudden cardiac death.

Management of patients with an ER pattern and syncope

Risk stratification in patients with an ER pattern remains a challenging task. The current consensus statement proposes device implantation based on the presence of arrhythmic syncope and a strong family history of sudden death at a young age.5 This study showed that

patients who developed ventricular arrhythmias during follow-up were more likely to present with syncope of arrhythmic origin. The QT interval was significantly shorter in these patients, consistent with previous studies in patients with an ER pattern, suggesting a higher risk associated with a short QT interval.[17] However, neither a family history of sudden cardiac death nor previously reported ECG parameters, such as large-amplitude ER, presence of a broad ER pattern, or a horizontal or descending ST segment, were found to be associated with ventricular tachyarrhythmias. This indicates that acquiring a detailed patient history is the only reliable factor for determining whether an ICD is indicated in a given case and may be the cornerstone for decision making.

Although further confirmation in larger groups of patients is still required, our results suggest that an ICD seems appropriate if the circumstances of the syncope are in favor of an arrhythmic event, as 25% of patients with arrhythmic syncope had ventricular arrhythmias or sudden cardiac death during the follow-up period. In cases of an indeterminate situation or recurrent syncope, ILR placement should be recommended. Vagal response–mediated bradycardia can be detected by an ILR even in patients with reflex syncope. When the link between syncope and asystole is confirmed, cardiac pacing may help limit the recurrence of syncope after cardioinhibitory reflex syncope.[7,18]

Limitations

The low incidence of ventricular tachyarrhythmic events that occurred in our population is the main limitation of this study, although this is the largest reported population in the literature. Previously reported high-risk ECG markers were not predictive of future ventricular arrhythmic events in this study; however, it has already been acknowledged that the risk of these ECG markers is too low to justify an ICD implantation in asymptomatic patients with an ER pattern.[19] Therefore, our study does not refute the association between these ECG markers and ventricular arrhythmias in patients with ERS. Furthermore, monomorphic VT is an atypical clinical presentation for ERS and an ER pattern might be an innocent bystander in these cases. As only a few patients with ERS were included in our cohort, elucidating the mechanism of ERS is beyond the scope of this study. This study consisted of relatively young patients; therefore, the generalizability of our findings to all age groups may not be appropriate, because older patients with an ER pattern and syncope may have different clinical characteristics and outcomes than do younger patients. Further studies with a larger sample size and longer follow-up are required to identify high-risk features that can predict future events.

Conclusion

Recurrent syncope or arrhythmia presumably responsible for syncope occurred in nearly a quarter of the large cohort of patients with ER pattern and a history of syncope during the 5.7-year follow-up period. Previously reported high-risk ECG parameters were not predictive of ventricular arrhythmia during follow-up in this series. Device implantation based on detailed history taking may form a reasonable strategy. The use of ILR can be helpful in guiding the management of patients with syncope of unknown origin and recurrent syncope.

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