Early Repolarization Syndrome

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Editor
Wataru Shimizu
Department of Cardiovascular Medicine
Nippon Medical School
Tokyo
Japan

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Contents

Chapter 1
Epidemiology, Prevalence of J Wave, and Early Repolarization Syndrome

Meiso Hayashi and Wataru Shimizu

Abstract The early repolarization pattern and J wave were recognized during the very early period after the invention of the ECG. While the J wave has been reported to become prominent in particular circumstances, i.e., hypothermia, hypercalcemia, and brain damages, early repolarization has long been considered to be a benign finding, which is attributable to the definition of early repolarization during the period that included not only end-QRS notching/slurring but also ST segment elevation continuing to the upward concave ST segment and tall T wave. The prevalence of an early repolarization pattern and its predictive value has varied widely among the studies published more recently, which presumably were due to the diversity of the definitions. In the reports, either in case control studies or population studies, showing an association between an early repolarization pattern and cardiac or arrhythmic death, the definition has been based on J point elevation with notched or slurred J wave in the inferior or lateral leads, while early repolarization based on ST segment elevation seldom has shown any increased risk. The accumulated evidence has also demonstrated that even in those with J point elevation, the arrhythmic risk does not increase with a concave ST segment morphology. The definition of an early repolarization pattern should be unified and standardized to better stratify the risk of arrhythmic death.

1.1 J Wave and an Early Repolarization Pattern in Electrocardiograms: A Historical View

The point between the QRS and ST segment in an electrocardiogram (ECG) was historically called the "RS-T junction" [1]. At this junctional point, later named the J point, depolarization ends and repolarization begins. In most ECG recordings, no particular deflections are seen at the J point, but distinct waves or end-QRS notching can be observed in rare cases, which are called J waves [2]. A burial of the J wave

M. Hayashi, M.D. (✉) • W. Shimizu, M.D., Ph.D.
Department of Cardiovascular Medicine, Nippon Medical School,
1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
e-mail: m-h4510@nms.ac.jp

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in the QRS can also be manifested as an end-QRS slurring. In 1938, Tomaszewski [3] reported a J wave in a case who accidentally froze to death. Fifteen years later, Osborn [4] described the J wave in dogs with experimental hypothermia as a "current of injury," because it manifested at a rectal temperature under 25 °C and gradually increased before the development of ventricular fibrillation (VF). After his outstanding work, the J wave was named the "Osborn wave," but earlier reports [5–9] suggested that the J wave was not specific for hypothermia. It was also seen in clinical cases or experimental models with hypercalcemia [8, 9], head injuries [5, 7], or subarachnoid hemorrhages [6].

Early repolarization was also recognized in the early period after the introduction of the ECG into clinical practice. The early definition of an early repolarization pattern was comprised of ST segment elevation, the J wave, and specific T wave characteristics. In 1936, Shipley and Hallaran [10] studied four-lead ECGs (leads I, II, III, and one apex-left leg lead) of 200 healthy individuals aged between 20 and 35, most of whom were medical students, interns, or nurses. They reported that ST segment elevation was observed in 11%, 22%, and 4% of the lead I, II, and III recordings, respectively. End-QRS notching or slurring was also frequently seen in 6.5%, 9.5%, and 44% of the lead I, II, and III recordings, respectively. In the following earlier studies [11–13], the early repolarization pattern on the ECG was defined as (1) an elevated takeoff of the ST segment at the J point, (2) a distinct notch or slur on the downstroke of the R wave, (3) an upward concavity of the ST segment, and (4) a tall upright T wave. This pattern was usually seen in the mid to left precordial leads (V3–V6). These reports [10–13] demonstrated that the early repolarization pattern was a sign of a normal variant which was not related to organic heart disease, because almost all of the patients did not show any abnormal symptoms or findings suggestive of cardiovascular diseases at the time of the ECG recordings.

The early repolarization pattern, thus, has long been considered to be a benign ECG manifestation, which was further supported by the results of the follow-up studies [14, 15]. In 1962, Fenichel [14] reported the follow-up results of 75 patients with apparently normal hearts who exhibited a concave RS-T elevation in the 12-lead ECG, which was most often seen in lead II (62%) followed by leads I (45%) and III (33%) with an average ST segment elevation of 0.9, 0.7, and 0.7 mm, respectively. It was also described that almost all of those patients exhibited a smooth curve from the descending limb of the R wave to the elevated ST segment, continuing in a concave course to a tall T wave, which was similar to the definition of the early repolarization pattern in the earlier studies [11–13]. During an average follow-up period of 8 years, heart disease developed in only two patients; both were angina pectoris. In 2003, Klatsky et al. [15] published a study examining the ECGs from 73,088 patients who underwent health examinations. They found 670 early repolarization ECGs (0.9%), and the participants with those ECG characteristics (37 ± 13 years old) were not more likely to be hospitalized (hazard ratio [HR] 1.0) or to die (HR 0.8) during a follow-up period of about 14 years. Early repolarization was more evident in the precordial leads (85%) than the limb leads, but only three

Table 1.1 The definition of early repolarization electrocardiograms in the population studies

Authors	Year published	Position of ERP	Definition of the early repolarization pattern
Klatsky et al. [15]	2003	All	ST segment elevation ≥1.0 mm
Tikkanen et al. [16]	2009	Inf or Lat	J point elevation ≥1.0 mm with notched or slurred J wave
Sinner et al. [17]	2010	Inf or Lat	J point elevation ≥1.0 mm with notched or slurred J wave
Uberoi et al. [18]	2011	Inf or Lat	ST segment elevation ≥1.0 mm with J wave or slurring
Olson [19]	2011	All	J point elevation ≥1.0 mm
Haruta et al. [20]	2011	Inf or Lat	J point elevation ≥1.0 mm with notched J wave or ST segment elevation ≥1.0 following slurred J wave
Rollin et al. [21]	2012	Inf or Lat	J point elevation ≥1.0 mm with notched or slurred J wave
Hisamatsu et al. [22]	2013	All	J point elevation ≥1.0 mm in Inf or Lat or J point elevation ≥2.0 mm in ant (V1–V4)
Aagaard [23]	2014	All	ST segment elevation ≥1.0 mm followed by an ascending/ upsloping ST segment
Ilkhanoff et al. [24]	2014	V3–V6	J point elevation >1.0 mm, prominent J point, upward concavity of the ST segment, and other criteria[a,b]

Ant anterior leads, *Inf* inferior leads, *Lat* lateral leads

[a]Definite and probable ERP requires a T-wave amplitude of ≥5.0 mm in V_3–V_6 and ≥8.0 mm in any chest lead, respectively

[b]Definite ERP further requires distinct notch or slur on the downstroke of the R wave

chest leads (V1, V3, and V5) were recorded. It is noteworthy in this study that the definition of early repolarization was only an ST segment elevation of ≥1.0 mm (0.1 mV) (Table 1.1). The J wave was seen in 29% of these patients, which was more frequent than that in the ECGs without early repolarization (0.4%), but the specific analytic data were not provided in those with early repolarization and the J wave.

In spite of the publications shown above, the association between early repolarization and an increased risk of death was not abandoned. In 1984, Otto et al. [25] reported three cases of sudden nocturnal death in Southeast Asian immigrants who had been resuscitated. There were no remarkable ECG findings in the two men, but another 30-year-old man, who had no evidence of coronary artery disease, was described as having "marked ST-segment elevation in leads V2 through V6" with a figure of ECG strip demonstrating a remarkable J wave. ST segment elevation related to sudden cardiac death in young to middle-aged healthy persons received a lot of attention after a historical report of eight Brugada syndrome patients in 1992 [26]. The following case reports [27, 28] showing recurrent VF in patients with the J wave and ST segment elevation in the inferior leads suggested that the J wave and early repolarization pattern were not always signs of a normal variant. In 2008, a

seminal work was published by Haissaguerre et al. [29], in which ECG characteristics were compared between 206 patients (36 ± 11 years old) resuscitated from idiopathic VF and 412 matched controls. Early repolarization was more frequently observed in the idiopathic VF patients than in the controls (31% vs. 4%, $P < 0.001$). Among the idiopathic VF patients, the incidence of recurrent VF during a mean follow-up of 61 ± 50 months was higher in those with early repolarization than in those without (HR 2.1, $P = 0.008$). In this study, the definition of early repolarization was an elevation of the J point ≥1.0 mm, either as QRS slurring or notching in at least two of the inferior or lateral leads. In the same year, Rosso et al. [30] also reported that an early repolarization pattern, defined as J point elevation with positive "hump-like" deflections in the inferior or lateral leads, was more frequent in 45 patients (38 ± 15 years old) with idiopathic VF than in matched controls (42% vs. 13%, $P = 0.001$). Interestingly, neither the presence of ST segment elevation nor QRS slurring was useful for identifying patients with VF in their study. These two studies [29, 30] emphasized that among the early-period criteria of the early repolarization pattern [11–13], a distinct notch or slur at the J point (J wave) was not a benign but a precarious sign possibly related to idiopathic VF.

In the HRS/EHRA/APHRS Expert Consensus Statement [31] published in 2013, early repolarization syndrome was diagnosed in the presence of a J point elevation ≥1.0 mm in ≥2 contiguous inferior and/or lateral leads in a patient resuscitated from otherwise unexplained VF/polymorphic VT. In a sudden cardiac death, the victim with a negative autopsy and medical chart showing such an ECG could also be diagnosed with early repolarization syndrome. In that statement, the early repolarization pattern was based on the J point elevation, not on the ST segment elevation. The J wave expert consensus report [32] endorsed by the APHRS, EHRA, HRS, and SOLAECE in 2016 updated the definition of the early repolarization pattern as the following: (1) an end-QRS notch (J wave) or slur on the downslope of a prominent R wave with and without ST segment elevation, (2) a peak of the notch or J wave ≥0.1 mV in ≥2 contiguous ECG leads excluding V1–V3, and (3) a QRS duration in the leads in which a notch or slur was absent <120 ms. The report [32] also proposed a diagnostic scoring system for early repolarization syndrome.

1.2 Prevalence and Prognostic Value of the Early Repolarization Pattern in the General Population

In studies [29, 30, 33–35] examining ECGs of idiopathic VF patients, the early repolarization pattern defined as a J point elevation ≥0.1 mV in ≥2 contiguous leads was seen in around 20–60% of those patients. As an early repolarization pattern is considered no longer to be a benign finding, the prevalence of this ECG manifestation naturally attracts our interest. Table 1.2 summarizes the results from the publication of the population studies [15–24], in which the prevalence of an early repolarization pattern was presented. The prevalence differs among the various

Table 1.2 The prevalence of early repolarization ECGs and their prognostic value in the population studies

Authors	Country	Individuals screened, *n*	Male sex	Mean age at baseline, years	Prevalence of repolarization		Mean follow-up period, years	Adjusted RR according to the ERP	
					≥0.1 mV, *n* (%)	≥0.2 mV, *n* (%)		Cardiac death	Sudden or arrhythmic death
Klatsky et al. [15]	USA	73,088	44%	Not described	670 (0.9)	494 (0.7)	14	0.8[a]	Not described
Tikkanen et al. [16]	Finland	10,864	52%	44 ± 8	630 (5.8)	67 (0.6)	30 ± 11	1.28[b] in Inf	1.43[b] in Inf
								1.34[b] in Lat	0.75 in Lat
Sinner et al. [17]	Germany	6213	49%	52 ± 10	812 (13.1)	Not described	19	3.44[b]	Not described
Uberoi et al. [18]	USA	29,281	87%	55 ± 15	664 (2.3)	0	8 ± 4	1.73 in Inf[a]	Not described
								0.83 in Lat[a]	
Olson [19]	USA	15,141	44%	54 ± 6	1866 (12.3)	Not described	17 ± 4	Not described	1.23 in all
									2.03[b] in whites
Haruta et al. [20]	Japan	5976	44%	Not described	1429 (23.9)	Not described	24 ± 15	0.75[b]	1.83[b]
Rollin et al. [21]	France	1161	52%	50 ± 9	159 (13.7)	74 (6.4)	14 ± 2	5.28[b] in Inf	Not described
								6.27[b] in Lat[a]	
Hisamatsu et al. [22]	Japan	7630	41%	52	264 (3.5)	Not described	15	2.54[b]	Not described
Aagaard [23]	USA	211,920	52%	58 ± 13	3450 (1.5)	Not described	8 ± 3	0.98[c]	Not described
Ilkhanoff et al. [24]	USA	5039	46%	25	1249 (20.9)[d]	Not described	23	0.96[a]	Not described

Ant anterior leads, *ECG* electrocardiogram, *ERP* early repolarization pattern, *Inf* inferior leads, *Lat* lateral leads, *RR* relative risk, *USA* United States of America

[a]For cardiovascular death

[b]Statistically significant

[c]Death from any cause

[d]At baseline

See Table 1.1

researches, ranging from 0.9% to 23.9%. Early repolarization ≥0.2 mV also varies from 0% to 6.4% [15, 16, 18, 21]. One reason for such diversity among the studies may come from the difference in the study cohorts, namely, the age, sex, and ethnic distribution, because early repolarization is shown to be more prevalent in those with a younger age, male sex, and African descents [19, 20, 23, 24, 36]. One study [24], showing a high prevalence of early repolarization (20.9%), examined a population with a mean age of 25 years old, while the others included the middle-aged subjects (Table 1.2). The methodology used in evaluating the ECGs and the frequency of the evaluation may also influence on the prevalence, as an intermittent appearance of an early repolarization pattern is observed [20, 24]. Haruta et al. [20] reported the highest prevalence of 23.9%, which was attributable to the serial ECG testing in their study in which an intermittent early repolarization ECG was recorded in 55% of the cases. The definition of the early repolarization pattern, which is shown in Table 1.1, is another reason and should be the primary reason for the differences. Among the ten studies listed [14, 16–23, 35], an ST elevation ≥1.0 mm, not J point elevation, was used for the early repolarization criteria in three studies [15, 18, 23], all of which revealed a low frequency of an early repolarization pattern, ranging from 0.9% to 1.5%. It seems not to have much of an influence on the prevalence of an early repolarization ECG, whether all ECG leads or only the inferior and lateral leads are evaluated (Tables 1.1 and 1.2).

Table 1.2 also demonstrated an adjusted relative risk of an early repolarization pattern on cardiac or sudden arrhythmic death. A statistically significant association was observed in only half of the studies listed. One possible reason for these results may be the ethnic or genetic contribution to the relationship between the early repolarization and cardiac/arrhythmic events. European studies [16, 17, 21] and Japanese studies [20, 22] showed a significant association between early repolarization pattern and cardiac or sudden arrhythmic death; however, it was hardly demonstrated in the studies conducted in the United States [15, 18, 19, 23, 24]. Olson et al. [19] showed that early repolarization was associated with an increased risk of sudden cardiac death in whites but not in blacks. Another and more plausible reason is, again, a difference in the definition of the early repolarization pattern. As seen in the Tables 1.1 and 1.2, early repolarization was not associated with an increased risk of future events in all three studies [15, 18, 23] using ST segment elevation in the definition. In two of the three studies [15, 23], the J wave was seen in only 29% and 39% of the patients with ST segment-based early repolarization. Another study [18] showed that lateral or global ST segment elevation was even associated with a decreased risk of cardiovascular death in an unadjusted Cox hazard analysis, and the trends without statistical significance remained after the analysis with a covariate adjustment. These results suggest that an ST segment elevation ≥1.0 mm itself is not an appropriate marker for evaluating the future risk of events or probably for a definition of an early repolarization pattern. On the contrary, the early repolarization pattern based on the J point elevation was associated with an increased risk of future events in five [16, 17, 20–22] out of the seven studies listed in Table 1.2. In four [16, 17, 20, 21] out of the five studies, notched or slurred J wave was mentioned in the definition of early repolarization (Table 1.1).

Not only J point elevation but also a following ST segment morphology may have an influence on the predictive value of the early repolarization pattern. One study [24] including J point elevation ≥1.0 mm in the definition of early repolarization did not show an increased risk of cardiovascular death, but the definition also required an upward concavity of the ST segment and tall T waves, which was similar to the definition used in the earlier studies [11–14] reporting that early repolarization was not an abnormal finding. Another recent study [23] with the early repolarization defined as an ST segment elevation ≥1.0 mm followed by an ascending/upsloping ST segment also showed no increased risk of death. These results suggest that J point/ST segment elevation with a concave (similar to ascending/upsloping) ST segment is a specific subset that does not increase the risk. Tikkanen et al. [37] reanalyzed their study cohort showing a positive association between early repolarization and cardiac/arrhythmic death [16] and found that an ST segment morphology had a significant prognostic impact. They classified an ST segment morphology as horizontal/descending and ascending/upsloping defined as a ≤1.0 and >1.0 mm elevation in the ST segment 100 ms after the J point, respectively. Among a 10,864 general middle-aged population, early repolarization defined as a J point elevation ≥0.1 mV in at least two inferior or lateral leads was present in 576 cases (5.3%) with a horizontal/descending and ascending/upsloping ST segment in 71.5% and 28.5%, respectively. An age- and sex-adjusted risk of sudden arrhythmic death was significantly higher in those with early repolarization with a horizontal/descending ST segment (HR 1.43; 95% CI 1.05–1.94) than in those without early repolarization, while it was not in those with early repolarization with an ascending/upsloping ST segment (HR 0.89; 95% CI 0.52–1.55). The increased risk from the early repolarization pattern with a horizontal/descending ST segment was also confirmed by Rosso et al. [38] They demonstrated that the J wave with a horizontal/descending ST segment was seen in 68%, 25%, and 14% among 19 patients with a history of idiopathic VF, 16 matched controls, and 28 young athletes, respectively. Recent consensus paper as well as these data strongly recommended standardizing a definition of the early repolarization pattern together with the ST segment morphology [39].

Other factors associated with arrhythmic death would be the lead location showing the J wave and degree of the J point elevation. Tikkanen et al. [16] demonstrated that the risk of arrhythmic death was not associated with the J point elevation in the lateral leads in the absence of the concomitant early repolarization in the inferior leads. Compared with individuals without early repolarization, the adjusted relative risk of arrhythmic death in those with J point elevation ≥0.1 mV in the inferior leads was 1.43 (Table 1.2) and was much higher (2.92) in those with a J point elevation >0.2 mV in the inferior leads. The adjusted relative risk was further increased to 3.14 (95% CI 1.56–6.30), in cases with J point elevation >0.2 mV with a horizontal/descending ST segment in the inferior leads.

Finally, even though the cardiac or arrhythmic event rates increase in those with early repolarization ECGs, the calculated relative risk seems modest (Table 1.2). Given the high prevalence of an early repolarization pattern, and the quite low odds for the occurrence of idiopathic VF in individuals aged 35–45 years (3.4 in 100,000

persons) [38], the early repolarization in asymptomatic individuals is not considered to be a sign of a high arrhythmic risk [30]. At the same time, however, the mounting data also suggest that the early repolarization pattern is a sign of arrhythmic events in those with Brugada syndrome [40, 41] or coronary artery disease [42, 43]. Further studies are warranted to better stratify the patients with early repolarization who really are at risk.

1.3 Conclusions

The early repolarization has long been recognized as a finding of normal variant. ST segment elevation continuing to the upward concave ST segment and tall T wave, one part of the classic definition of the early repolarization pattern, has been demonstrated a benign clinical course, but since the last decade of the twentieth century, many reports have notified the association between end-QRS notching/slurring, another part of the definition, and an increased risk of death. The prevalence and predictive value of early repolarization pattern also varied among the studies due to the diversity of its definition. Early repolarization pattern based on J point elevation with notched or slurred J wave in the inferior or lateral leads has associated with statistically significant increase of arrhythmic or cardiac death risk, while that based on ST segment elevation seldom has shown any increased risk. There also were evidences demonstrated that sudden arrhythmic death risk was higher in early repolarization with a horizontal/descending ST segment but not in that with an ascending/upsloping ST segment. To better stratify the risk of arrhythmic death, standardized definition of the early repolarization pattern and ST segment morphology are warranted.

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Chapter 2
Clinical Diagnosis and Manifestation of Early Repolarization Syndrome

Hiroshi Watanabe and Tohru Minamino

Abstract Although early repolarization has generally been considered benign for decades, there is increasing evidence that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death. Early repolarization pattern in the inferior and/or lateral leads has recently been associated with increased risk of sudden cardiac death, and early repolarization syndrome has been proposed as a new entity of idiopathic ventricular fibrillation. Diagnostic criteria for early repolarization syndrome proposed in the expert consensus statement is available, but there are still some controversies about the diagnosis. Early repolarization syndrome shares clinical characteristics with Brugada syndrome, but the unique characteristics may be helpful for diagnosis and risk stratification.

2.1 Introduction

Early repolarization or J wave is characterized by an elevation at the junction between the end of the QRS complex and the beginning of the ST segment (J-point) in a 12-lead electrocardiogram and has generally been considered benign for decades [1]. However, early repolarization can be observed under various negative biological conditions, such as low body temperature and ischemia [2–4], and there is increasing evidence that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death [5–7].

In 2008, Haissaguerre et al. reported that early repolarization pattern in the inferior and/or lateral leads is associated with increased risk of sudden cardiac death, and early repolarization syndrome has been proposed as a new entity of idiopathic ventricular fibrillation [5]. Moreover, early repolarization in the right precordial leads has also been associated with idiopathic ventricular fibrillation [8]. Heritability

H. Watanabe, M.D., Ph.D., F.E.S.C. (✉) • T. Minamino, M.D., Ph.D., F.E.S.C., F.A.H.A.
Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Niigata 951-8510, Japan
e-mail: hiroshiwatanabe@med.niigata-u.ac.jp

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of early repolarization has been shown in a recent population-based study [9], and as in other arrhythmia syndromes such as long QT syndrome and Brugada syndrome [10], ion channel genes are responsible for early repolarization syndrome [11–14].

2.2 Diagnosis of Early Repolarization Syndrome

Early repolarization was defined as an elevation of the J-point either as QRS slurring or notching ≥0.1 mV in ≥2 consecutive leads of a standard 12-lead electrocardiogram in the original report by Haissaguerre et al., and the criteria is used for diagnosis of early repolarization syndrome [15].

In 2013, diagnostic criteria were proposed in the expert consensus statement of Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society (Table 2.1) [15]. In a patient resuscitated from sudden cardiac death, early repolarization syndrome is diagnosed if J-point elevation ≥1 mm is present in ≥2 consecutive inferior and/or lateral leads of a standard 12-lead electrocardiogram. Furthermore, in a patient with sudden cardiac death who is negative for autopsy and medical chart review, early repolarization syndrome can be diagnosed if J-point elevation ≥1 mm is present in ≥2 consecutive inferior and/or lateral leads of a standard 12-lead electrocardiogram.

However, there are various problems in diagnosis of early repolarization syndrome. Early repolarization is affected by various factors such as autonomic tone and heart rate [16, 17]. The amplitude of J-point elevation is associated with severity of early repolarization syndrome and is often elevated before events of ventricular fibrillation (Fig. 2.1) [5]. On the other hand, early repolarization pattern may disappear [17].

There are similarities of clinical characteristics between early repolarization syndrome and Brugada syndrome, and Brugada syndrome should always be considered as a differential diagnosis in the diagnostic process of early polarization syndrome. In the expert consensus statement for diagnosis, the presence of early repolarization pattern is limited in inferior and lateral leads of 12-lead electrocardiogram [15]. However, J-point elevation in the right precordial leads, which does not meet the criteria for diagnosis of Brugada syndrome, can be seen in those with idiopathic ventricular fibrillation and those with sudden cardiac death [8, 18]. Actually, 21–39%

Table 2.1 Diagnostic criteria for early repolarization syndrome

1. Early repolarization syndrome is diagnosed in the presence of J-point elevation ≥1 mm in ≥2 consecutive inferior and/or lateral leads of a standard 12-lead electrocardiogram in a patient resuscitated from sudden cardiac death
2. Early repolarization syndrome can be diagnosed in a patient with sudden cardiac death and early repolarization in inferior and/or lateral leads of electrocardiogram who is negative for autopsy and medical chart review

Modified from HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

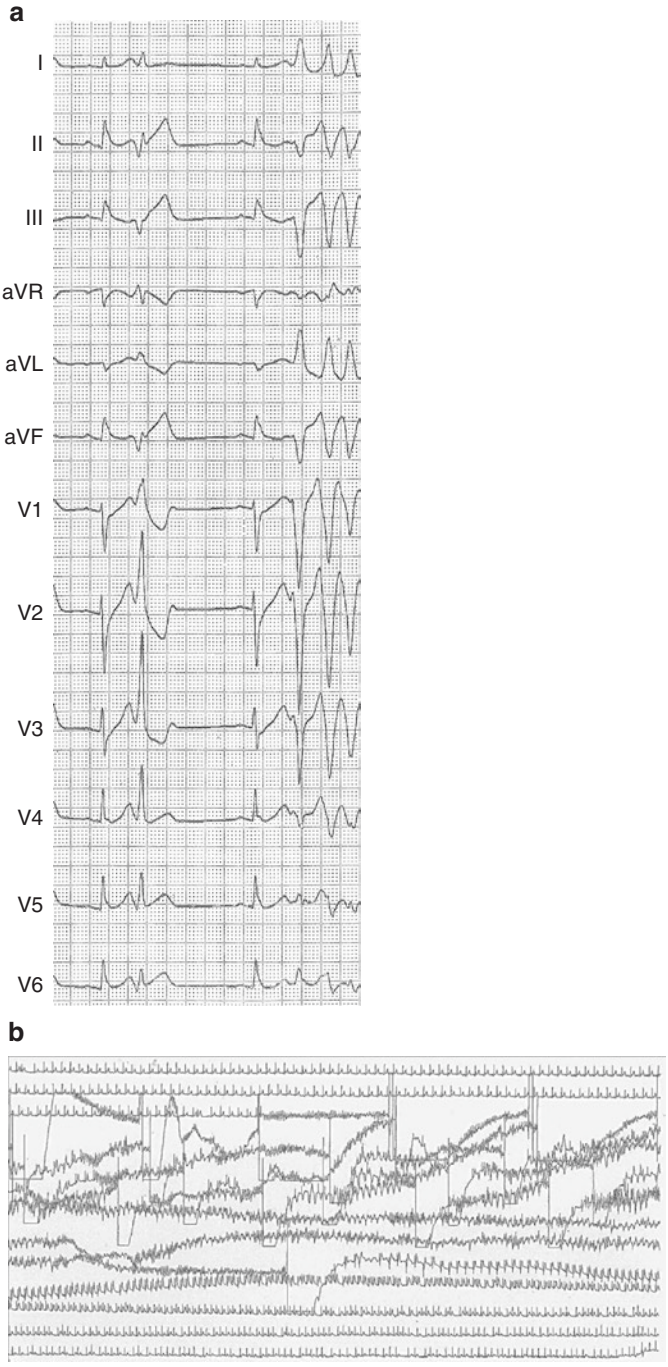

Fig. 2.1 Electrocardiograms showing ventricular fibrillation in a patient with early repolarization syndrome. (**a**) Development of ventricular fibrillation following augmentation of early repolarization. (**b**) Repetitive ventricular fibrillation events requiring multiple electrical shocks

of patients with early repolarization syndrome have J-point elevation in the right precordial leads [18, 19]. Characteristic J-point and ST segment elevation of Brugada syndrome in the right precordial leads sometimes disappear and can be seen only in the right precordial leads placed at the high costal space or during sodium channel blocker challenge, and there may be patients with undiagnosed Brugada syndrome among those with aborted sudden cardiac death. Actually, in the recent study, diagnostic type I Brugada pattern is found at the high costal space in about 30% of patients with previous diagnosis of early repolarization syndrome [20].

According to the expert consensus statement, early repolarization syndrome is diagnosed if patients who are resuscitated from otherwise unexplained ventricular fibrillation or polymorphic ventricular fibrillation have early repolarization pattern in the electrocardiograms [15]. Therefore, patients with early repolarization syndrome should have a history of resuscitation. However, in a community-based general population, early repolarization in the inferior leads is associated with an increased risk of death from cardiac causes [7]. Early repolarization is a common electrocardiogram finding, which can be found in 1–13% in the general population [1, 7, 21], and it is difficult to find individuals with an increased risk of death from cardiac causes such as early repolarization syndrome among healthy individuals without a history of resuscitation.

2.3 Manifestation of Early Repolarization Syndrome

The prevalence of early repolarization syndrome is unknown, and ethnic difference in prevalence is also unclear. In patients with idiopathic ventricular fibrillation, early repolarization in the inferolateral leads is found in 31% of patients in a worldwide study [5] and 54% in a Japanese single-center study [22]. Furthermore, early repolarization is found in 19% of patients with syncope compared to 2% of healthy controls [23].

In addition to idiopathic ventricular fibrillation, early repolarization has been associated with increased risk of ventricular tachyarrhythmia in various cardiac diseases [24–28]. Patients with early repolarization are at increased risk of arrhythmia events in arrhythmia syndromes including Brugada syndrome, short QT syndrome, and arrhythmogenic right ventricular cardiomyopathy [24–26]. In patients with coronary artery disease, early repolarization is associated with risk of ventricular fibrillation in acute phase and that of ventricular tachyarrhythmia and sudden death in chronic phase [27, 28].

In patients with early repolarization syndrome, there is male dominance, and 74–87% of patients are men (Table 2.2) [18, 29]. Patients usually have initial events of ventricular fibrillation at an age of around 40 years. There are 13–17% of patients who have a history of electrical storm [18, 29]. Family history of sudden death is present in 13–18% of patients, indicating that early repolarization syndrome is an inherited disease at least in part. Actually, some causative genes, all of which are

Table 2.2 Clinical characteristics of 53 patients in Japanese multicentric study

Male sex, *N* (%)	46 (87%)
Age, years	44 ± 17
Family history of sudden death, *N* (%)	7 (13%)
Activity at initial cardiac arrest, *N* (%)	
Sleeping	14 (26%)
Rest	12 (23%)
Physical effort	10 (19%)
Other activities	17 (32%)
Atrial fibrillation, *N* (%)	12 (23%)
History of electrical storm, *N* (%)[a]	9 (17%)
Inducible ventricular fibrillation	15/31 (48%)
Mutation in SCN5A, *N* (%)	4/29 (14%)
Location of early repolarization, *N* (%)	
Inferior	37 (70%)
Lateral	37 (70%)
Right precordial	11 (21%)
Multiple location of early repolarization	28 (53%)

[a]An electrical storm was defined as ≥3 episodes of VF within 24 h

cardiac ion channel genes, have been associated with early repolarization syndrome [11–14]. About 20% of patients also have atrial fibrillation [18].

Ventricular fibrillation recurs within 1 year after the initial cardiac arrest in 28% of patients, and the incidence of recurrences is 5.9 per 100 person-years [18, 29]. Arrhythmia recurrences are more common, and the risk of arrhythmia events is 2.1–3.9 times higher in patients with early repolarization syndrome than those with idiopathic ventricular fibrillation [5, 30].

Although ventricular fibrillation events occur mainly at night and at rest in patients with Brugada syndrome, which shares clinical characteristics with early repolarization syndrome, the events occur at various situations in those with early repolarization syndrome. In a study for circadian variations of ventricular fibrillation events, there is a nocturnal peak of arrhythmia events [31]. Ventricular fibrillation occurs during sleeping in 19–26% of patients and occurs during sleep and at rest in about half of patients [5, 18]. All of the evidence suggests that vagal tone has an important role for arrhythmogenicity in early repolarization syndrome. However, arrhythmia events are not always associated with vagal tone. Ventricular fibrillation also occurs during physical activity in 9–19% [5, 18]. Multiple causative genes have been associated with early repolarization syndrome, and the differences of genetic background may play a role for the triggers of ventricular fibrillation [11–14]. Interestingly, there also is a seasonal variation of ventricular fibrillation events, and events mainly occur from spring to summer, although the mechanism is not known [31].

Amplitude of J-point elevation varies and is augmented after pause and during bradycardia. Because the augmentation of early repolarization pattern after pause is observed only in patients with early repolarization syndrome but not in control subjects without ventricular fibrillation events in a previous study, the pause-dependent augmentation of early repolarization pattern may be useful as a tool for diagnosis and risk stratification [16]. Usually, amplitude of J-point elevation is markedly augmented before development of ventricular fibrillation, suggesting that early repolarization indicate arrhythmogenicity [5]. Early repolarization pattern sometimes disappears. There is no diagnostic test to unmask early repolarization, and sodium channel blockers, which are useful as a diagnostic test for Brugada syndrome, attenuate early repolarization [32].

Patients with early repolarization syndrome also have electrocardiographic characteristics in addition to early repolarization pattern. Compared with patients with idiopathic ventricular fibrillation who do not have any significant findings in the electrocardiograms at rest, QT interval is slightly but significantly shorter in patients with early repolarization syndrome [18, 29]. Heart rate is shorter and PR interval is longer in patients with early repolarization syndrome than those with idiopathic ventricular fibrillation [14]. QRS duration is longer in patients with early repolarization syndrome than those with idiopathic ventricular fibrillation in one study but is not different in another one [18, 29]. *SCN5A*, which encodes cardiac predominant sodium channel, is one of the causative genes, and sodium channel dysfunction may cause slow conduction in early repolarization syndrome [14, 33, 34].

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Chapter 3
Molecular Genetics of ERS

Seiko Ohno and Minoru Horie

Abstract Early repolarization syndrome (ERS) is characterized by early repolarization (ER) and ventricular fibrillation. Heritability of the ER pattern has been shown, and the search for the genetic factors associated with ERS is in progress. Until now, genetic variants in seven genes, namely, *KCNJ8*, *ABCC9*, *SCN5A*, *CACNA1C*, *CACNB2b*, *CACNA2D1*, and *KCND2*, have been reported as potential causative genes of ERS. These genes encode potassium, sodium, and calcium ion channels on cardiomyocytes and control the action potentials of cardiomyocytes. The gain or loss of ion channel functions with genetic variants in these genes has been shown, and these functional changes have been linked to ERS. However, the pathogenesis of ERS by mutations in these genes is controversial. In addition, a genome-wide association study failed to identify any specific single nucleotide polymorphisms or genes associated with ER. Therefore, further investigation is required to explore the genetic background of ERS.

3.1 Introduction

Early repolarization syndrome (ERS) is characterized by early repolarization (ER) and ventricular fibrillation (VF) [1]. The reported prevalence of the ER pattern in healthy populations is <6%, and inheritance of the ER pattern has been reported in community-based studies [2, 3]. Although ER was thought to be a benign variant on electrocardiography (ECG) for a long time, a report by Haissaguerre and his colleagues [4] showed that people with ER had a higher risk for VF than those without ER. After that first report, many investigators started to search for the

S. Ohno, M.D., Ph.D. (✉)
Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga Prefecture 520-2192, Japan
e-mail: seikoono@belle.shiga-med.ac.jp

M. Horie, M.D., Ph.D.
Cardiovascular and Respiratory Department, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga Prefecture 520-2192, Japan

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Table 3.1 Genes related with early repolarization syndrome

	Gene	Protein	Ion channel	Reference
K channel	*KCNJ8*	Kir6.1	$I_{K\text{-}ATP}$	[5–8]
	ABCC9	SUR2A	$I_{K\text{-}ATP}$	[9]
	KCND2	$K_V4.2$	I_{to}	[10]
Ca channel	*CACNA1C*	$Ca_V1.2$	I_{Ca}	[11]
	CACNB2b	$Ca_V\beta2b$	I_{Ca}	[11]
	CACNA2D1	$Ca_V\alpha2\delta1$	I_{Ca}	[11]
Na channel	*SCN5A*	$Na_V1.5$	I_{Na}	[12]

genetic background of ER and ERS. Until now, mutations in seven genes have been reported to be associated with or causative of ERS (Table 3.1). However, the mechanisms of ERS potentially caused by mutations in those seven genes are controversial and need further investigation. In this section, we describe the ERS-related genes that have been reported to date and discuss the mechanism underlying ERS. Brugada syndrome (BrS) is one of the malignant primary arrhythmia syndromes and is analogous to ERS. In this section, however, we do not discuss the genes associated with BrS.

3.2 Genes Related with ERS

3.2.1 KCNJ8

In 2009, immediately after the report from Prof. Haissaguerre and his colleagues that ER was significantly associated with the recurrence of VF among VF survivors [4], a heterozygous missense mutation in *KCNJ8*, p. S422L, was identified in a 14-year-old female who suffered VF with prominent ER. She had no structural cardiac abnormality on echocardiography [7]. Her VF occurred during the night or early morning, and various medications failed to prevent her VF. Finally, her VF episodes were suppressed by quinidine, which is an I_{to} blocker with multiple channel blocking effects. *KCNJ8* encodes Kir6.1, a subunit of the K_{ATP} channel. After the first report of *KCNJ8*-S422L, the same mutation was identified in one ERS patient and 1 BrS patient among 101 unrelated patients [8]. Thereafter, three BrS patients and one ERS patient among 204 unrelated patients were identified carrying the same mutation [5]. A functional analysis of the mutant Kir6.1 channel was performed by assembling the K_{ATP} channel with its SUR2A subunit. The Kir6.1-S422L mutant increased the outward potassium current by both voltage-dependent activation and lowering the sensitivity for ATP-dependent closure of the channels. The increased K_{ATP} channel current was supposed to cause ER and ventricular arrhythmias.

However, homozygous *KCNJ8*-S422L was identified in a boy without ER or ventricular arrhythmias. His parents both carried the mutation in a heterozygous manner, and the variant was found to be frequently identified in Ashkenazi Jews (~4% preva-

lence) [13]. In the ExAC database (http://exac.broadinstitute.org/), which holds exome sequencing data from a wide variety of large-scale sequencing projects, *KCNJ8*-S422L was identified in 200 of 121,836 alleles and was especially high in people of European descent (168/66,726 alleles). The minor allele frequency of *KCNJ8*-S422L in those of European descent is 0.0025. According to the analysis of two missense mutation prediction software programs, PolyPhen2 [14] and SIFT [15], *KCNJ8*-S422L is classified as benign or tolerated. In a Japanese cohort, *KCNJ8* was screened in 230 ERS and BrS patients, but no pathogenic mutations were identified [16]. These recent reports imply that *KCNJ8* is not a major causative gene for ERS.

3.2.2 ABCC9

ABCC9 encodes SUR2, a subunit of the K_{ATP} channel, which is comprised of four pore-forming inward rectifier potassium channel proteins (Kir6.1 or Kir6.2) and four regulatory sulfonylurea receptors (SUR1 or SUR2). There are two subtypes of SUR2, namely, SUR2A and SUR2B, which differ by 42 amino acids in the C-terminus [17]. The combination of the Kir6.1 or Kir6.2 and SUR proteins comprising the K_{ATP} channel varies among different organs. In cardiomyocytes, the K_{ATP} channel consists of Kir6.2 and SUR2A, while in vascular endothelial cells, it consists of Kir6.1/Kir6.2 and SUR2B [18].

After the identification of the *KCNJ8*-S422L mutation, researchers sought to identify other causative genes of ERS having a functional relationship with the K_{ATP} channel. In 150 BrS and/or ERS patients, 8 *ABCC9* mutations in 11 probands were identified [9]. Among these mutations, four mutations were from seven ERS patients. They performed functional analysis of one ERS-related mutation, *ABCC9*-V734I, through the co-transfection of cells with *ABCC9*-V734I and *KCNJ11* encoding Kir6.2. The mutant channel caused a reduced sensitivity of the K_{ATP} channel to ATP; thus, the mutant K_{ATP} channel produced an increased outward potassium current even in the presence of a high concentration of ATP. The minor allele frequencies of two *ABCC9* mutations identified in ERS patients were more than 0.008 in the exome sequencing project (http://evs.gs.washington.edu/EVS/), which means that more than 1.6% of healthy people carry these variants identified in ERS patients. Therefore, the variants may not be unique causes of ventricular arrhythmias.

3.2.3 SCN5A

SCN5A encodes the cardiac sodium channel, $Na_V1.5$, and has been reported as a causative gene of various inherited arrhythmia syndromes, including long QT syndrome (LQTS) and BrS [19]. The functional effect of mutant $Na_V1.5$ in LQTS is characterized by an increased late sodium current, in contrast with the decreased peak sodium current in BrS.

In ERS, three *SCN5A* mutations, namely, A226D, R367H, and L846R, were identified in three patients: a 36-year-old man, a 27-year-old man, and a 37-year-old female, all of whom suffered aborted cardiac death associated with ER [12]. No one showed Brugada-type ECG by the provocation test using sodium channel blockers, but two of them suffered VF after pilsicainide injection. Two of them showed PR prolongation on ECG. These mutations were located in residues that are conserved across mammals. In a functional analysis by patch-clamp methods, the mutant channels showed no currents. Therefore, they concluded that the loss-of-function mutations in *SCN5A* caused ERS.

After that first report, another two papers reported *SCN5A* mutations in ERS. The first reported mutation was G1433R, which is located in the pore region of $Na_V1.5$ domain III [20]. The mutation was identified in a 19-year-old female who experienced frequent syncope since the age of 16. Her ECG, recorded in the emergency department, showed prominent J wave augmentation in multiple leads. Another mutation, Y352C, which is located in the pore region of $Na_V1.5$ domain I was identified in a 67-year-old male who had syncope [21]. The functional analysis of both G1433R and Y352C showed a decreased peak sodium current.

As shown in these studies, all of the mutations of $Na_V1.5$ showed a decreased peak sodium current and loss of function, which were similar changes to those observed in BrS. However, the phenotypic difference between ERS and BrS was not explained in these functional studies.

3.2.4 L-Type Calcium Channel (LTCC) Related Genes

LTCC in cardiomyocytes consists of four subunits, namely, $Ca_V1.2$ encoded by *CACNA1C*, $Ca_V\beta2b$ encoded by *CACNB2b*, $Ca_V\alpha2$, and $Ca_V\delta1$ encoded by *CACNA2D1*. As with mutations in *SCN5A*, mutations in *CACNA1C* also cause various arrhythmia syndromes including LQTS and BrS [22]. Mutations in *CACNB2b* have been reported as causative gene variants of BrS [23, 24]. These mutations found in LQTS caused a gain of LTCC function, and those in BrS caused a loss of LTCC function.

In 2010, a comprehensive genetic analysis of 162 probands diagnosed with BrS (n = 152), IVF (n = 19), short QT syndrome (n = 10), and ERS (n = 24) was performed, and 23 mutations were identified [11]. In ERS probands, one mutation in *CACNA1C*, two mutations in *CACNB2b*, and one mutation in *CACNA2D1* were identified. The functional effects of these mutations in relation to ERS remain unknown.

3.2.5 KCND2

KCND2 is a gene encoding $K_V4.2$, one of the subunits of the transient outward potassium current (I_{to}) channel [25]. I_{to} has been a candidate ion current for various arrhythmias since the experimental model supported the proarrhythmic effect of the modified I_{to} channel [26].

In 51 J wave syndrome probands including BrS, genetic screening for I_{to}-related genes, namely, *KCND2* encoding $K_V4.2$, *KCND3* encoding $K_V4.3$, and *KCNA4* encoding $K_V1.4$, was performed [10]. A *KCND2* mutation, D612N, was identified in a 51-year-old male who suffered cardiac arrest while eating and was rescued by two successive cardioversions. His ECG showed a prominent ER in the anterior precordial leads. Functional analysis of $K_V4.2$-D612N performed by co-expressing it with *KChip2*, an ancillary subunit of I_{to}, showed an increase in the current densities of the I_{to} current, even when it was also co-expressed with $K_V4.2$-WT. A simulation model that integrated the data from the functional analyses showed that the $K_V4.2$-D612N mutation resulted in a stable loss of the dome of the action potential in the epicardial layer. The loss of the dome was implicated in the prominent ER of the patient [10].

3.2.6 Summary

Seven genes encoding potassium, sodium, and calcium channels have been reported to be associated with ERS. The functional analyses of the mutant ion channels encoded by these genes showed alterations that could potentially cause ERS. However, the patient characteristics and the definition of ER varied among these studies. In addition, the presence and amplitude of ER varied among measurements taken at different times [27], and augmentation of ER was recorded just prior to VF occurrences [28]. Therefore, the diagnosis of ERS or differential diagnosis between ERS and idiopathic VF is difficult for general physicians and cardiologists.

To search for a novel causative gene of an inherited disease, familial analysis is important to analyze phenotype-genotype correlations. In the previous reports on familial analysis in ERS, all the families with ERS-related gene mutations failed to show clear phenotype-genotype correlations. One of the reasons is likely to be the difficulty of diagnosing ERS before cardiac events such as sudden cardiac arrest.

3.3 ER Pattern and Inheritance

The ER pattern has been reported to relate to multiple factors including male gender, young age, and blood pressure [2]. Among the multiple factors, the relative risk of the ER pattern for individuals whose parents carried the ER pattern has been reported to be approximately two [2, 3], which strongly suggests that ER has genetic background of ER.

To show the inheritance of the ER pattern in sudden arrhythmic death syndrome (SADS), relatives of SADS probands were screened by 12-lead ECG [29]. A SADS proband was defined as sudden death in individuals who lacked a history of cardiac disease and were confirmed as being anatomically normal by coroners or cardiac pathologists. Among 363 first-degree relatives from 144 families, 23% of the relatives showed the ER pattern in the inferolateral leads on ECG. The prevalence of the ER pattern in the relatives of SADS patients (23%) was significantly higher compared to that in unrelated healthy controls (11%).

3.4 Genome Wide Association Study (GWAS) of ER

Following the recent progress of DNA sequencing technologies, GWAS is now widely used to detect causative genes or single-nucleotide polymorphisms (SNP) associated with various diseases. In the ECG field, the QT interval was first shown to be associated with a specific SNP in *NOS1AP* by GWAS [30]. Many related genes were subsequently discovered in atrial fibrillation patients by GWAS [31–33]. Through performing a GWAS of BrS, we detected SNPs that were highly associated with BrS in *SCN5A*, *SCN10A*, and a novel target gene, *HEY2* [34]. Heterozygous *HEY2* knockdown mice exhibited prolonged conduction velocity.

Only one GWAS study of ER has been reported to date [35]. That study included three large cohorts comprising participants of European ancestry, namely, the Framingham Heart Study (FHS) in the United States [36], the Health 2000 Study (H2K) in Finland, and The Cooperative Health Research in the Region of Augsburg F4 Study (KORA F4) in Germany. In the first step of their analysis, they included 7482 participants, comprising 3726 from FHS, 2082 from H2K, and 1674 from KORA F4. Among the participants, 227 participants from FHS, 61 from H2K, and 164 from KORA F4, totaling 452 participants (6%), showed the ER pattern on ECG. The number of SNPs analyzed was 2,523,555 including imputation, representing a predicted value from the ethnicity-matched genomic data. In their first analysis, they found eight SNPs (Table 3.2) with a p value of $<1 \times 10^{-5}$, which showed a high correlation with ER. One of the SNPs was rs17029069 in the intron of *KCND3*, which encodes the α subunit of the I_{to} channel. Next, a replication study was performed in 7151 participants, including 488 ER positives (6.8%); however, none of the eight SNPs tested in the replication cohorts reached significance. Finally, the GWAS and replication data were combined, but no SNP showed genome-wide significance [35].

As described in the previous section, the ER patterns detected by 12-lead ECG are heterogeneous, and the homogenization or classification of the ER pattern in many people is difficult. In contrast, GWAS studies need a huge number of participants with qualified characteristics. Therefore, the detection of SNPs associated with the ER pattern by GWAS will be a challenging task without the definite classification of it.

Table 3.2 SNPs identified in GWAS

SNP	Chromosome	Closest gene(s)
rs11653989	17	*MGAT5B*, *SEC14L*
rs6585436	10	*PDZD8*, *EMX2*
rs17029069	1	*KCND3*
rs17097328	14	*C14orf177*
rs17012480	2	*LTBP1*
rs1541064	1	*UBE2U*
rs6988260	8	*FAM110B*
rs1382629	4	*KIAA1211*

3.5 Conclusion

From the familial cases of the ER pattern, ERS has been considered to be one of the inherited arrhythmia syndromes. However, multiple studies attempting to identify the causative genes have failed to find a specific gene associated with ERS. Although mutations in seven genes have been reported to be causative for ERS, its pathogenesis has not been sufficiently well explained by the existing data. One of the reasons is the heterogeneity of the ER pattern. Further studies will be indispensable to clarify the complicated genetic background of ERS.

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Chapter 4
Ionic and Cellular Basis Underlying ERS

Takeshi Aiba

Abstract The early repolarization pattern (ERP) or J wave in the ECG is commonly observed but associated with an increased risk of sudden cardiac death in some cases, so-called early repolarization syndrome (ERS). ERP is often overlapped with the Brugada syndrome. Although a lot of clinical and basic studies about the ERS and Brugada syndrome have been reported in the past two decades, the mechanisms of the ERP by which the risk of arrhythmias increased are still controversial. There are mainly two hypotheses for the ionic and cellular basis underlying the ERP: repolarization and depolarization abnormalities. The former is based on the transient outward potassium current (I_{to})-mediated action potential notch in the epicardium but not endocardium, giving rise to transmural heterogeneity of ventricular repolarization, whereas the latter is based on the clinical electrophysiology such as late potentials and fractionated delayed potential in the epicardium. The repolarization and depolarization abnormalities are impossible to be completely separated in the same heart, and both contribute to the manifestation of the J wave/ERP and arrhythmogenicity.

4.1 Introduction

The J wave (or early repolarization pattern, ERP) in the ECG had been considered as benign; however, some of the cases with J wave/ERP, including the Brugada syndrome or short QT syndrome, had been reported as a risk of ventricular fibrillation (VF) leading to sudden cardiac death [1, 2]. However, the mechanisms of the J wave or early repolarization syndrome (ERS) and VF cannot completely be elucidated.

Recently, two major hypotheses for the mechanisms of the J wave/ERS and its related VF occurrence are proposed; one is the transient outward potassium current (I_{to})-mediated action potential notch in the epicardium (repolarization

T. Aiba, M.D., Ph.D.
Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine,
National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai,
Suita, Osaka 565-8565, Japan
e-mail: aiba@ncvc.go.jp

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hypothesis), and the other is an intraventricular conduction delay (depolarization hypothesis); thus, both repolarization and/or depolarization abnormalities play an important role for development of VF in ERS. In this chapter, we would review the ionic and cellular mechanisms of J wave/ERS associated with arrhythmic diseases.

4.2 Cellular Mechanisms of J Wave

4.2.1 Repolarization Theory

The J wave/ERP in the ECG is inscribed as a consequence of the presence of a prominent I_{to}-mediated action potential notch in the epicardium but not in the endocardium giving rise to a transmural voltage gradient. Direct evidence in support of this hypothesis derives from data first reported using the arterially perfused canine ventricular wedge preparation (Fig. 4.1) [3–5].

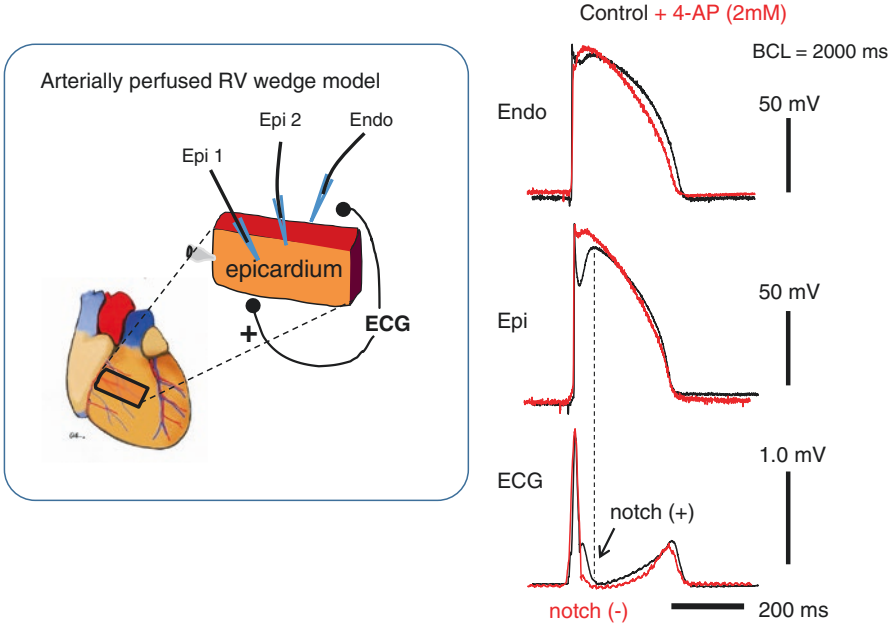

Fig. 4.1 Arterially perfused canine right ventricular (RV) wedge preparation model revealed a prominent I_{to}-mediated phase 1 notch in the epicardial electrodes but not in the endocardial electrode, associated with J wave in the transmural ECG. I_{to} blocker, 4-aminopyridine (4-AP), diminished the phase 1 notch in the epicardium but not endocardium resulting in disappearance the J wave/ERP (Aiba et al. [3])

Factors that augment or reduce I_{to} or that speed or slow the kinetics of the current can importantly modify the manifestation of the J wave/ERP on the ECG. Whether augmented by exposure to hypothermia [4], I_{Ca} and I_{Na} blockers [6], or I_{to} agonists such as NS5806 [7] or reduced by I_{to} blockers such as 4-aminopyridine (4-AP), quinidine, or premature activation [4] or changes in the magnitude of the epicardial AP notch parallel those of the J wave.

On the other hand, it has still been unclear why the J waves can be seen as the slur pattern or notch pattern. The same wedge experimental model also revealed that accentuated $I_{K\text{-}ATP}$ by pinacidil may change the pattern of J wave from notch to slur pattern (Fig. 4.2) [3].

These experimental findings are consistent with the clinical findings that J wave/ERP in idiopathic VF is accentuated in bradycardia [8] or pause-dependent manner [9, 10] whereas it is diminished at tachycardia or premature electrical activities (Fig. 4.3) [2]. Furthermore, the J wave in idiopathic VF patients has a circadian rhythm, as well as a day-to-day variation [11]. Shinohara et al. reported J wave amplitude is increased at night depending on the heart rate [12]. These studies could show the pause-dependent accentuation of the J wave/ERP notch, which is consistent to the experimental ECG of canine wedge model of the J wave syndrome (Fig. 4.4).

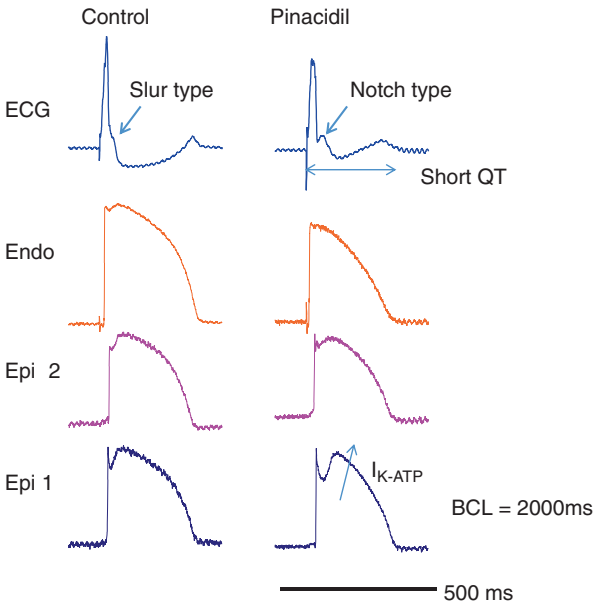

Fig. 4.2 Increased outward K^+ current by pinacidil caused larger phase 1 notch in the epicardium resulting in changing the early repolarization from slur to notched pattern J wave as well as shorter QT interval (Aiba et al. [3])

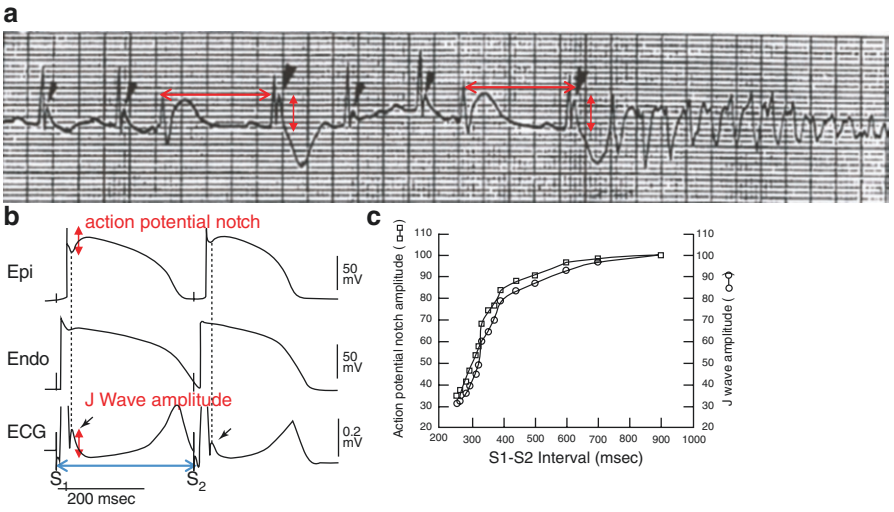

Fig. 4.3 (**a**) Pause-dependent augmentation of the J wave/ERP in idiopathic ventricular fibrillation. (**b**, **c**) Effect of premature stimulation on the amplitude of action potential phase 1 notch in the epicardium as well as the J wave amplitude on the ECG in arterially perfused wedge model (Yan et al. [4]; Aizawa et al. [8])

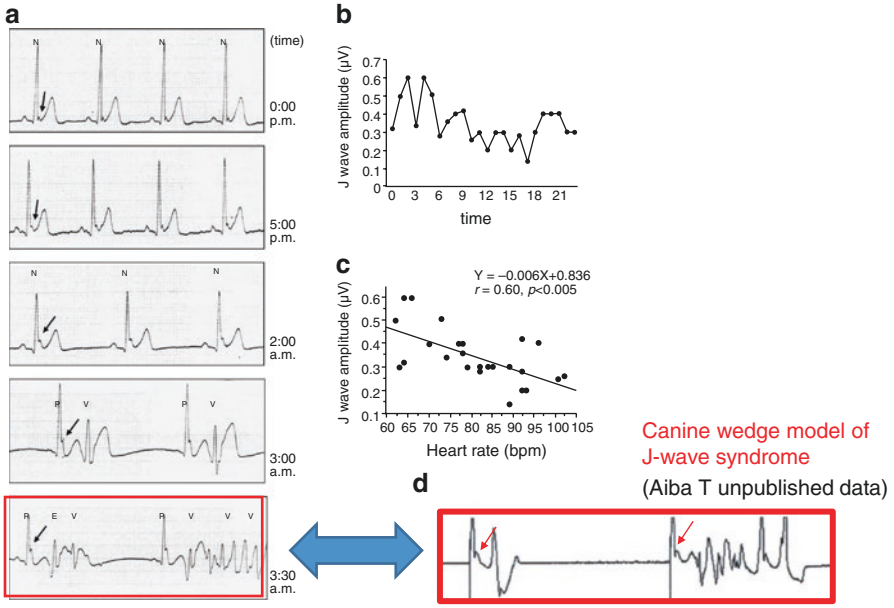

Fig. 4.4 Characterization of J wave in a patient with idiopathic ventricular fibrillation. (**a**) time-dependent change of the J wave between day and night. (**b**, **c**) At night bradycardia increased J wave amplitude and might be associated with spontaneous ventricular arrhythmias at 3 a.m. (**d**) Experimental ECG in the canine wedge model of the J wave/ERS, similar spontaneous premature ventricular arrhythmia, and non-sustained polymorphic VT followed by a pause-dependent augmentation of phase 1 notch could be observed (Shinohara et al. [12]; Aiba et al. unpublished data)

4.2.2 *Sodium Channel Blocker*

In ERS, sodium channel blockers often appear to diminish the appearance of J waves [13]. In contrast, in Brugada syndrome, sodium channel blockers such as procainamide, pilsicainide, propafenone, and flecainide cause a further outward shift of current flowing during the early phases of the action potential and are therefore effective in inducing or unmasking concealed Brugada syndromes [14]. This might be due to in part the prolongation of the R wave masking the J wave in ERS. In the wedge experimental preparation, we have shown that additional pilsicainide in baseline diminished the phase 1 action potential notch in the epicardium, resulting in disappearance of the J wave/ERP. In contrast, in the Brugada syndrome model by terfenadine and pinacidil [6], addition of pilsicainide accentuated the phase 1 notch in the epicardium and changed the coved ST elevation (type 1 Brugada ECG) (Fig. 4.5).

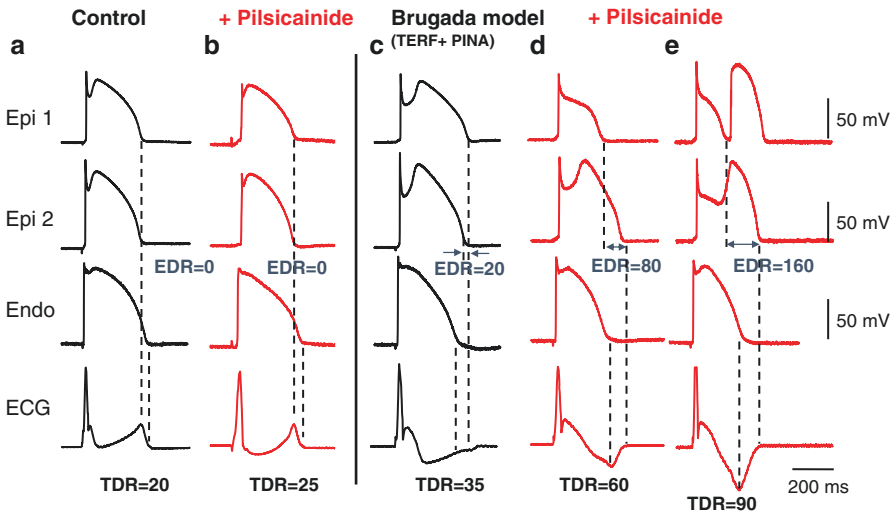

Fig. 4.5 Pilsicainide masks J wave in the control but not in the Brugada syndrome model showing transmembrane activities recorded simultaneously from the two epicardial and one endocardial sites together with a transmural ECG at a basic cycle length (BCL) of 2000 ms. Pilsicainide (5 μmol/L) under baseline condition increased QRS as well as QT interval but neither changed ECG into the typical coved-type ST segment elevation (Brugada ECG) nor induced ventricular arrhythmias, whereas Ito-mediated phase 1 action potential notch in the epicardium were diminished after pilsicainide, resulting in disappearance of the J wave/ERP on ECG (**a**, **b**). On the other hand, terfenadine (5 μmol/L) combined with pinacidil (2 μmol/L) increased J-point ratio of ECG and epicardial dispersion of repolarization (EDR) (**c**). Addition of pilsicainide under terfenadine and pinacidil caused heterogeneous loss of action potential dome in the epicardium but not endocardium and resulted in increasing EDR and transmural dispersion of repolarization (TDR) as well as changing ECG into Brugada ECG (**d**). Moreover, under the Brugada ECG, further abbreviation of action potential duration in some area (Epi 1) of the epicardium but not others (Epi 2) much more increased EDR and developed concealed phase 2 reentry (**e**) (Aiba et al. [3])

4.2.3 Male Predominance of J Wave

The predominance of the Brugada phenotype in males is considered to be responsible for the presence of a more prominent I_{to}-mediated phase 1 notch in males compared with females [15]. Similar to the Brugada syndrome, the J wave/ERP of ECG is more predominant in male compared with female.

4.2.4 Temperature Dependent

During hypothermia, a pretty positive deflection at the J-point of ECG (Osborn wave) could be observed [16], although it is not pathogenic. Yan et al. had revealed the cellular basis of this temperature-dependent change of the J-point elevation as a cause of the same transmural voltage gradient at the phase 1 action potential [4].

4.2.5 Depolarization Theory

The most important responsible gene in the Brugada syndrome is *SCN5A*, α subunit of the Na channel, which is also identified in the idiopathic VF, ERS patients with J wave or ERP. Several clinical studies have shown that the Brugada syndrome causes increased H-V interval, QRS duration with fragmentation, which may be due to the epicardial abnormal conduction delay [17, 18]. Many Brugada patients show positive criteria for late potentials (LPs) in the signal-averaged ECG (SAECG). Moreover, the circadian pattern of LPs is different from those of arrhythmogenic right ventricular cardiomyopathy [19] and eliminated by quinidine [20]. Recent invasive catheter mapping on the epicardial surface in the Brugada syndrome directly demonstrated the fractionated delayed potentials on the epicardium of the right ventricular outflow tract as a substrate of VF in the Brugada syndrome [21]. These findings support the idea that depolarization abnormalities are the main causes of the Brugada and its related syndromes.

However, most of these depolarization findings are focused on the Brugada syndrome but not directly associated with the ERS or idiopathic VF, although there are many similarities between the two syndromes. Recent studies demonstrated that idiopathic VF patients with J waves had a high incidence of LP showing circadian variation with night ascendancy [22], and the J wave/ERP may be more closely associated with autonomic modulation [23]. Mellor et al. reported the J wave/ERP were more common in family members of sudden arrhythmic death syndrome (SADS) than controls and altered by ajmaline provocation and exercise ECG underlying mechanisms of both abnormal repolarization and depolarization [24]. Furthermore, Kamakura et al. reported that in the ERS patients (except for the Brugada type 1 ECG), recurrence of VF was more common in the ERS with non-type 1 Brugada-like pattern ECG than those without Brugada pattern ECG. [25].

4.2.6 *Distinguish Between Repolarization and Depolarization?*

The end of the QRS, resembling a J wave, has been proposed to be due to intraventricular conduction delay. The two ECG patterns such as I_{to}-mediated phase 1 notch and intraventricular conduction delay can be distinguished based on their response to heart rate. Slower heart rate usually augments the J wave/ERP, and pause-dependent manifestation of J wave/ERP sometimes induces arrhythmias, while conduction delay-induced loss of action potential dome was accentuated at higher rate, resulting in QRS widening with J-point elevation (Fig. 4.6) [26].

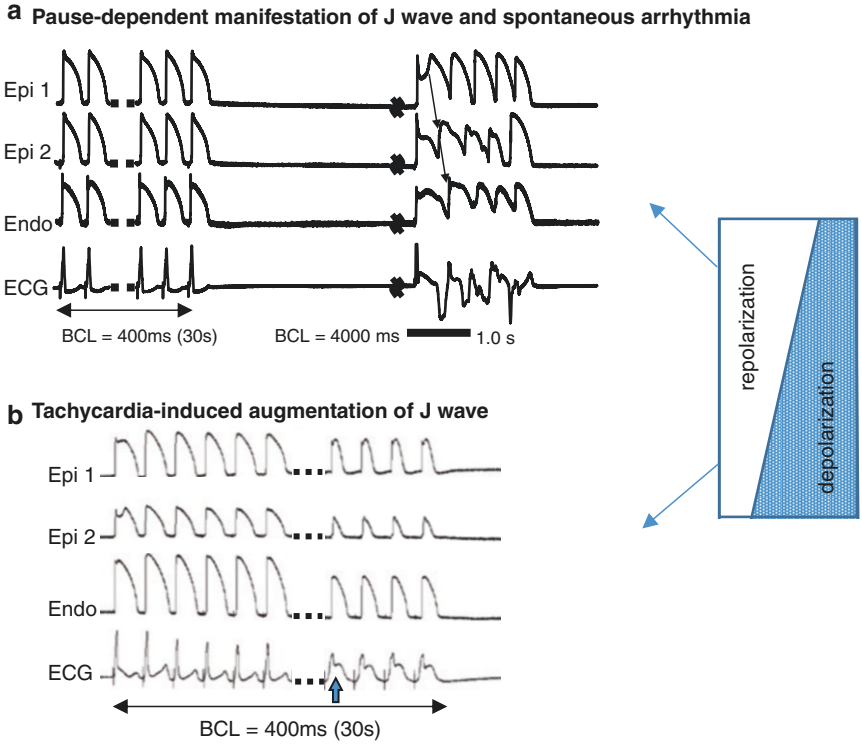

Fig. 4.6 Manifestation of J-point elevation by a pause-dependent or tachy-induced matter. (**a**) Addition of pilsicainide (5 μmol/L) under terfenadine and pinacidil in arterially perfused canine RV wedge model. Abrupt increase in basic cycle length from 400–4000 ms caused accentuated phase 1 action potential notch in the epicardium (Epi 1) but not in the other epicardium (Epi2) and endocardium (Endo), giving rise to spontaneous phase 2 reentrant arrhythmias. (**b**) Addition of pilsicainide (10 μmol/L) under terfenadine and pinacidil in the same preparation. Tachy-pacing (BCL = 400 ms) diminished phase 1 action potential notch in the epicardium thus eliminated the J wave/ERP. However, further tachy-pacing caused conduction delay and loss of action potential dome, resulting in prolongation of QRS duration with a significant J-point elevation

4.2.7 J Wave and False Tendon

The false tendons (FTs) are fibromuscular bands that transverse the left ventricular cavity and often contain conduction tissue, suggesting that FTs may contribute to the occurrence of ventricular arrhythmias. Nakagawa et al. [27] reported that the presence of FTs may be associated with the J waves as a possible mechanism of vulnerability to ventricular arrhythmias in ERS.

4.3 Summary

There are two hypotheses for the ionic and cellular mechanisms of J waves and ERS and Brugada syndromes, repolarization and depolarization abnormalities, which are still controversial. The repolarization and depolarization abnormalities are impossible to be completely separated in the same heart, and both contribute to the manifestation of the J wave/ERP and arrhythmogenicity.

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Chapter 5
ERS in Relation to Brugada Syndrome

Tsukasa Kamakura and Shiro Kamakura

Abstract Early repolarization (ER) is a common electrocardiographic finding characterized by elevation of the J point with notching or slurring on the electrocardiogram (ECG) followed by ST-segment elevation. Although this condition has been considered benign, Haïssaguerre et al. demonstrated that patients with J waves in the inferolateral leads were likely to be associated with idiopathic ventricular fibrillation (VF) and reported this entity as inferolateral early repolarization syndrome (ERS) in 2008. Brugada syndrome (BrS) is another clinical entity that causes sudden death due to VF in patients with apparently structurally normal hearts and is characterized by coved ST-segment elevation in the right precordial leads. ERS and BrS are considered to share a similar genetic background and to represent a continuous spectrum of phenotypic expression. However, the exact pathophysiological mechanisms underlying ERS and BrS remain unknown, and some clinical manifestations reportedly differ between these syndromes. In this chapter, we introduce our current understanding of ERS and BrS.

5.1 Introduction

J wave or early repolarization (ER) is a common electrocardiographic finding that affects 1–13% of individuals and is characterized by elevation of the J point with notching or slurring on the electrocardiogram (ECG) followed by ST-segment elevation [1–4]. Although this condition has been considered benign, Haïssaguerre et al. demonstrated that patients with J waves in the inferolateral lead (I, II, III, aVL, aVF, and V_4–V_6) were likely to be associated with idiopathic ventricular fibrillation (VF) and reported this entity as inferolateral early repolarization syndrome (ERS) in 2008 [1]. Since then, the J wave has come to be known as a possible indicator of an increased risk for death due to cardiac arrhythmia.

T. Kamakura, M.D., Ph.D. (✉) • S. Kamakura, M.D., Ph.D.
Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine,
National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai,
Suita, Osaka 565-8565, Japan
e-mail: tkamakura@live.jp

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Brugada syndrome (BrS) is another clinical entity that causes sudden death due to VF in patients with apparently structurally normal hearts and is characterized by coved ST-segment elevation in the right precordial leads (V_1–V_3) [5, 6]. Since the original description of BrS in 1992 [7], there has been notable progress in our understanding of BrS with respect to genetics, epidemiology, electrophysiology, and clinical findings. Hundreds of mutations in genes that encode sodium, potassium, or calcium ion channels have been identified. The prevalence, incidence, and short- to midterm prognosis have also been clarified. However, exact pathophysiological mechanism underlying BrS remains a matter of debate.

Because accentuated J waves characterize both ERS and BrS, these syndromes have been considered to share a similar genetic background and to represent a continuous spectrum of phenotypic expression, termed J wave syndromes [8]. Manifestation of ER in the inferolateral leads is thought to be analogous to that of ER in the right precordial leads. Here, we wish to introduce our current understanding of ERS and BrS.

5.2 Clinical Characteristics of BrS and ERS

BrS and ERS have been reported to share a number of common clinical features (Table 5.1). Both BrS and ERS are male dominant and mainly affect middle-aged males [1, 6, 9]. The peak incidence of VF occurs in the third or fourth decade of life. J wave and ST segment are accentuated in both syndromes during bradycardia or after pauses [10]. Approximately 30% of ERS patients show multiple episodes of VF and respond to isoproterenol, quinidine, cilostazol, and bepridil, which are effective in patients with BrS [1, 9, 11]. BrS has been associated with mutations in 19 different genes including *SCN5A*, *CACNA1C*, *CACNB2b*, and *CACNA2D1*. Although the genetic evidence for ERS is restricted to either case reports or preliminary studies, the familial nature of ERS has been demonstrated [12], and seven gene mutations in *SCN5A*, *KCHJ8*, *ABCC9*, *CACNA1C*, *CACNB2*, *CACNA2D1*, and *SCN10A* are reported to associate with ERS to date [13–18]. However, all of these gene mutations are also identified in patients with BrS [15, 16, 18–20] and are considered to lead to enhancement of the underlying inward-outward current imbalance responsible for accelerated epicardial repolarization in both syndromes.

In spite of the similarity of these clinical features to BrS, some clinical manifestations reportedly differ between ERS and BrS, whereby VF in patients with inferolateral ERS occurs less frequently at night, originates mainly from the left ventricle, and is inducible to a lesser degree by programmed electrical stimulation compared with BrS patients [1, 9, 21]. Responses to sodium channel blockers also differ between ERS and BrS [22, 23]. The amplitude of ER in inferolateral leads was attenuated by a sodium channel blocker, whereas it was augmented in the right precordial leads in patients with BrS. The positive rate of late potentials on the

Table 5.1 Clinical characteristics of BrS and ERS

	BrS	ERS
Male predominance	Yes	Yes
Age at the first VF (years)	30–40	30–40
Incidence of VF during sleep (%)	50–60%	20–30%
Dynamicity of ECG	Yes	Yes
Vagally mediated accentuation of ECG pattern	Yes	Yes
Response to sodium channel blocker	Augmentation	Attenuation
VF induction by EPS (%)	50–70%	30%
Positive late potential (%)	60–70%	10–20%
VF trigger	Late-coupled PVCs (400 ms)	Short-coupled PVCs (< 340 ms)
VF initiation	Sudden onset	Non-sudden onset (short-long-short pattern)
Genes	*SCN5A*, *SCN10A*, *CACNA1C, CACNB2b*, *CACNA2D1*, *KCNJ8*	*SCN5A*, *SCN10A*, *CACNA1C, CACNB2b*, *CACNA2D1*, *KCNJ8*
Effective drug in suppressing VF	Isoproterenol, quinidine, cilostazol, bepridil	Isoproterenol, quinidine, cilostazol, bepridil

BrS Brugada syndrome, *ERS* early repolarization syndrome
VF ventricular fibrillation, *ECG* electrocardiogram
EPS electrophysiological study, *PVC* premature ventricular contraction

signal-averaged ECG was significantly lower in patients with ERS than in those with BrS [22]. VF episodes were more commonly initiated by premature ventricular contractions (PVCs) with a short-long-short sequence with relatively short-coupled PVCs in patients with ERS compared with those in BrS [24]. These clinical features are inconsistent with a theoretical basis for a resemblance between ERS and BrS and have caused confusion and difficulty in understanding ERS.

5.3 Diagnosis of BrS and ERS

ERS is diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG when structural and non-structural heart diseases including BrS are excluded as a cause of VF [1, 25]. The new diagnostic criteria allow diagnosis of BrS when type 1 ST-segment elevation is observed either spontaneously or after drug provocation tests in at least one of the right precordial leads (V_1 and V_2) positioned in the second, third, or fourth intercostal spaces [26, 27]. These criteria proposed in 2013 have been reported to increase diagnostic sensitivity without increasing specificity [28].

Since inferolateral ER was reported in association with idiopathic VF in 2008 by Haïssaguerre et al. [1], several studies on ERS have been published [2–4]. However, these were mostly reported before 2013 and excluded BrS according to the 2002 [5] and 2005 criteria [6]. Therefore, there is a possibility that previously reported cases of ERS may have included patients with Brugada-pattern ECG in high intercostal spaces only. Unless high intercostal recordings with or without drug provocation tests were conducted, some BrS patients could have been misdiagnosed as having ERS under the previous criteria.

We evaluated high intercostal ECGs of ERS patients and showed that 16% of patients diagnosed with ERS on the basis of the previous criteria could be diagnosed as BrS with inferolateral ER; this showed a type 1 Brugada-pattern ECG in high intercostal spaces only, which would not have been previously recognized unless high intercostal ECG recordings in the presence or absence of sodium channel blocker challenge test were performed (Fig. 5.1) [29]. Thus, a systemic search for Brugada-pattern ECG with high intercostal ECG recordings with or without drug challenge test is required to exclude BrS.

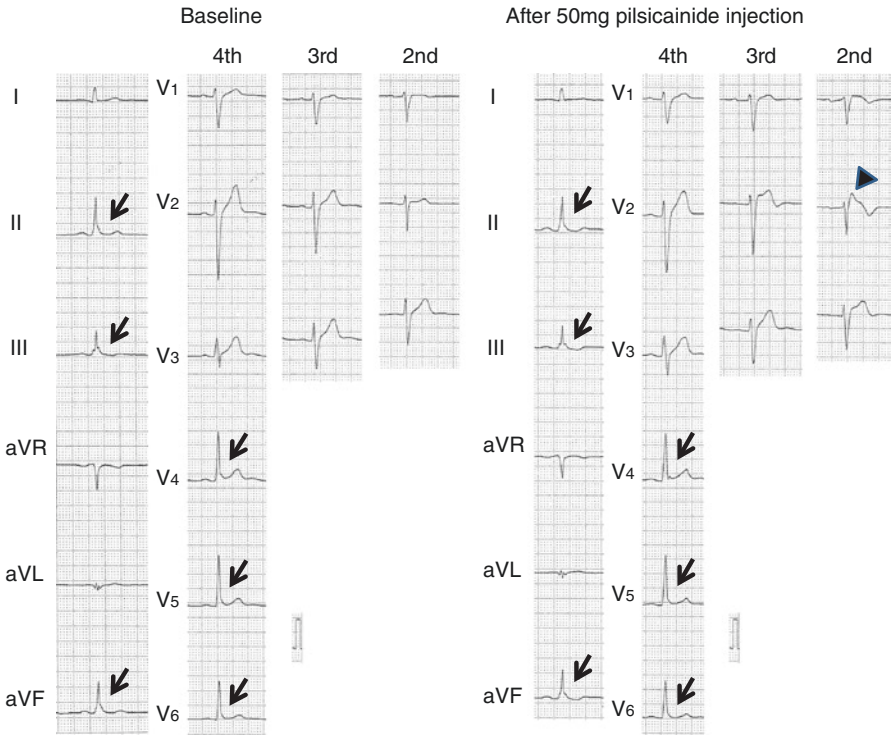

Fig. 5.1 At baseline, ECGs of a 26-year-old male exhibited J waves (*arrows*) followed by near horizontal ST segments in leads II, III, aVF, and V_6 and ascending ST segments in V_4 and V_5. There was no sign of coved or saddleback ST elevation in any chest leads. After injection of 50 mg pilsicainide, type 1 ST elevation (*broad arrow*) was noted in V_2 only in the second intercostal space. The patient experienced VF recurrence 4 years after ICD implantation

5.4 Significance of Non-type 1 Brugada-Pattern ECG in the Right Precordial Leads in ERS

Kamakura et al. previously reported in a Japanese Brugada registry using the standard 12-lead ECG that patients with a history of VF and non-type 1 ST elevation even after drug provocation tests show poor prognosis equally as those with type 1 BrS [30]. Theoretically, VF patients with non-type 1 Brugada-pattern ECG in the right precordial leads can include those with ERS or BrS only in high intercostal spaces.

We investigated the significance of the non-type 1 Brugada-pattern ECG, which was not converted to a type 1 ECG in standard and high intercostal ECG recordings even after drug provocation tests, in 31 patients with ERS [31]. ERS patients with non-type 1 Brugada-pattern ECG in the right precordial leads (Fig. 5.2) (ERS (A)), who comprised 39% of our ERS cohort, had clinical profiles similar to BrS. VF mainly developed during sleep in this group. The recurrence rate of VF was also

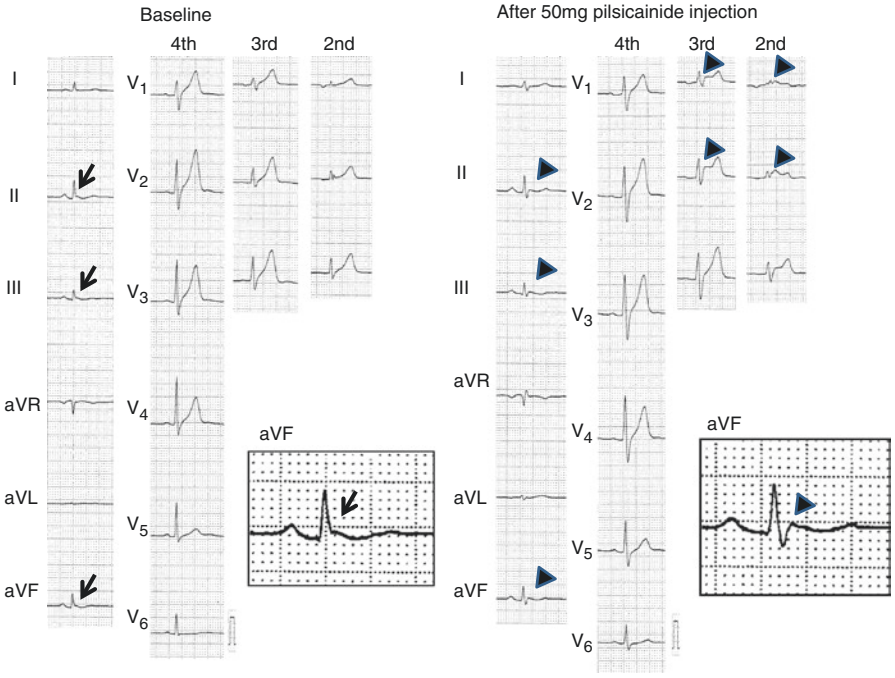

Fig. 5.2 At baseline, ECGs of a 51-year-old male exhibited J waves followed by horizontal or descending ST segments in leads II, III, and aVF (*arrows*). There was no sign of coved or saddleback ST elevation in any chest leads. After injection of 50 mg pilsicainide, saddleback ST elevation (*broad arrows*) appeared in leads V_1 and V_2 in the second and third intercostal spaces with augmented J waves (*broad arrows*) preceded by newly appearing s-waves in leads II, III, and aVF (shown in expanded ECGs). The patient experienced spontaneous VF 1 month after ICD implantation

similar to that in patients with BrS and documented VF. Quinidine, bepridil (multichannel blocker with a transient outward potassium current-blocking effect), and cilostazol (phosphodiesterase III inhibitor that augments $I_{Ca\text{-}L}$ current), which have been reported to be effective in suppressing VF in patients with BrS [11], were also effective in these ERS (A) patients. In contrast, the remaining ERS patients, who exhibited an ER only in the inferolateral leads (Fig. 5.3) (ERS (B)), showed different clinical profiles such as VF episodes in an awake state and few VF recurrences (Table 5.2 and Fig. 5.4). Responses to sodium channel blockers also differ between patients in the ERS (A) and ERS (B) groups. Following sodium channel blocker provocation, inferolateral J waves disappeared or were attenuated with appearance of s-waves and slight prolongation of QRS interval in all patients of the ERS (B) group (Fig. 5.3); conversely, J waves were augmented in the right precordial leads in most patients, and inferolateral J waves showed varied responses in the ERS (A) group (Fig. 5.2).

The modes of onset of ventricular tachyarrhythmia (VTA) also differed between the two groups [32]. VTA episodes were more commonly initiated by PVCs with a sudden onset pattern (ERS (A): 67% vs. ERS (B): 19%, $P = 0.0045$), and coupling intervals of PVCs were significantly longer in the ERS (A) group (ERS (A): 388.8 ± 50.6 vs. ERS (B): 330.6 ± 35.7 ms, $P < 0.0001$). In contrast, VTA episodes

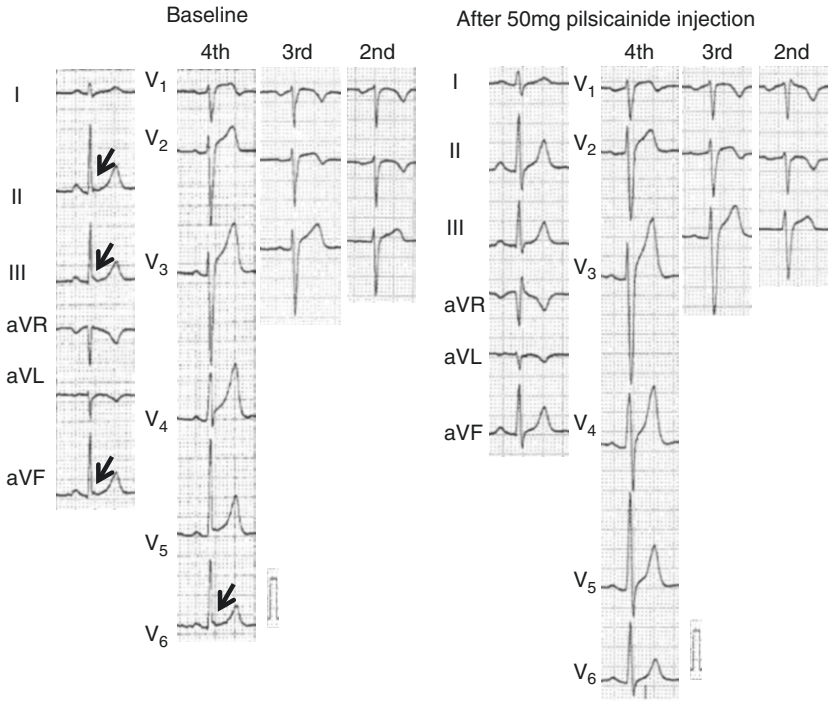

Fig. 5.3 In the baseline ECGs of this 39-year-old male, J waves were present in leads II, III, aVF, and V6 (*arrows*). After pilsicainide injection, these all disappeared with appearance of s-waves. ECGs in leads V_1–V_3 during standard and high intercostal recording remained normal even after pilsicainide injection. This patient experienced no VF recurrence

Table 5.2 Clinical characteristics of ERS (A) and ERS (B)

	ERS (A) (n = 12)	ERS (B) (n = 19)
ER distribution	Right precordial and inferolateral	Inferolateral
Male (%)	75%	95%
Age at the first VF (years)	41.2 ± 11.4	42.5 ± 15.8
Incidence of VF during sleep (%)	83%	11%
Response to sodium channel blocker	Augmentation	Attenuation
VF induction by EPS (%)	50%	30%
Positive late potential (%)	17%	10%
VF trigger	Late-coupled PVCs (400 ms)	Short-coupled PVCs (<340 ms)
VF initiation	Sudden onset	Non-sudden onset (short-long-short pattern)
VF recurrence	Frequent	Rare
Effective drug in suppressing VF	Isoproterenol, quinidine, cilostazol, bepridil	Unknown

ERS early repolarization syndrome, *ER* early repolarization
ERS (A): ERS with non-type 1 Brugada-pattern ECG in the right precordial leads
ERS (B): pure inferolateral ERS without Brugada-pattern ECG in the right precordial leads
VF ventricular fibrillation, *EPS* electrophysiological study
PVC premature ventricular contraction

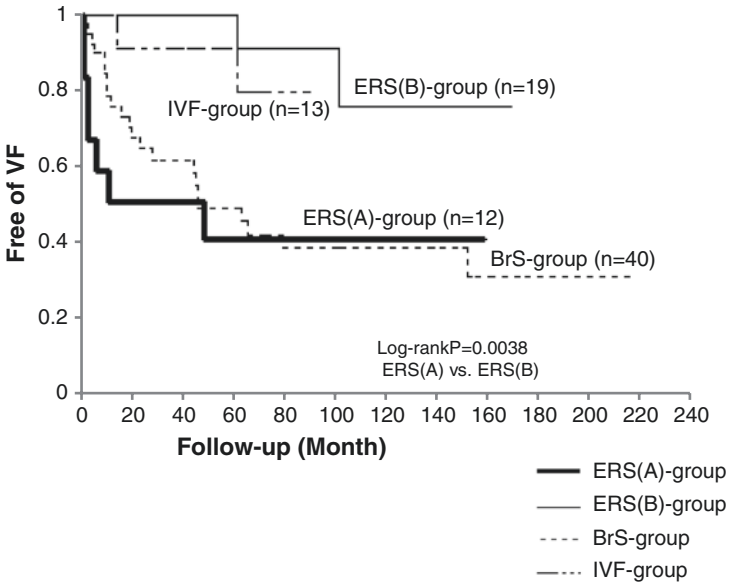

Fig. 5.4 Kaplan-Meier analysis of lethal arrhythmic events (documented ventricular fibrillation) during follow-up according to clinical subgroups (ERS(A) group, ERS(B) group, BrS group, and IVF group) in patients with a prior VF. ERS(A) group: ERS patients with non-type 1 Brugada-pattern ECG. ERS(B) group: ERS patients without non type-1 Brugada-pattern ECG. BrS group: Patients with type 1 BrS and a history of VF. IVF group: Idiopathic VF patients without J waves

with non-sudden onset, in particular those with short-long-short sequence (ERS (A) vs. ERS (B): 33% vs. 81%, $P = 0.0045$) and shorter PVC coupling, were more commonly observed in the ERS (B) group. These results indicated that ERS comprised two subtypes with heterogeneous clinical profiles.

In other words, ERS patients with frequent VF recurrences in previous reports were considered to be those who exhibited a type 1 ECG only in the high intercostal spaces in the right precordial leads or non-type 1 Brugada-pattern ECG, i.e., ERS (A) patients. We have previously reported that VF mostly recurred in such patients showing a Brugada-pattern ECG in any precordial lead including high intercostal spaces, who comprised 50% of our cohort diagnosed with ERS on the basis of the previous criteria [29]. The existence of a Brugada-pattern ECG in half of the ERS patients could account for the similar clinical and genetic characteristics, such as the effectiveness of quinidine and isoproterenol in suppression of electrical storm to those in the BrS patients.

5.5 Mechanisms of ERS and BrS

The pathophysiological mechanisms underlying these syndromes also remain a matter of debate. There are two main theories that explain the mechanism of J wave and ST-segment elevation in BrS: the repolarization hypothesis and the depolarization hypothesis [8, 33]. The repolarization hypothesis has been supported by studies using animal models and relies on I_{to}-mediated transmural dispersion of repolarization between the right ventricular (RV) endocardium and epicardium. This theory provides an explanation for the trigger (phase 2 reentry) underlying the development of VF, ST-segment elevation by calcium channel blockers or potassium channel openers, ST-segment normalization by quinidine or isoproterenol, and the strong association between spontaneous type 1 ECG and cardiac events.

In contrast, the depolarization hypothesis relies on conduction delay in the RV outflow tract caused by structural abnormalities. Although this theory has not been demonstrated in experimental models, various data supporting the existence of RV conduction delay have been obtained from electrophysiological and clinical studies involving signal-averaged ECGs and body surface, epicardial, and endocardial mapping. Furthermore, Nademanee et al. [34] have demonstrated that abnormal low-voltage, prolonged, and fractionated late potentials exist in the epicardial aspect of the RV outflow tract in selected BrS patients who received multiple shocks from an implantable cardioverter-defibrillator (ICD). Radiofrequency ablation of the epicardial sites of slow conduction resulted in normalization of the Brugada-pattern ECG and prevented VF.

Although inferolateral ER is considered as a repolarization phenomenon in the left ventricular wall, there are various data contradicting the repolarization hypothesis. Abe et al. suggested that circadian changes of signal-averaged ECG parameters in patients with inferolateral J waves implied an association with depolarization abnormalities [35]. Nakagawa et al. reported the high incidence of false tendon in patients with inferolateral ER [36]. These data may indicate an arrhythmogenic mechanism other than repolarization abnormality, such as micro-reentry or triggered

activity due to a depolarization abnormality, which is often observed in cases of idiopathic VF caused by PVCs originating from the Purkinje network. These two theories are not mutually exclusive and may indeed be synergistic. Considering the differences in clinical characteristics and prognosis between patients in ERS (A) and ERS (B) groups, the mechanism underlying ER in the right precordial leads (Brugada-pattern ECG) and ER in the inferolateral leads may differ.

In both syndromes, strong male predominance is observed, and the highest incidence of VF or sudden cardiac death occurs in the third decade of life. A higher testosterone level is reported to have a significant role in Brugada phenotype and male predominance in BrS [37]. Inferolateral ER has been observed with age dependency toward higher prevalence in young males, and testosterone levels have also been reported to be significantly higher among males with inferolateral ER than those without [38]. In addition to the proposed hypothesis, these data suggest a potential influence of testosterone on both syndromes. Further studies will be needed to clarify the mechanisms underlying ERS and BrS.

5.6 Conclusions

Although ERS and BrS are considered to share similar pathophysiology, previous ERS studies may have included patients with BrS only in the high intercostal spaces. ERS patients with non-type 1 Brugada-pattern ECG in the right precordial leads (ERS (A)) showed similar clinical characteristics and prognosis to patients with type 1 BrS. Our hypothesis regarding ERS in relation to BrS is illustrated in Fig. 5.5.

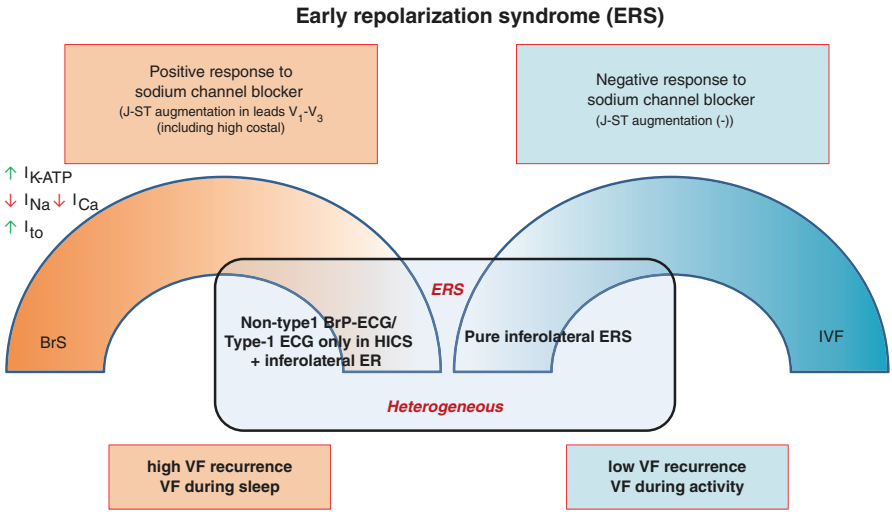

Fig. 5.5 Schematic depicting hypothesis of ERS. Inferolateral ERS can be divided into two. *ERS* early repolarization syndrome, *ER* early repolarization, *BrS* Brugada syndrome, *IVF* idiopathic ventricular fibrillation, *BrP-ECG* Brugada-pattern electrocardiogram, *HICS* high intercostal space, *VF* ventricular fibrillation

Many previously reported ERS patients with poor prognosis may be patients with type 1 Brugada-pattern ECG only in the high intercostal ECG recordings or non-type 1 Brugada-pattern ECG in any lead. This could account for the clinical and genetic similarity of half of the ERS patients to BrS patients. In contrast, most ERS patients lacking a Brugada-pattern ECG in any of the right precordial leads exhibited a favorable outcome and clinical profiles dissimilar to BrS. Provided that half of ERS cases are nearly identical to BrS, the remaining ERS cases without Brugada-pattern ECG may be considered as true ERS possibly caused by a different mechanism. The mechanism may also differ between ER in inferolateral leads and the right precordial leads. In ERS, clinical parameters and risks probably should not be assessed in the context of a homogeneous disorder.

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Chapter 6
Risk Stratification of the J Wave Syndrome

Atsuyuki Watanabe and Hiroshi Morita

Abstract Appearance of a J wave is a potent risk for idiopathic ventricular fibrillation (VF). The incidence of inferolateral J wave is higher in patients with idiopathic VF than that in control subjects. Patients having a higher and widespread J wave with horizontal/descending ST segments are at high risk for arrhythmic events (malignant early repolarization (ER)), and it is associated with arrhythmic storm. J wave dynamicity, fragmented QRS, and T wave abnormality will be even more high-risk signs in patients with malignant ER. Occurrence of short coupled premature ventricular contractions can be a precursor of VF and sudden death. Patients who have experienced aborted cardiac arrest or ventricular tachyarrhythmias should receive an implantable cardioverter defibrillator.

Cohort studies have shown that inferolateral J wave is also a risk marker for the cardiovascular and arrhythmic events. High and widespread J wave is also a risk for the arrhythmic events in general population, but the occurrence of idiopathic VF is very rare. The incidence of the idiopathic VF will be 90:100,000 in persons with a tall J wave with a horizontal/descending ST segment. The existence of J wave will increase the risk of VF during acute ischemia or in patients with structural heart diseases. In patients with inherited arrhythmic syndrome, J wave also increases the risk of VF.

6.1 Introduction

Early repolarization (ER), a concave ST elevation in the left precordial leads, is a common finding in young people, particularly males and athletes, and it had been believed to be an innocent sign of the ECG. The J wave can appear along with the ST elevation of ER. A prominent J wave was also reported in a hypothermic condition [1] and is known as Osborn wave. ST elevation in the right precordial leads was

A. Watanabe, M.D., Ph.D.
Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

H. Morita, M.D., Ph.D. (✉)
Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
e-mail: hmorita114@aol.com

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reported in the 1950s and was thought to be ER in the right ventricle. Both ER patterns in the right and left precordial leads had not been recognized for a long time as a significant prognostic sign. However, in 1992, Brugada et al. reported idiopathic ventricular fibrillation (VF) with ST elevation in the right precordial leads [2], which has attracted cardiologist's attention as Brugada syndrome. In the case of a J wave, Aizawa et al. reported a patient of idiopathic VF with a prominent J wave in 1992 [3], and Gussak and Antzelevitch reported the possibility of arrhythmogenesis of the J wave in 2000 [4]. However, there was no clinical recognition of the importance of the J wave until 2008, when the initial report of idiopathic VF associated with ER was published by Haïssaguerre et al. [5] Thereafter, the prognostic significance of ER and the J wave has applied to the general population and to various heart diseases such as ischemic heart disease, inherited arrhythmic syndromes, and cardiomyopathies.

When the importance of ER and the J wave became widely known, the definition of ER was changed. ER is historically defined as "J-point elevation and rapidly upsloping or normal ST segment (Fig. 6.1a)" [6]. In a recent scientific statement [7], ER pattern was defined as "ST-segment elevation in the absence of chest pain, terminal QRS slur, or terminal QRS notch," and an isolated J wave can thus been called as ER (Fig. 6.1b). The definition of ER/J has been commonly

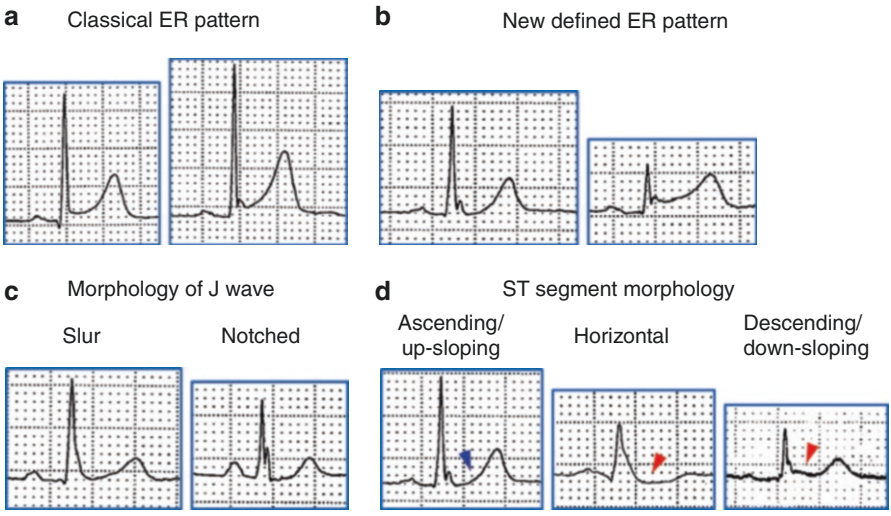

Fig. 6.1 Pattern of early repolarization. (**a**) Classical early repolarization (ER) pattern. ER was defined as ST elevation with or without a J wave. (**b**) New definition of ER pattern. The presence of a notched or slurred J wave is important, and ST elevation is not essential for the definition of ER. (**c**) Morphology of the J wave. J waves are divided into two types: slurred and notched J waves. (**d**) ST-segment morphology. A J wave with upsloping ST morphology is a benign form, but a J wave with horizontal or downsloping ST morphology is thought to be a malignant type of ER

used in recent studies in accordance with the definition of by Haïssaguerre et al. [5], i.e., elevation of the QRS–ST junction (J point) in at least two leads. The amplitude of J-point elevation had to be at least 1 mm (0.1 mV) above the baseline level, either as QRS slurring (a smooth transition from the QRS segment to the ST segment) or notching (a positive J deflection inscribed on the S wave) in the inferior lead (II, III, and aVF), lateral lead (I, aVL, and V4–V6), or both (Fig. 6.1c) [5].

In 2010, Antzelevitch and Yan proposed the term "J wave syndrome (JWS)." JWS includes various conditions with the appearance of a prominent J wave and with a risk of VF. It includes idiopathic VF with a J wave, Brugada syndrome (BrS), acquired arrhythmias associated with hypothermia, and acute myocardial infarction [8]. Antzelevitch and Yan categorized idiopathic VF with a J wave as ER syndrome (ERS) types 1–3 according to the distribution of J waves (type 1, J wave in lateral leads; type 2, J wave in inferior or inferolateral leads; type 3, globally distributed J wave) (Fig. 6.2). In a recent scientific statement [7], ER syndrome was defined as "a syndrome occurring in patients with an ER pattern who have survived idiopathic VF with clinical evaluation unrevealing for other explanations," and JWS was defined as "a syndrome occurring in patients with terminal QRS slurs or notches associated with cardiac arrest."

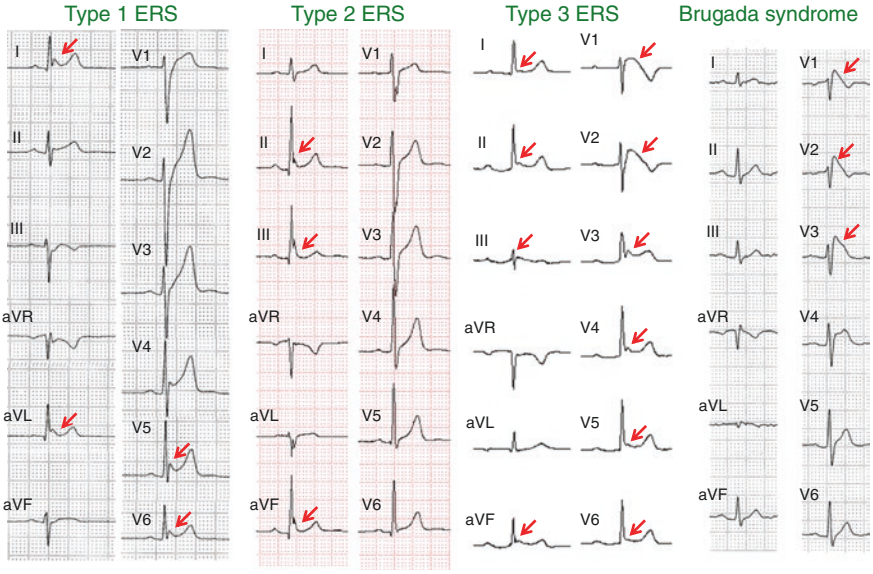

Fig. 6.2 Inherited J wave syndrome. Type 1 ER, J wave in lateral leads; type 2 ER, J wave in inferior or inferolateral leads; type 3 ER, globally distributed J wave and Brugada syndrome

Idiopathic VF with ER is a rare disease. Rosso et al. estimated that the risk of developing idiopathic VF (at less than 45 years of age) is 3:100,000 and that the risk increases to 11:100,000 when J waves are present [9, 10]. Furthermore, if the J wave is followed by a horizontal ST segment, the risk of idiopathic VF increases to 30:100,000 [9]. The incidence will increase to 90:100,000 in persons with a tall J wave with a horizontal/descending ST segment. It is difficult to evaluate arrhythmic risk in all subjects with a J wave, and the extraction of high-risk subjects from the general population with a J wave is of importance. We review the various risk markers that have been reported in ERS.

6.2 Risk Stratification of Early Repolarization Syndrome

6.2.1 Clinical Characteristics

ER pattern is frequently observed in males in the general population [11–13] The incidence of ER pattern increases and has a peak around the age of 20 years and then gradually decreases at middle age to elderly. A predominance of male is reported in patients with ERS as Brugada syndrome (proportions of males, 72–92.5%) [5, 14–17]. However, male predominance does not mean that female patients have a good prognosis. Aizawa et al. reported that patients with ERS who experienced an electrical storm included two females (15%) [18]. Therefore, gender does not provide additional prognostic value for patients with ERS [19] or asymptomatic patients with J wave/ER.

A family history of sudden death (SD) is thought to be a malignant sign of ERS. The incidence of a family history of SD in patients with ERS was reported to be 18% [17]. Another study showed that the incidence of ER was 23% in a family with victims of sudden arrhythmic death syndrome [20]. Although other studies showed low incidences of family history of SD in ERS (0–9%) [10, 14, 16], detailed evaluation of the family members revealed that 33–61% of the family members had ER [21]. In patients with ERS and VF, a family history of SD is a risk factor for recurrent VF [22]. The prognostic value of existing of the familial SD is unclear, but we should pay attention to asymptomatic ERS patients with a family history of SD.

Self-terminating VF causes a syncope episode. VF in ERS usually occurs at night, and syncope associated with ventricular arrhythmia occurs at rest or during sleep. Agonal respiration during sleep also occurs in association with VF events. Neurally mediated syncope is not infrequent in subjects with a J wave [23]. However, patients with arrhythmic syncope, which is strongly suspected to be associated with malignant ventricular arrhythmias, experience less prodromal symptoms. Moreover,

arrhythmic syncope usually does not occur in particular circumstances, such as urination [24, 25]. Taking a detailed history of syncope is of particular importance for the diagnosis of arrhythmic syncope.

6.2.2 ST Segment and J-Point Elevation

Before the report by Haïssaguerre et al. in 2008 [5], ER was thought to have no prognostic significance. The difference in the prognosis of ER before and after 2008 might be due to the different definitions of ER. Recent reports have used "J-point elevation with slurred or notched J wave" as the definition of ER, whereas previous reports usually used the historical definition of ER, "ST-segment elevation" [26]. Different from the classical definition of ER as ST-segment elevation, J-point elevation with a slurred or notched J wave is important for risk stratification. Tikkanen et al. who showed that ER is associated with risk of death defined ER as "ER patterns being stratified according to the degree of J-point elevation (≥0.1 mV or >0.2 mV) that was either notched (a positive J deflection inscribed on the S wave) or slurred (a smooth transition from QRS to ST-segment) in at least two consecutive inferior or lateral leads" [27]. On the other hand, ST elevation in inferior or lateral leads and absence of J wave did not predict cardiovascular death [10, 28].

6.2.3 Amplitude of J Wave

Haïssaguerre et al. showed that amplitude of the J wave was higher in ERS patients with VF than in control subjects (2.0 ± 0.9 mm vs. 1.2 ± 0.4 mm) [5]. They also reported the J wave became large in association with frequent occurrence of ventricular arrhythmias (2.6 ± 1 mm to 4.1 ± 2 mm) [5]. Accentuation of the J wave immediately before the onset of VF has long been reported [3, 29], and the recent studies showed that high amplitude of the J wave was frequent in patients with VF [10, 30, 31]. Thus, a high amplitude of the J wave is a high-risk sign in patients with idiopathic VF and ERS (Fig. 6.3a).

A high amplitude of the J wave is also a predictor of prognosis in the general population. The relative risk (RR) of death from cardiac cause in subjects with J point ≥0.1 mV is 1.28, whereas the RR in subject with J point ≥0.2 mV increases to 2.98 [27]. A meta-analysis study also showed that the J-point elevation (≥0.2 mV) in inferior leads was a higher risk for death from arrhythmia (RR, 3.02) and cardiac cause (RR, 2.98) than was the J-point elevation (≥0.1 mV) in inferior leads (RR of arrhythmic death 1.58, RR of cardiac death 1.48) [32].

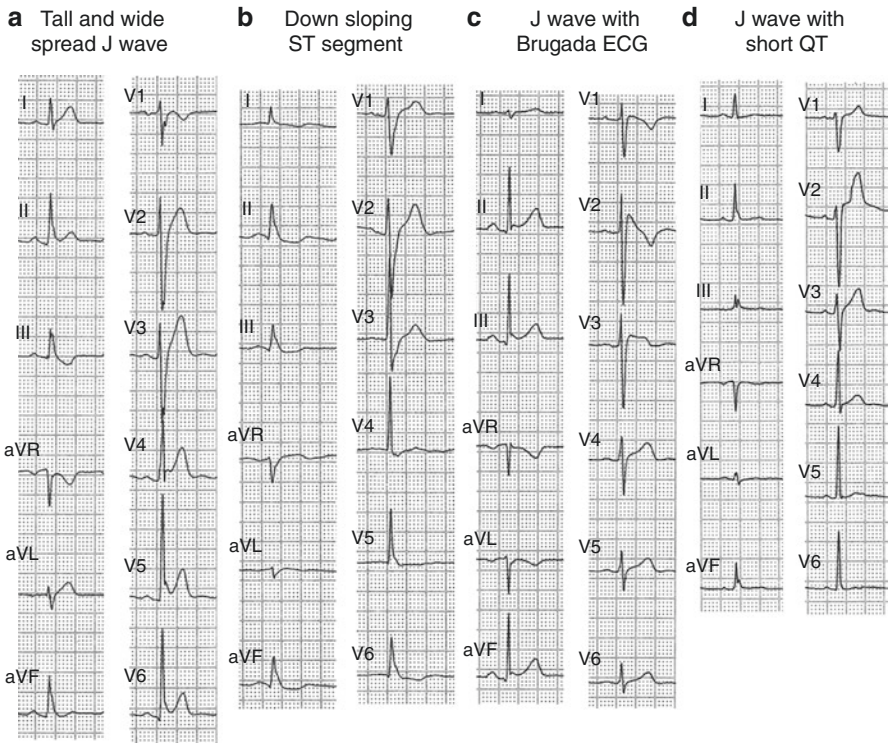

Fig. 6.3 Various type of J wave. (**a**) Tall and widespread J wave that was observed in a healthy asymptomatic person. (**b**) Slurred J wave with a down-sloping ST segment in a patient who was resuscitated from VF. (**c**) A patient with Brugada syndrome and widely distributed J waves. (**d**) A J wave with a short QT interval in a healthy asymptomatic person

6.2.4 Distribution of J Waves

J waves in inferior and lateral leads were shown to be frequent in patients with idiopathic VF (inferior 27%, lateral 13%) than in control subjects (inferior 8%, lateral 11%), whereas the frequencies of J waves in leads V4–6 were similar between the idiopathic VF patients (6.7%) and the control subjects (7.3%) [10]. In patients with ERS, the J wave is most frequently observed in inferior leads (42–44%) and next most frequently observed in lateral leads (9–10.5%) [31, 33], and J wave also appears in both inferior and lateral leads (37–47%) [5, 30]. The incidences of J wave increase in familial ERS [20], and J waves appear in multiple regions in patients with a severe form of ERS with VF storms [18].

Cohort studies and meta-analysis also showed that J-point elevation in inferior leads was associated with an increased risk of death from cardiovascular causes [32,

34–36] and from arrhythmia [27, 32, 37]. Moreover, a widely distributed J wave in both inferior and lateral leads was associated with the occurrence of unexpected death [38]. Several studies failed to show prognostic significance of the J wave for 5–10 years of follow-up [39–42], whereas the subjects in studies that showed prognostic significance of the J wave were followed up for longer periods of 17–50 years [27, 35–37, 43]. Long-term follow-up should be required to unmask the prognostic significance of the J wave.

Antzelevitch and Yan [8] reported that ERS type 1, commonly seen in healthy men and athletes, has anterolateral J waves (leads I and V4–6), and VF occurrence is rare. ERS type 2, commonly seen in males, has inferior J waves (leads II, III, and aVF) and has an association with VF. ERS type 3 has globally distributed J waves and is associated with VF occurrence. This type can also promote electrical storms of VF.

6.2.5 Types of J Waves

J waves are classified into two types (Fig. 6.1c): (1) terminal QRS notching which is characterized by low frequency deflection at the end of the QRS complex and (2) terminal QRS slurring, which is defined as an abrupt change in the slope of the last deflection at the end of the QRS complex [7]. QRS notching is "J wave" in a narrow sense.

QRS notching was reported to be more prevalent in ERS patients than in controls and to be more malignant in the form of ER [10, 44]. The presence of QRS slurring did not add diagnostic value to the presence of J-point elevation. A notched type J wave was frequently observed in large families with ERS, and the prevalence of the notched type J wave was 78–92% in four families [21]. In other studies, the definition of J wave or ER included both QRS notching and slurring [5, 14, 20, 30, 31], and the prevalence of QRS slurring was reported to be 29–60% [14, 30, 31, 33]. Antzelevitch and Yan showed that the J wave represented a phase 1 notch of action potential. They suggested that a notched J wave is coincident with the accentuation of the phase 1 notch and conduction slowing [45] and that the notched type J wave may have more arrhythmogenetic potential. A case-control study showed that patients with ERS had a wide J wave regardless of the type of J wave and that control subjects had a short and steep J wave. That study showed that the cutoff values of J wave angle and duration were >30° and >60 ms, respectively [46].

In a general population, it seems that the notched J wave has a worse prognosis than that of the slurred J wave, but the slurred type J wave with high voltage or the simultaneous appearance of both types of J wave will be also associated with lethal arrhythmias [32, 38, 47, 48].

6.2.6 Morphology of the ST Segment

Tikkanen et al. found that ST-segment morphology had an impact on prognosis of the general population with a J wave [48]. They showed that a J wave with a horizontal or descending ST-segment morphology was a sign of high for arrhythmic death (Figs. 6.1d and 6.3b). Rosso et al. applied the classification of ST-segment morphology to patients with ERS. They found that a notched type J wave with a horizontal/descending ST segment increased the odds ratio for having idiopathic VF to 13.8, whereas only a J wave showed an odds ratio of 4.0 [19]. They called a J wave with this type of ST-segment morphology "malignant ER" [19]. Some case-control studies have shown the same impact of ST-segment morphology, and this type of ST-segment abnormality was observed in 68–100% of ERS patients [14, 19, 31].

In the general population, the HR of arrhythmic death increased to 3.14 in people with a high amplitude ER (>0.2 mV) in inferior leads and a horizontal/descending ST segment. However, in subjects with an ascending ST segment, the risk for arrhythmic death was not increased [48]. Epicardial action potential usually has a shorter repolarization time than that of endocardial action potential, and horizontal or descending ST morphology might represent prolongation of the repolarization time at the epicardial action potential that generates reverse of transmural dispersion of the repolarization promoting ventricular tachyarrhythmias [45].

6.2.7 T Wave Abnormality

A lower T wave frequently appeared in patients with malignant ER. The T wave is qualified by the T-wave/R-wave (T/R) ratio in leads II and V5. The presence of low-amplitude T waves is usually defined as T-wave amplitude <0.1 mV or <10% of R-wave amplitude in lead I, II, or V4–V6. Patients with a malignant inferolateral J wave had a higher prevalence of dysmorphic T waves, such as low-amplitude T waves (OR, 3.53) and lower T/R ratio in lead II or V_5 (OR per 0.1 unit, 0.62). The QTc interval in patients with ERS (388 ms) was slightly longer than that in controls with an inferolateral J wave (377 ms) [49]. The interval between the peak of the T wave and the end of the T wave (Tp-Te) and the Tp-Te/QT ratio were significantly increased in patients with ERS compared to those in controls with an ER pattern [50–52]. The response of QT interval to heart rate was disrupted in patients with ERS [53, 54] as well as in patients with Brugada syndrome [55].

6.2.8 Pause-Dependent J Wave and Occurrence of VF

The J wave shows daily fluctuation and accentuates immediately before the VF [18]. Premature ventricular contractions (PVCs) frequently occur associated with VF episodes [52]. PVC results in a long pause and the next PVC occurs on

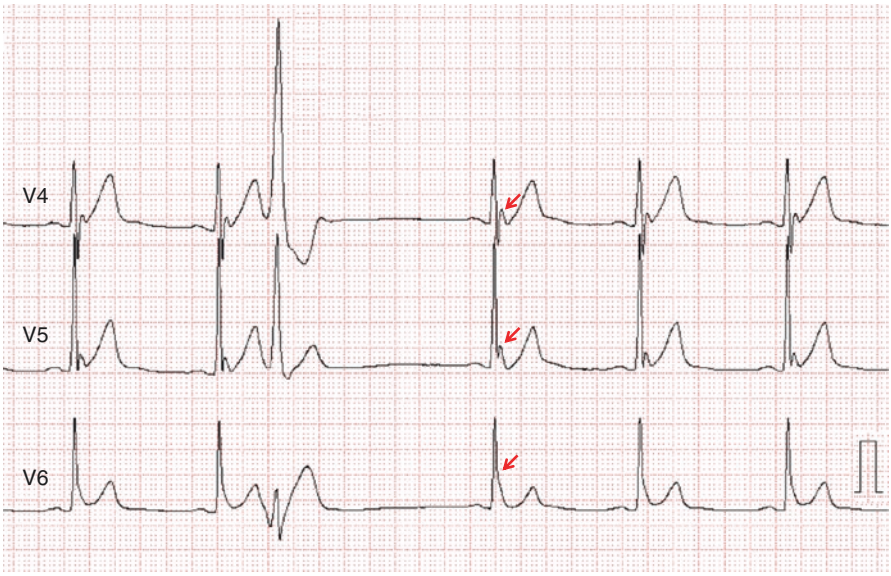

Fig. 6.4 J wave augmentation after a long pause. The J wave was augmented after a long pause created by a premature ventricular contraction in a patient who was resuscitated from VF

the T wave [5, 17, 52] of the beat (short-long-short sequence) that has an augmented J wave [15] and initiates VF (Fig. 6.4). Pause-dependent augmentation of J wave was 56% of sensitivity but high specificity (100%) to predict ERS patients with VF (Fig. 6.4). In the general population, the J wave usually attenuates after long pause. The observation of pause-dependent augmentation of the J wave in ERS accords with the experimental observations, in which the phase 1 notch of the action potential represents the mechanism of the J wave [8, 45, 56, 57].

6.2.9 Programmed Electrical Stimulation and Drug Provocation Test

Programmed electrical stimulation (PES) induced VF in 28–34% of patients with ERS, and its incidence was not significantly different from that of idiopathic VF without a J wave (20%) [5, 17]. A recent study showed that the inducibility of VF was not associated with recurrent VF episodes [58].

Although a sodium channel blocker unmasks and augments ST elevation in patients with BrS, it does not enhance and, in fact, often attenuates the inferolateral J wave [59, 60]. A sodium channel blocker augments local J wave recorded by a catheter in the coronary vein, but widening of the QRS complex by the sodium channel blocker masked the local J wave [61]. A sodium channel blocker

occasionally enhanced the J wave and induced ventricular arrhythmia [62], but the prognostic value of the drug challenge test is unclear.

6.2.10 J Wave in Inherited Arrhythmic Diseases

BrS is also categorized as JWS, and ST elevation at right precordial leads is considered to be ER in the right ventricle. An inferolateral J wave was observed in 11–12% of patients with BrS [63, 64] (Fig. 6.3c). It has been reported that the inferolateral J wave in BrS was an independent predictor of VF [65–67], sudden death, and electrical storm [68].

Short QT syndrome is a rare inherited arrhythmic disorder, which is characterized by a short QT interval, VF, and sudden death. The incidence of J waves was higher in patients with short QT syndrome (50–65%) than in a short QT cohort without arrhythmia (30%) and normal QT controls (10%) [69, 70]. The J wave often appears in patients with lethal arrhythmic events. Because subjects with ER in general population also have a short QT interval [71] (Fig. 6.3d), it is sometimes difficult to determine whether patients with both moderate QT shortening and a J wave have ERS or short QT syndrome.

The J wave was observed in 44% of patients with long QT syndrome. Seventeen percent of the patients had a significant J wave of ≥0.2 mV. Risk factors of syncope events in long QT syndrome are J wave of ≥0.2 mV (OR, 5.97), QTc >500 ms (OR, 4.50), and female gender (OR, 5.21) [72].

6.2.11 Treatment of Patients by J Wave Consensus Document

The recent document of the J Wave Consensus Conference [73] recommended treatment for the patients with ER > 0.1 mV in at least two contiguous inferolateral leads. In asymptomatic patients, high-risk ECG pattern (prominent J waves, horizontal/descending ST segment, high dynamicity) and strong family history of unexplained death at a young age should be evaluated. If the patient has both a strong family history and any of the ECG markers, implantation of an ICD is recommended (Class IIb) (Fig. 6.5). If the patient does not have any of the ECG factors and family history, the clinician should follow up the patient. Implantation of ICD is recommended for patients with VT/VF events, and additional treatment with quinidine or cilostazol can reduce cardiac events. If the patient has experienced syncope, seizure or nocturnal agonal respiration, and strong family history of sudden death at a young age, the characteristics of the symptoms should be carefully evaluated. If the symptoms are thought to be of arrhythmic origin, ICD implantation is recommended (Class IIb). If the symptoms are judged to be of non-arrhythmic origin, the patient should be followed with or without an implantable loop recorder.

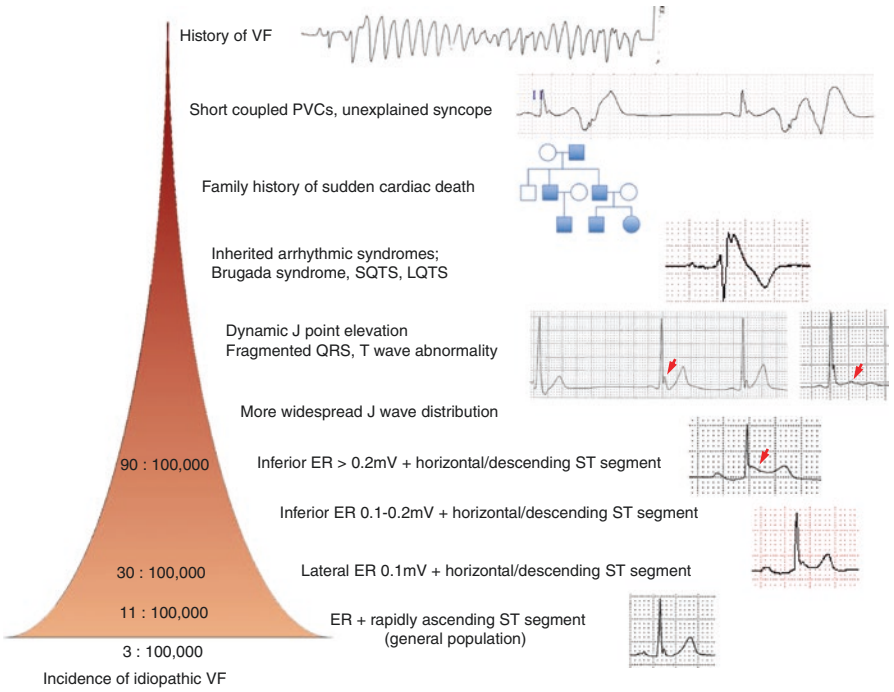

Fig. 6.5 Risk stratification of J wave syndrome. Prominent widespread J waves with a horizontal ST segment are a malignant J wave, but the incidence of idiopathic VF is still low in such a population. A strong family history of sudden death or ERS and occurrence of short-coupled extrasystoles will represent the high-risk sign

6.3 Conclusion

Inferolateral J wave is frequently observed in patients with idiopathic VF. J wave shows daily fluctuation, and it accentuates immediately before the onset of VF. Higher and widespread J wave with horizontal or descending morphology of ST segments is thought to be malignant J wave because it is associated with severe form of ERS. Inferolateral J wave sometimes appears in general population, but the occurrence of idiopathic VF is rare. To detect high-risk subjects in general population, clinical information, such as symptoms or family history of sudden death, and detailed ECG recordings should be evaluated.

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Chapter 7
Catheter Ablation for ERS

Akihiko Nogami, Yumie Matsui, Yasutoshi Shinoda, Kenji Kurosaki, and Kazutaka Aonuma

Abstract Since its first clinical evidence in 2008, there have been only few clinical reports of ablation in early repolarization syndrome (ERS). What is still undetermined is whether the mechanism of the ablation effect is due to the suppression of the trigger or substrate modification. In idiopathic ventricular fibrillations (VFs), the triggering sources mainly arose from either the Purkinje system or, less commonly, from the ventricular muscle. In ERS, VF sources from right or left Purkinje tissue are dominant (83%), with the site of origin correlating with the electrocardiographic location of early repolarization. RF catheter ablation of ERS is feasible and can be used as a bailout therapy for drug-refractory VF storms. Further studies are needed to evaluate the precise mechanisms of this arrhythmia.

7.1 Introduction

While previous studies have shown that ventricular fibrillation (VF) is perpetuated by reentry or spiral waves, recent data suggest the role of specific sources triggering this arrhythmia. Haïssaguerre et al. [1] reported that idiopathic VF could be suppressed by catheter ablation of those triggers originating from the Purkinje system or right ventricular outflow tract (RVOT), and the ablation therapy for VF has been increasingly reported during the last decade. However, little is known about the initiating mechanism of VF. Furthermore, it is still unclear whether the mechanism of the ablation effect is due to the suppression of the trigger or substrate modification.

A. Nogami, M.D., Ph.D. (✉) • Y. Shinoda, M.D. • K. Aonuma, M.D., Ph.D.
Department of Cardiology, Faculty of Medicine, University of Tsukuba,
1-1-1 Tennodai Tsukuba, Ibaraki 305-8575, Japan
e-mail: akihiko-ind@umin.ac.jp

Y. Matsui, M.D.
Department of Cardiology, Saiseikai Izuo Hospital, Osaka, Japan

K. Kurosaki, M.D.
Department of Heart Rhythm Management, Yokohama Rosai Hospital,
Yokohama, City, Japan

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In 2008, Haïssaguerre et al. reported an association between inferolateral early repolarization (ER), also called the J-wave, and unexplained sudden cardiac death [2]. Since then, inferolateral ER has been identified as a marker of arrhythmic risk in the general population [3]. Since its first clinical evidence in 2008, there have been only few clinical reports of ablation in early repolarization syndrome (ERS) [4–6].

7.2 Role of the Purkinje System in Triggering VF

The involvement of the Purkinje system can be categorized into VF initiation (trigger) and VF maintenance (substrate). Automatic diastolic depolarization and triggered activity with abnormal Ca^{2+} sparks linked to K^+ and Ca^{2+} current changes were shown in Purkinje cells [7, 8]. Clinical studies have demonstrated that Purkinje ectopies are prominent triggers of VF in humans in a wide spectrum of cardiac diseases, and the role of the Purkinje system in triggering VF has been confirmed by the efficacy of discrete ablation. In idiopathic VFs, the triggering sources were localized to the site with the earliest electrical signal and mainly arose from either the Purkinje system (93%; from the right or the left side or from both) or, less commonly, from the ventricular muscle (7%) [1]. In ERS, VF sources from right or left Purkinje tissue are dominant (83%), with the site of origin correlating with the electrocardiographic location of early repolarization [2, 4–6].

Ablation is performed at the earliest Purkinje site using radiofrequency (RF) applications, often producing a flurry of premature beats and polymorphic ventricular tachycardia (PVT), followed by complete quiescence [9].

7.3 Case 1 (Patient No. 5)

Figure 7.1 shows ECG from a 24-year-old female who was admitted after frequent episode of syncope. Frequent isolated VPCs with left bundle branch block (LBBB) configuration and superior axis were observed, and there were small J-waves in the inferior lead during sinus rhythm. After the admission the patient experienced VF storm, and the morphology of the trigger VPC was same as the previously documented VPC (Fig. 7.2). Right ventricular (RV) endocardial mapping showed an earliest activation located at the inferior wall of the RV, and spiky potential preceded the onset of the QRS by 133 ms (Fig. 7.3). Furthermore, paced mapping at this site reproduced the identical QRS to the trigger VPC. Purkinje potentials during sinus

rhythm were also recorded at this site. However, Purkinje potential was buried into the ventricular potential because this site locates the distal Purkinje network. RF energy application to this site eliminated the trigger VPC. After the additional RF energy applications to the adjacent sites, J-wave in the inferior leads disappeared (Fig. 7.1b). The patient underwent the implantation of implantable cardioverter/defibrillator (ICD). During 42-month follow-up when the patient received no drug therapy, neither episodes of syncope nor VF recurrence occurred. In this patient the elimination of the trigger VPC itself could be obtained by the RFCA to the single site at the distal Purkinje system, although the additional RF energy applications were delivered for the confirmation.

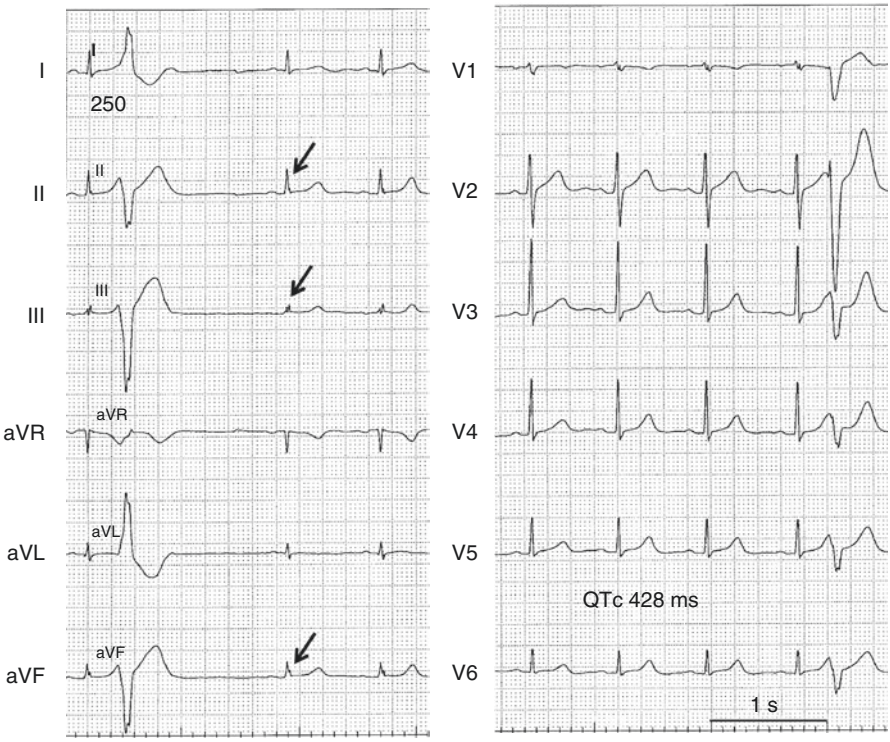

Fig. 7.1 Surface 12-lead ECGs from a female patient with early repolarization associated with VF (patient no. 5). (**a**) Frequent isolated VPCs with left bundle branch block (LBBB) configuration and superior axis were observed, and there were small J-waves in the inferior lead during sinus rhythm (*arrow*). (**b**) RF energy application to the site of origin eliminated the trigger VPC, and J-wave disappeared after the additional RF energy applications to the adjacent sites

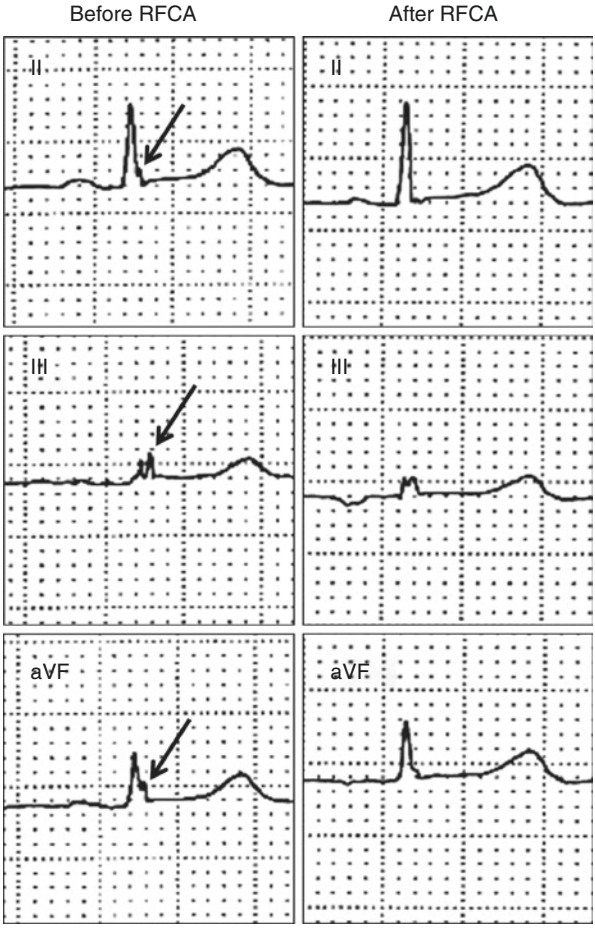

Fig. 7.1 (continued)

7.4 Case 2 (Patient No. 6)

A 67-year-old female patient with ICD appeared with frequent episodes of ICD shock for VF. ICD was implanted 3 years ago because of unexplained syncope and J-wave. There were J-waves in the inferior leads during sinus rhythm and VPC with right bundle branch block (RBBB) configuration, and north-west axis was induced by bolus injection of epinephrine 70 mcg (Fig. 7.4a). Bolus injection of epinephrine 90 mcg repeatedly induced PVT and VF (Fig 7.4b). The morphology of trigger VPC which induced VF was changed and, however, was basically RBBB configuration and superior axis. RF energy applications to the Purkinje network at the apical area in the left ventricle (LV) were delivered (Fig. 7.5). Because the VPCs had a variety

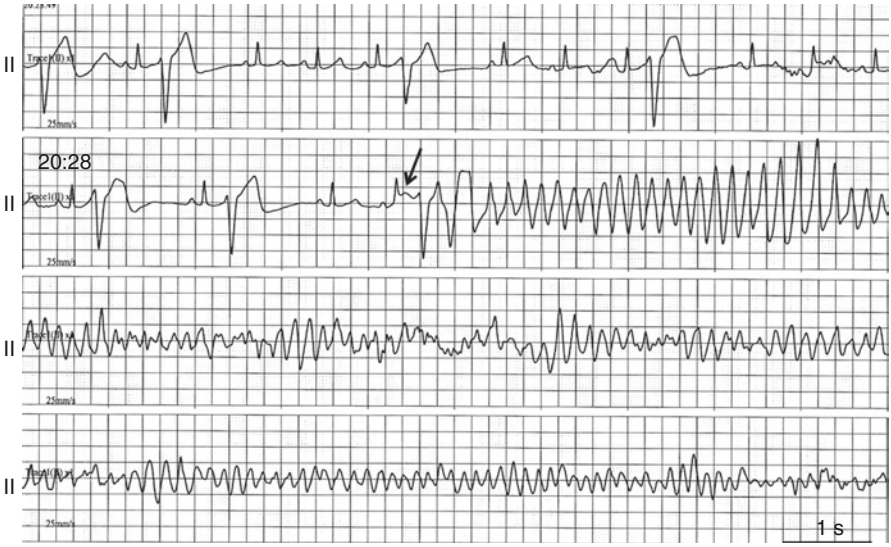

Fig. 7.2 ECG monitor tracings at the initiation of spontaneous VF (patient no. 5). After admission, the patient experienced VF storm. The trigger VPC was the same as the previously documented VPC. There was a significant ST elevation during preceding sinus beat at the initiation of VF (*arrow*)

of QRS morphologies, RF energy applications to the wide area at apical area in the LV were needed to suppress VPCs. After RFCAs, VPC became noninducible and VF was suppressed. There was no change in J-wave during sinus rhythm in this patient. During 24-month follow-up, neither episodes of syncope nor VF recurrence occurred.

7.5 The Results of Catheter Ablation of ERS

Table 7.1 shows our experience of catheter ablation for ERS. Between 2000 and 2015, a total of eight consecutive patients with early repolarization associated with VF and/or PVT underwent RF ablation therapy at our hospitals. These patients were five male and three female, age range 16–67 years (mean 38 ± 19 years). Documented ventricular arrhythmias were VF in seven patients and PVT with syncope in one. Target of RFCA was left Purkinje system in three patients, right Purkinje system in four patients, and RVOT in one. While the elimination of trigger VPC was achieved in six patients, VPC could not suppress in two patients (patient nos. 1 and 2). In those patients VF was successfully suppressed by disopyramide (patient no. 1) and amiodarone (patient no. 2). Patient no. 3 underwent successful RFCA of trigger VPC from right Purkinje system and had a VF recurrence 43 months after RFCA. However, the burden of VF was significantly reduced (several ICD shocks per month before RFCA). In the remaining five patients, no episodes of syncope or VF recurrence occurred during follow-up period (6–63 months).

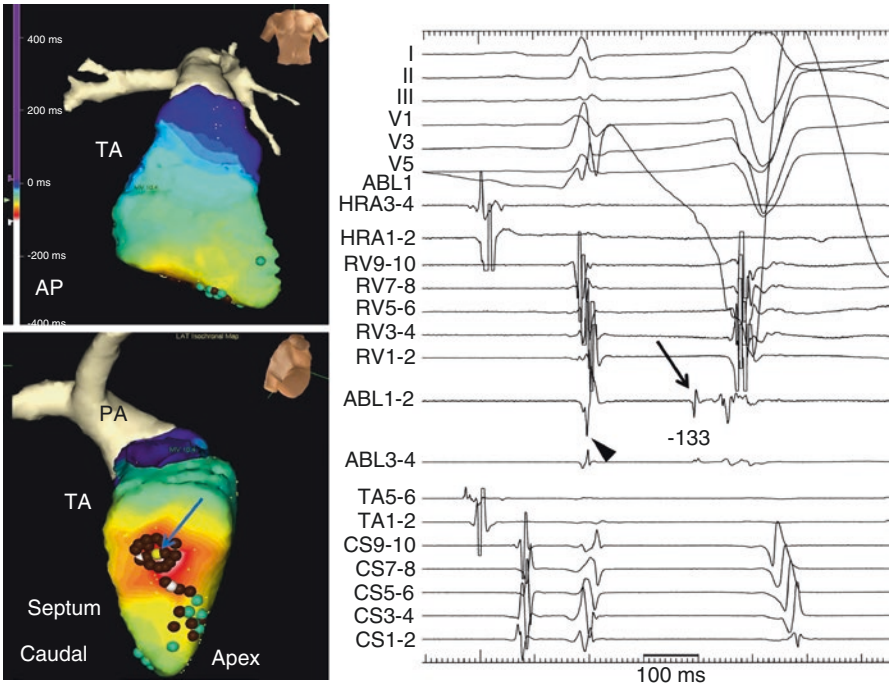

Fig. 7.3 Successful ablation site for VT (patient no. 5). Right ventricular (RV) endocardial mapping was performed during trigger VPC. Activation map using 3D map (NavX, St. Jude Medical) shows centrifugal pattern from the basal inferior wall of the RV (*blue arrow*) (*left panel*). At an earliest activation site, spiky presystolic potential was recorded and preceded the QRS onset by 133 ms (*arrow*) with a unipolar QS pattern (*right panel*). During sinus rhythm, Purkinje potentials were also recorded at this site; however, Purkinje potential was buried into the ventricular potential because this site locates the distal Purkinje system (*arrow head*). RF energy application to the earliest activation site eliminated the trigger VPC, and the additional RF energy applications to the adjacent sites (*red tags*) were also delivered

7.6 Importance of 12-Lead Recording of Triggering VPCs

Most cases of VF appear to originate from the Purkinje system, and some cases report initiating events that are distinct from the cardiac conduction system such as the RVOT [1]. Recording of the 12-lead ECG of the triggering event can prove invaluable information in regionalizing the origin of the triggering VPC for more detailed mapping, and an effort to record such a trigger should be routine. The target site can be speculated with the 12-lead ECG documentation: RVOT, right distal Purkinje, left posterior Purkinje, or left anterior Purkinje system. In the patients without ectopy, the putative source of the VPC can be ablated in sinus rhythm based on pace mapping followed by RF energy delivery. In the patients with multifocal

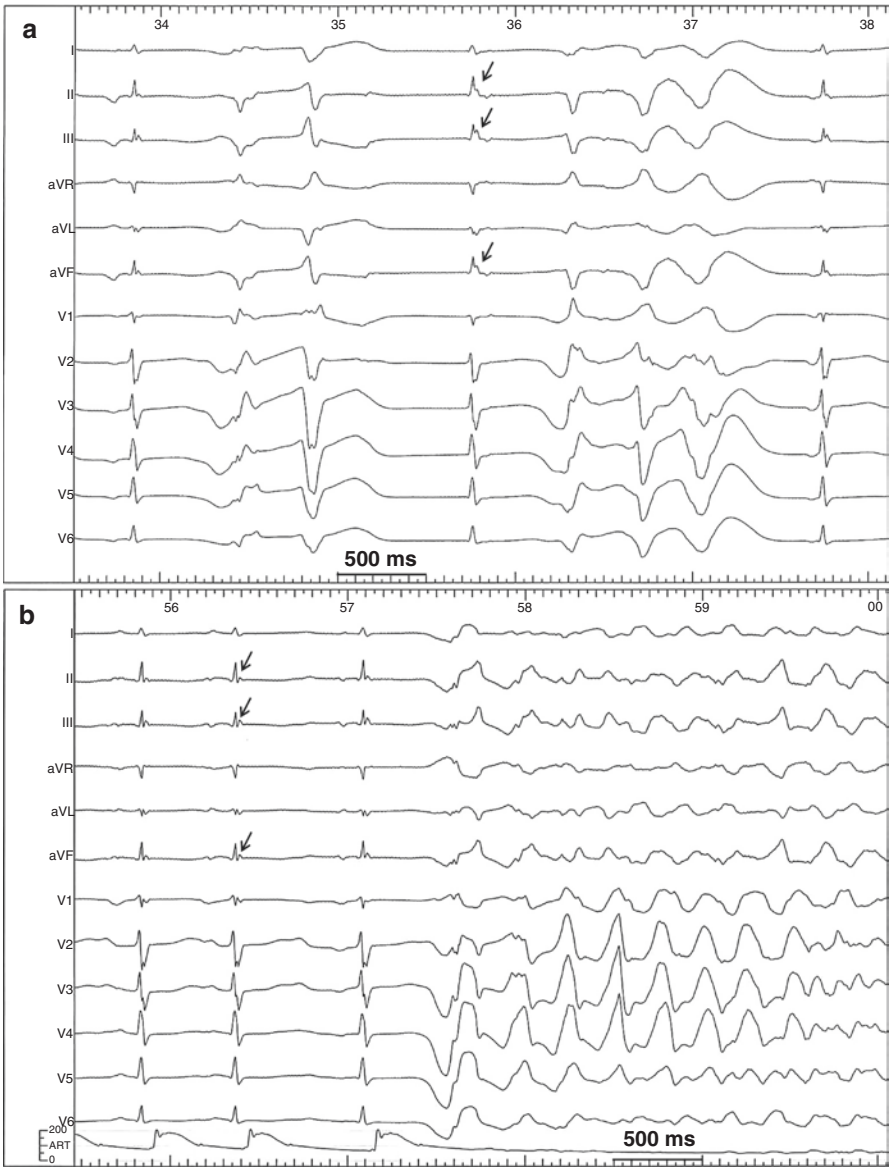

Fig. 7.4 Surface 12-lead ECGs from a female patient with early repolarization and the induction of VF (patient no. 6). (**a**) J-wave was observed in the inferior leads during sinus rhythm (*arrow*), and VPC with RBBB configuration and north-west axis was induced by bolus injection of epinephrine 70 mcg. (**b**) Bolus injection of epinephrine 90 mcg induced VF. The morphology of trigger VPC which induced VF was changed and, however, was basically RBBB configuration and superior axis

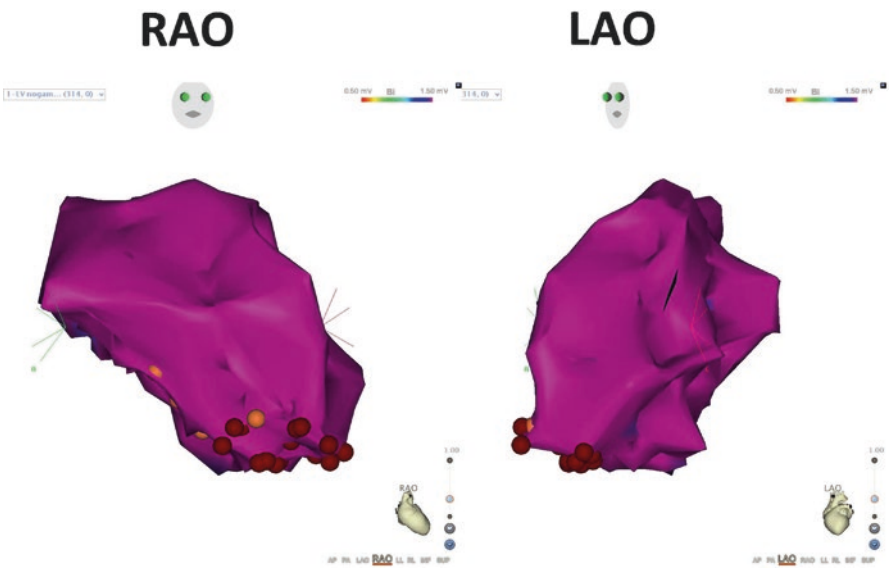

Fig. 7.5 Successful ablation sites for VF (patient no. 6). RF energy applications to the Purkinje network at the apical area in the left ventricle (LV) were delivered (*red tags*). There was no low-voltage area in the LV (CARTO, Biosense Webster). Because the VPCs had a variety of QRS morphologies, RF energy applications to the wide area at apical area in the LV were needed to suppress VPCs

Table 7.1 Results of catheter ablation of ERS

Pt#	Age	Gender	Documented VA	Target of RFCA	Acute success	Recurrence	FU (mo)
1	61	F	VF	Left Purkinje	None	Yes	165
2	24	M	VF	Right Purkinje	None	Yes	137
3	33	M	VF	Right Purkinje	Yes	Yes	115
4	16	M	PVT	RVOT	Yes	None	68
5	24	F	VF	Right Purkinje	Yes	None	42
6	67	F	VF	Left Purkinje	Yes	None	24
7	30	M	VF	Left Purkinje	Yes	None	16
8	46	M	VF	Right Purkinje	Yes	None	6
	Mean ± SD = 38 ± 19	M/F = 5/3					Median = 55

ERS = early repolarization syndrome, FU = follow-up, mo = month, Pt = patient, PVT = polymorphic ventricular tachycardia, RFCA = radiofrequency catheter ablation, RVOT = right ventricular outflow tract, SD = standard deviation, VA = ventricular arrhythmia

VPCs, the true triggering VPC that initiates VF or nonsustained PVT has to be confirmed. It is essential that there is accurate documentation of the triggering VPC, with a 12-lead ECG.

Figure 7.6 shows ECGs from a 59-year-old female patient with early repolarization associated with VF [10]. Each panel shows the QRS complexes during sinus rhythm and the VPC. In the emergency room (ER), significant J-ST elevation in the inferolateral leads and VPC bigeminy with an RBBB configuration and superior axis were observed after the spontaneous termination of PVT (Figs. 7.6A and 7.7A). After admission spontaneous VF was documented in the night (Fig. 7.7B). Therefore, ICD was implanted. One month after, a triggering VPC ablation was performed due to repeated ICD shocks. During the ablation session, frequent monofocal VPCs were observed (Fig. 7.6B), and Purkinje potentials on the posterior left ventricular septum preceded the onset of the VPC by 65 ms. An RF energy application at that site immediately eliminated the VPC (Fig. 7.8). However, a few days after the session, VF recurred. A 12-lead Holter recording could record the initiation of the VF (Fig. 7.6C).

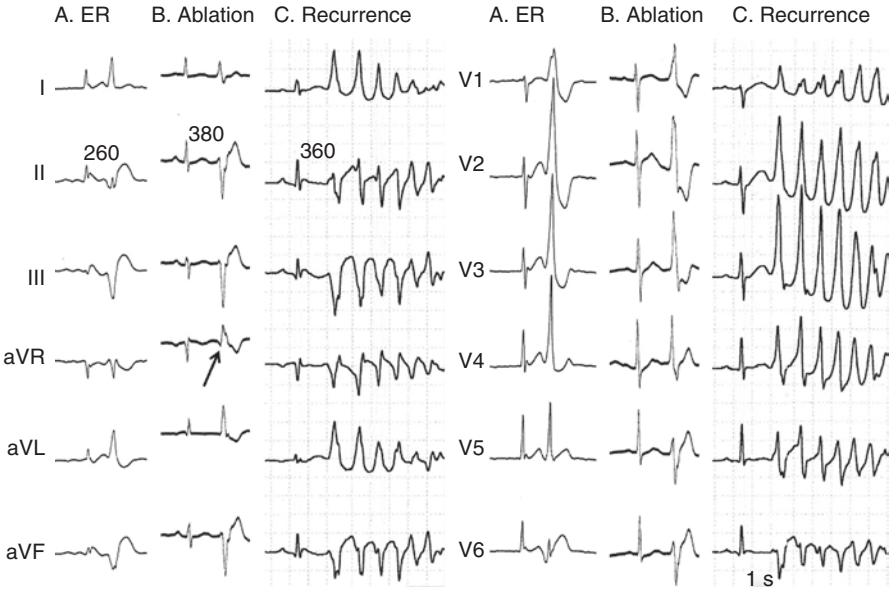

Fig. 7.6 Surface 12-lead ECGs from a female patient with early repolarization associated with VF (patient no. 1). (**a**) In the emergency room, significant J-ST elevation in the inferolateral leads and VPC bigeminy with an RBBB configuration and superior axis were observed after the spontaneous termination of polymorphic ventricular tachycardia (VT). (**b**) During the ablation session, frequent monofocal VPCs with an RBBB configuration and superior axis were observed. (**c**) A 12-lead Holter recording could record the VF recurrence. The "true" triggering VPC is similar to the ablated VPC, but is different (especially lead aVR) (*arrow*). Interestingly, while J-ST elevation was recorded in the emergency room and during the VF recurrence, it was not observed during the ablation session (From Nogami A., Mapping and ablating ventricular premature contractions that trigger ventricular fibrillation: trigger elimination and substrate modification. J Cardiovasc Electrophysiol 2015; 26: 110–115. With permission from John Wiley and Sons)

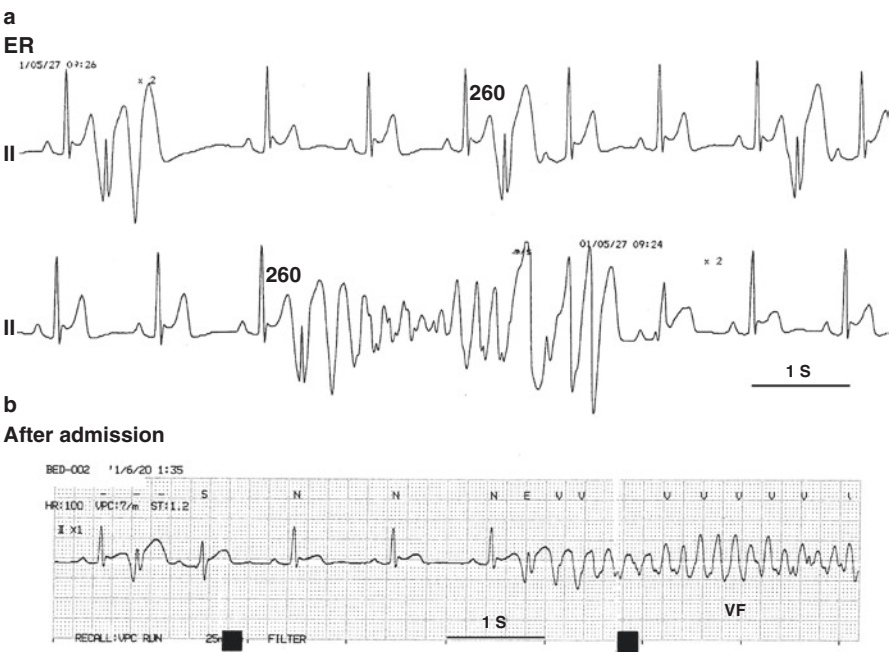

Fig. 7.7 ECG monitor tracings from a female patient with early repolarization associated with VF (patient no. 1). (**a**) In the emergency room (ER), the spontaneous nonsustained polymorphic ventricular tachycardia (VT) was recorded. (**b**) After admission spontaneous VF was documented in the night

The "true" triggering VPC was similar to the ablated VPC, but different (especially lead aVR). Interestingly, while J-ST elevation was recorded in the emergency room and during the VF recurrence, it was not observed during the ablation session. There was a possibility that the true triggering VPC appeared only during the J-ST elevation. The patient did not prefer to undergo a re-ablation session, and the oral administration of disopyramide successfully suppressed the VF recurrence.

In the intensive care unit, a synthesized 12-lead ECG from the signals recorded using three to five electrodes is sometimes used. In our experience, the limb leads in the synthesized 12-lead ECG are similar to the Mason-Likar lead configuration, in which the limb lead electrodes are placed on the torso rather than the distal extremities, and can be used for the morphology analysis of VPCs. However, the chest lead information in the synthesized ECG is less useful because of its inaccuracy. Twelve-lead Holter monitoring also uses a Mason-Likar lead configuration similar to the limb leads and the real six chest electrodes for the chest leads and appears to be highly reliable and useful for the diagnosis of "true" triggering VPCs.

An important limitation of trigger ablation is that triggers are momentary and might be absent if mapping is programmed later. When feasible, ECG documentation of culprit ectopy is essential to permit future ablation of VF sources using pace mapping techniques or potentially by using the electrogram morphology or sequence stored in the defibrillator.

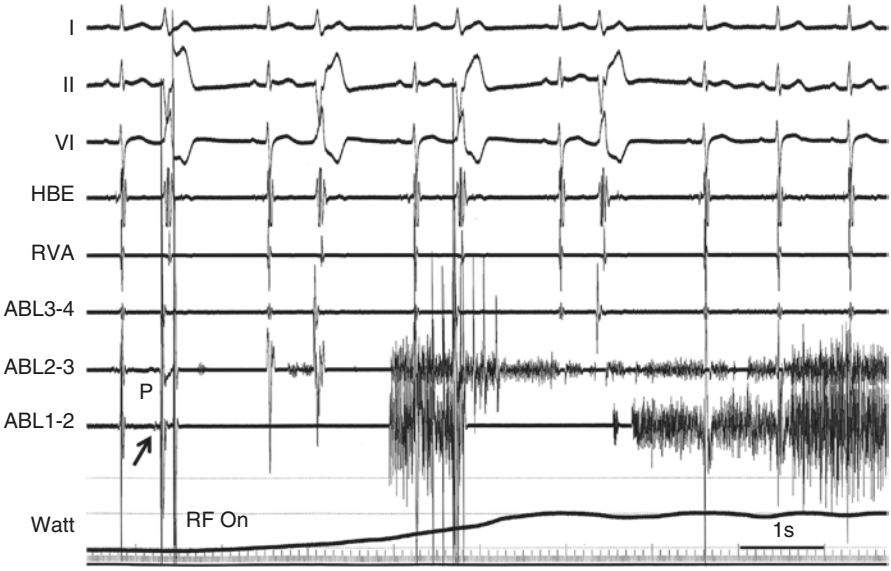

Fig. 7.8 Ablation of "trigger VPC" (patient no. 1). During the ablation session, frequent monofocal VPCs were observed, and Purkinje potentials on the posterior left ventricular septum preceded the onset of the VPC by 65 ms. An RF energy application at that site immediately eliminated the VPC

7.7 Importance of the Diagnosis of ERS

Figure 7.9 shows the ECGs from a 37-year-old male patient with VF storm. VF storm subsided by isoproterenol infusion. During isoproterenol infusion, 12-lead ECG shows significant J-wave in lead I, II, III, aVF, and V3–V6, suggesting ERS. However, the intravenous administration of pilsicainide 5 mg (low dose) unmasked the coved-type ST-T change in V1 and V2. Therefore, this patient was diagnosed as Brugada syndrome with VF. Epicardial mapping and ablation of the right ventricle was performed. After the epicardial ablation, VF was suppressed even after the discontinuation of isoproterenol, and there was no ST-T change after the intravenous administration of pilsicainide 50 mg.

Because inferior and/or lateral J-wave can be observed in 3.3–5% of the normal subject [2, 11], in 12% of Brugada syndrome [12], and in 63% of Brugada syndrome associated with documented VF [13], the true diagnosis of ERS is important.

7.8 Elimination of the Trigger and/or Substrate Modification of the Purkinje Network

The Purkinje system is the most frequent site of initiation of VF. Recent work has demonstrated that the Purkinje network is critical in the triggering and maintenance of VF in animal experiments and patients. Catheter ablation targeting the Purkinje

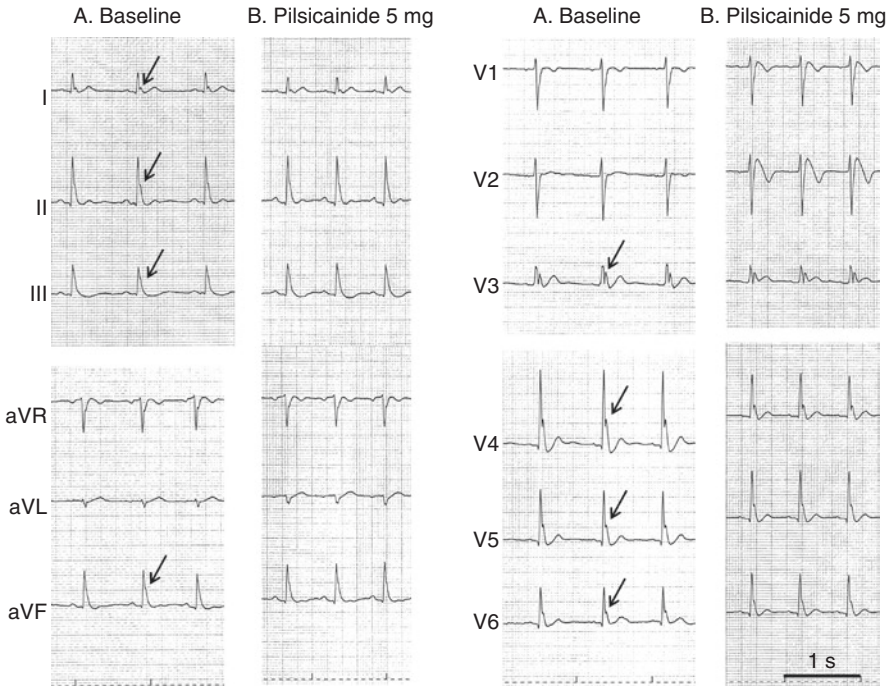

Fig. 7.9 Surface 12-lead ECGs from a female patient with VF storm. (**a**) During isoproterenol infusion for VF storm, 12-lead ECG shows significant J-wave in leads I, II, III, aVF, and V3–V6, suggesting ERS. (**b**) However, the intravenous administration of pilsicainide 5 mg (low dose) unmasked the coved-type ST-T change in V1 and V2. Therefore, this patient was diagnosed as Brugada syndrome with VF

potentials responsible for triggering VF has been shown to be possible and efficacious in a number of conditions such as idiopathic VF (short-coupled variant of torsade de pointes), ischemic VF, and chronic myocarditis. What is still undetermined is whether the mechanism of the ablation effect is due to the suppression of the trigger or substrate modification.

Haïssaguerre et al. [1] reported that VPCs originating from the distal Purkinje system triggered VF or PVT in patients without structural heart disease. In this report, the coupling interval of the first initiating VPC of VF was relatively short (297 ± 41 ms), and the PVBs originated from both the LV and RV. Several reports described triggered activity, abnormal automaticity, or reentry as possible underlying mechanisms of IVF originating from the Purkinje system [1, 9, 14–16]. On the other hand, Haïssaguerre et al. also reported that triggered PVBs of IVF with ER in the inferolateral leads, also called the J-wave syndrome [17], originated from the left ventricular myocardium or Purkinje system [2].

During activation mapping of the triggering VPC, attention should be paid to the preceding sharp Purkinje-like signals. Mapping should be focused on the earliest activation of this potential, and determining the earliest potential is the key to a

successful ablation. However, the potential may sometimes be seen to occur with intra-Purkinje block to the myocardium, and not produce a VPC. This means that there is the possibility that not only the elimination of the triggering VPC but also the conduction block in the Purkinje network can suppress the triggering VPC and VF. In fact, dissociated firing from the Purkinje network is sometimes seen after a successful ablation.

7.9 Conclusion

RF catheter ablation of ERS is feasible and can be used as a bailout therapy for drug-refractory VF storms. Suppression of VF can be achieved by the elimination of triggering VPCs from left or right of the Purkinje network. Further studies are needed to evaluate the precise mechanisms of this arrhythmia.

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Chapter 8
Early Repolarization Syndrome and Implantable Cardioverter–Defibrillators

Takashi Kurita

Abstract The role of an implantable cardioverter–defibrillator (ICD) in patients with ERS still needs to be considered, since there have been no prospective, randomized studies that have examined the effect of ICDs compared with antiarrhythmic drugs in patients with ERS and ventricular fibrillation (VF). However, theoretically, ICDs must be the first-line strategy for patients with ERS because ICDs are effective in patients with a high risk of sudden cardiac death, regardless of underlying heart disease. An essential problem of ICDs is that they cannot prevent the occurrence of tachycardia attacks, and this limits their clinical usefulness. Especially during an electrical storm, it induces multiple shocks to terminate VF and may deteriorate the patients' outcome. Another unresolved problem of ICDs is inappropriate therapy which demonstrated a 10–20% incidence in the previous large clinical trials. To program relatively high tachycardia detection rate and long detection rate are possible strategy to reduce risks of inappropriate and unnecessary ICD shocks. Another attractive capability of ICD is that it stores electrograms during the episode of VF. Analyzing the mode of onset or electrocardiographic manifestations at the episodes of ventricular arrhythmia is an effective strategy to clarify the underlying mechanism of ER and VF.

8.1 Introduction

Several large, randomized trials have demonstrated an important role of the implantable cardioverter–defibrillator (ICD) for improvement of mortality in patients with a high risk of sudden cardiac death, regardless of its purpose (primary or secondary prevention) and of underlying heart disease (ischemic or nonischemic) [1–8]. Such large clinical trials were mainly accomplished in patients with organic heart diseases and impaired ventricular function. Therefore, the role of

T. Kurita, M.D.
Division of Cardiovascular Center, Department of Internal Medicine, School of Medicine, Kindai University, Higashiosaka, Osaka, Japan
e-mail: kuritat@med.kindai.ac.jp

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ICDs in patients with idiopathic VF with early repolarization (ER) still needs to be investigated. However, the ICD must be the first-line strategy for high-risk patients with ER because several retrospective studies have demonstrated a successful defibrillation rate and limited role of antiarrhythmic drugs or catheter ablation. An essential problem of ICDs is that they cannot prevent the occurrence of tachycardia attacks itself, resulting in the limitation of their clinical usefulness. The presence of ER in patients with idiopathic VF is thought to be a major factor for VF storm [9, 10]. Frequent ICD shock during a VF storm or inappropriate detection deteriorates patients' quality of life and may lead to sudden death in the worst case scenario. Furthermore, appropriate risk stratification of asymptomatic patients with ER (aiming for primary prevention) is almost impossible owing to a much lower evidence compared with other primary electrical diseases, such as asymptomatic Brugada syndrome [11–14]. Expensive ICDs impose a burden on limited resources and sometimes deteriorate a patient's quality of life (QOL) if they are used without distinction.

The purpose of this article is to address the efficacy of ICDs in patients with idiopathic VF and ER (so-called ERS) by reviewing published studies, which described the efficacy of ICD. This article also discusses the possibility of effective intervention from electrical devices to prevent sudden cardiac death or VF based on proposed electrophysiological mechanisms of ER.

8.2 The Role of ICDs for Patients with ERS

The role of an ICD in patients with ERS still needs to be considered, since there have been no prospective, randomized studies that have examined the effect of ICDs compared with antiarrhythmic drugs in patients with ERS. However, theoretically, ICDs must be the first-line strategy for patients with ERS because ICDs are effective in patients with a high risk of sudden cardiac death, regardless of underlying heart disease (ischemic or nonischemic) [1–10].

8.2.1 Role of ICDs in Improved Survival Rate in Patients with ERS and Its Related Disorders

In 1987, Belhassen et al. performed the first systematic report of five cases of idiopathic VF and demonstrated that pharmacological evaluation using an electrophysiological (EP) study provides a good prognosis for patients with idiopathic VF (IVF) [15]. However, the possible role of ICDs was not discussed in literature at that time, probably because of the limited use of this device in the

1980s. The first study that demonstrated the efficacy of ICD was performed by Meissner et al. [16]. In this study, 28 patients from ten centers were enrolled and were followed for 3 years after "thoracotomy" ICD implantation. Sixteen patients experienced 36 ventricular tachycardia (VT)/ventricular fibrillation (VF) episodes with a total of 88 shock deliveries, and finally, all cases of VF were successfully terminated. In the early 1990s, the concept of "Brugada syndrome" was not widely recognized, and that of ERS had not yet been recognized. Therefore, there was no description of detailed subtype classification of IVF in this study [16].

In 2008, Haïssaguerre et al. found a significantly higher prevalence of ER in patients with IVF and proposed a new concept of a malignant entity of ERS [9]. They reviewed data from 206 patients at 22 centers who were resuscitated after cardiac arrest due to IVF and showed that 31% of their subjects had ER. Subjects with ER showed a higher incidence of recurrent VF than those without such an abnormality (hazard ratio, 2:1; 95% confidence interval, 1.2–3.5; $P = 0.008$) during a mean follow-up of 61 ± 50 months using reliable event monitoring of ICDs. ICDs were successful for terminating spontaneous VF. However, three patients with the highest J-point elevation (>5 mm) had more than 50 episodes of VF, leading to death of one patient.

8.2.2 Limitations of ICDs

8.2.2.1 Shock Therapy and Patients' Prognosis

An essential problem of ICDs is that they cannot prevent the occurrence of tachycardia attacks, and this limits their clinical usefulness. An extreme example of a serious situation for patients with an ICD is an electrical storm (frequent VF episodes) [17, 18]. During an electrical storm, an ICD cannot avoid delivering multiple shocks to terminate VF, but these may deteriorate the patients' outcome [19]. Aizawa et al. demonstrated that in patients with IVF, ER (J wave) was observed in 13/14 (92.9%) patients with an electrical storm but was only observed in 28/77 (36.4%) patients without an electrical storm. If a J wave is present in patients with IVF, there is 31.7% possibility of substantial occurrence of an electrical storm during a mean follow-up period of 4.0 years [10].

Several clinical studies (MADIT-II, SCD-HeFT, and MADIT–Reduce Inappropriate Therapy trial) described that shock therapies from an ICD may result in occurrence of heart failure and higher mortality in patients with VT/VF because these studies enrolled patients with organic heart disease and poor left ventricular (LV) systolic function [19–21]. Therefore, the main cause of death after shock therapies might have been due to heart failure induced by ICD shocks. However, because patients with ERS generally have preserved cardiac function, multiple shocks may

not have a direct effect on mortality due to heart failure. Deterioration of patients' QOL should be the biggest concern after shock therapies (this issue will be discussed in the following paragraph).

8.2.2.2 VF (Electrical) Storm and the Risk of Sudden Death

In the newest ICD generation, the maximum number of shock deliveries during one episode of VF is "nine." For all ICD machines, normal (or non-tachycardia) rhythm after a shock should be maintained for several seconds to recognize VF attacks as separated episodes. Therefore, if frequent (>10) VF attacks appear in a short interval, an ICD may recognize all VF as one continuing episode, and it does not deliver shock for the final VF episode. As previously mentioned [9], more than 50 times of VF attacks were described in three patients with ERS, and unfortunately, as the worst-case scenario, sudden death occurred in one patient. This finding suggests that intervals between VF termination and the next appearance of VF are not sufficient for an ICD to recognize these as different (independent) episodes. Therefore, because the presence of ER may facilitate frequent occurrence of VF in patients with IVF, additional methods (e.g., catheter ablation or use of antiarrhythmic agents) to prevent VF should be challenged to minimize the possibility of arrhythmic death after ICD implantation.

8.2.2.3 Inappropriate Shock Therapy

Another unresolved problem of ICDs is inappropriate therapy. Several large, clinical trials using traditional discriminating algorithms demonstrated a 10–20% incidence of inappropriate therapy from ICDs [18–21]. However, adoption of novel enhanced detection algorithms in conjunction with routine implementation of modern programing strategies may lead to a low inappropriate shock rate with less than 2% of the annual inappropriate therapy rate [22, 23]. Patients who have overlap between the highest rate during supraventricular tachycardia and the lowest rate of ventricular tachyarrhythmia may have a higher risk of inappropriate therapy. Moreover, programing of the VT therapy zone (even an independent slower detection zone) tends to provide inappropriate therapy of ICDs. However, because targeted tachyarrhythmia in most patients with ERS is only VF (not VT), a much higher detection rate (≥200 beats/min) can be programed without having a VT zone, which may be favorable for preventing inappropriate therapy. Sinus tachycardia with greater than 200 beats/min is rare in patients with a poor ejection fraction. However, because patients with ERS are younger, healthier, and much more physically active compared with those with organic heart disease, they may have sinus tachycardia of greater than 200 beats/min. In such cases, negative chronotropic agents (e.g., beta-blockers) aiming to decrease maximum sinus rate should be prescribed. A VF zone setting above 240 beats/min should not to be programed to avoid underdetection of VF.

Extending the detection duration (longer waiting time) for VT/VF is another strategy to reduce risks of inappropriate and unnecessary ICD shocks. "Unnecessary ICD shock" means shock delivery to a true VT/VF, which may have been self-terminating, and it can be avoided only by programing for a longer duration. The PREPARE study demonstrated a moderately extended detection duration (30 beats counted before therapy) with fast rate cutoffs (≥182 beats/min) and a reduced shock rate without an increase in the incidence of arrhythmic syncope and death in primary prevention patients [24]. Recently, the MADIT–Reduce Inappropriate Therapy trial evaluated two different more rigorous ventricular arrhythmia detection algorithms as follows: high-rate therapy (initiation of therapy at 199 beats/min) and delayed ICD therapy (with a 60-s delay at 170–199 beats/min, a 12-s delay at 200–249 beats/min, and a 2.5-s delay at 249 beats/min) [25]. In both groups, the first and total occurrences of appropriate and inappropriate therapies were significantly reduced. Although these studies demonstrated that programing for a longer duration is effective for reducing unnecessary shock, the results were obtained in primary prevention patients with poor LV function. Particularly in patients with ERS, VF with an extremely long duration (e.g., 60 s) may cause brain or myocardial ischemic damage, leading to trauma due to syncope and/or an increase in the defibrillation threshold. Because the likelihood of spontaneous termination of VF or how many beats can be expected for spontaneous termination of VF in patients with ERS is unclear, evidence-based recommendation of the appropriate detection duration is impossible. Empirically, however, moderate prolongation of a detection interval longer than the nominal setting is expected to be desirable.

Detailed analysis and correct diagnosis of stored electrograms during episodes without ICD shock are useful for predicting the risk of inappropriate or unnecessary shock. If a short duration of supraventricular tachycardia is detected within a VF zone, an increase in rate or duration for VF detection is effective. In the case of a non-sustained episode of VF, a longer duration may be effective for avoiding unnecessary shock. To detect episodes with a rate closer to the VF zone, a monitor zone setting is useful. As previously mentioned, negative chronotropic agents, such as beta-blockers, are useful for separating the maximum rate of supraventricular tachycardia and that of the VF zone.

Extending a discriminating algorithm within a VF zone is another option for inhibiting inappropriate shock therapy [22]. Older diagnostic algorithms were not recommended to use within a VF zone because they were immature and might have induced undersensing of VF. However, newly advanced algorithms have achieved a high sensitivity and specificity in distinguishing between VF and supraventricular tachycardia. Therefore, these new algorithms can be programed at a slower part of the VF zone. However, to maximize these differentiating capabilities of ICDs, sensing of atrial signals is essential [22]. Adding an atrial lead (selecting a dual-chamber ICD) does not always provide an advantage to patients with ERS because a fewer number of ICD leads are desirable for many younger patients with ERS (see Sect. 8.2.5).

8.2.2.4 ICD and Health-Related QOL

Several studies have suggested that health-related QOL is adversely affected in patients who experience ICD shocks, regardless of whether they are appropriate or inappropriate [26–28]. ICD shocks also induce psychological disorders. Anxiety is the most common disorder, and 24–87% of patients with ICD shock events show worsened symptoms and diagnosis of anxiety disorders [28]. Patients who have more shocks have further anxious and depressed conditions compared with patients not experiencing shocks. Before ICD implantation, patients with ERS are thought to have a much better basic QOL score compared with patients with organic heart disease included in previous large trials. Whether patients' QOL after ICD implantation or after shock is related to their original (basic) QOL score is unclear. Because patients with ERS are much healthier and younger compared with those with organic heart disease, we should pay more attention to adverse effects of ICD shock on QOL in these patients.

8.2.3 Single-Chamber or Dual-Chamber ICD?

The advantage of a dual-chamber ICD for patients with VT/VF is that it provides either atrial bradycardia pacing or enhancement of the diagnostic algorithm by detecting atrial signals [28–30]. Significant sinus bradycardia, whether spontaneous or drug induced, is rare in patients with ERS. Therefore, the aim of selecting dual-chamber ICD is to optimize the detection algorithm to avoid inappropriate shock. As previously mentioned, an apparent difference in rate between maximum sinus tachycardia and VF results in preference of a single-chamber ICD for patients with ERS. Additionally, a single lead system provides an advantage, especially for younger patients, to maintain patency of venous access and to make extracting a lead system easier in the future. Therefore, implantation of a dual-chamber ICD in patients with ERS is not preferable with the exception of documentation of rapid supraventricular tachycardia of greater than 200 beats/min.

8.2.4 Primary Prevention for Asymptomatic Patients with ER

In the Nippon Storm Study (Japanese prospective cohort study with more than 15,000 patients), no patients with idiopathic VF had an ICD implanted for the purpose of primary prevention [31]. The extensive implantation of ICDs in asymptomatic patients with ER can impose a burden on our limited resources and sometimes deteriorate a patient's QOL if they are used without distinction.

8.2.5 The Role of a Subcutaneous ICD

In the traditional ICD system, cardiac sensing and shock delivery completely depend on transvenous atrial or ventricular leads. However, many complications during ICD implantation relate to insertion of the leads, such as pneumothorax, hemothorax, and cardiac tamponade, and lead to dislodgement [32, 33]. Furthermore, during long-term follow-up, venous occlusion, lead fracture, and bacterial infection are other major serious complications of ICD. These complications require additional interventions, such as insertion of new leads or removal of the system [34]. To address these unresolved problems of traditional ICDs, an entirely subcutaneous ICD (S-ICD) has been developed [35]. At the present time, the S-ICD is a "shock-only device," and it has no capabilities of backup pacing and anti-tachycardia pacing. Therefore, indication of this device is limited, especially for patients with monomorphic VT and/or bradycardia. However, because cardiac pacing is not necessary for the majority of patients with idiopathic VF and ERS, they can be good candidates for S-ICD.

The major concern with S-ICDs is the incidence of inappropriate therapy. According to the largest trial, which examined the efficacy of S-ICDs, the first annual rate of inappropriate shock therapy of S-ICDs was approximately 7% by programing with a dual zone setting [35]. Patients with ERS are younger, healthier, and more physically active compared with those with organic heart disease. Therefore, we should pay much more attention to the selection of devices and programing to avoid inappropriate shock therapy, especially in patients with ERS.

8.3 The Role of Wearable Cardioverter–Defibrillators for Patients with ERS

The wearable cardioverter–defibrillator (WCD) is an external device with the capability of autonomic detection and shock therapy for VT/VF. The WCD was designed for specific patients, such as patients who are thought to be at high risk for sudden cardiac death, but who cannot or should not receive an ICD during a brief period of time (e.g., after acute myocardial infarction, newly diagnosed cardiomyopathy, or after ICD removal) [36, 37]. Patients with ERS are thought to have a constant chronological risk for sudden cardiac death, and thus the usefulness of the WCD is limited. The WEARIT-II trial was the first prospective registry of the WCD to evaluate the safety and efficacy of the WCD [37]. This trial enrolled 268 (13.4%) patients with inherited or congenital disease in which idiopathic VF may be included, but there was no further detailed description of this category. Only one patient with idiopathic VF (survivor from sudden cardiac death) was reported in a small patient cohort from Japan [38]. This patient was wearing a WCD during his stay in hospital and subsequently underwent ICD implantation. The main purpose of WCD use in

this patient was only to act as a bridge for implantation of an ICD within a short time. Therefore, the true purpose and efficacy of WCDs for outpatients with idiopathic VF have not been clarified.

8.4 Analysis of Stored Therapy History or Monitoring Data of ICDs and Possible Preventive Interventions

Analyzing the mode of onset or electrocardiographic manifestations at the episodes of ventricular arrhythmia is an effective strategy to clarify the underlying mechanism. Matsuo et al. analyzed 30 VF episodes from six patients with Brugada syndrome by investigating the stored data log (day and time) in ICDs [39]. They found that VF events occurred most frequently during the night (sleep), which suggests that parasympathetic nerve activity has an important role in the development of VF. Moreover, Kakishita et al. evaluated electrocardiographic features of 33 VF episodes with Brugada syndrome obtained from stored electrograms in ICDs and/or ECG monitoring [40]. They demonstrated that a specific premature ventricular contraction (PVC) probably originating from the RV free wall triggered VF and suggested that elimination of a proper PVC can inhibit VF attacks in Brugada syndrome (Figs. 8.1 and 8.2).

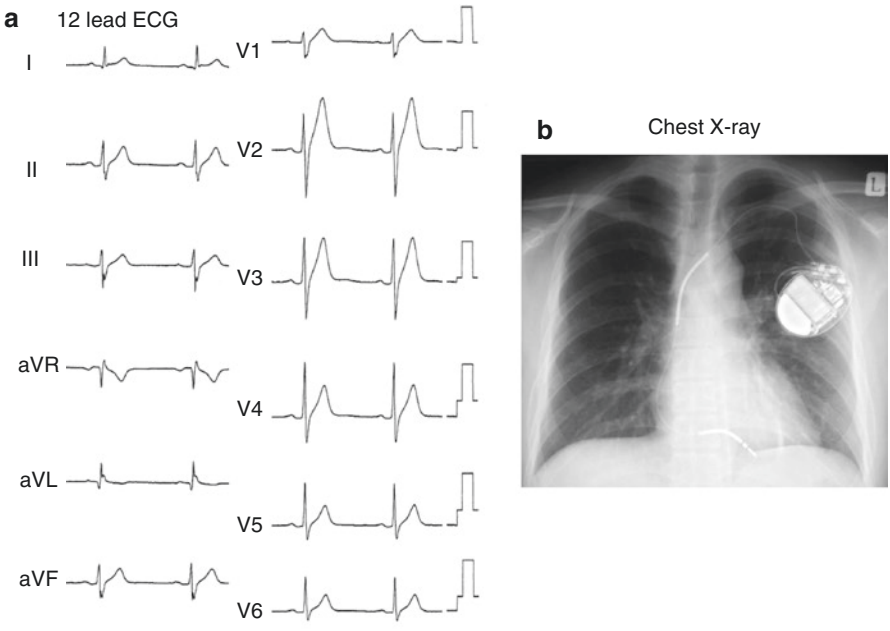

Fig. 8.1 Twelve-lead ECG (**a**) and chest X-ray (**b**) in a patient with idiopathic ventricular fibrillation and early repolarization. Early repolarization (>0.1 mV J-point elevation) was observed in I and aVL, and the J wave was observed in aVL. A chest X-ray shows precordial implantation of a single-chamber implantable cardioverter–defibrillator

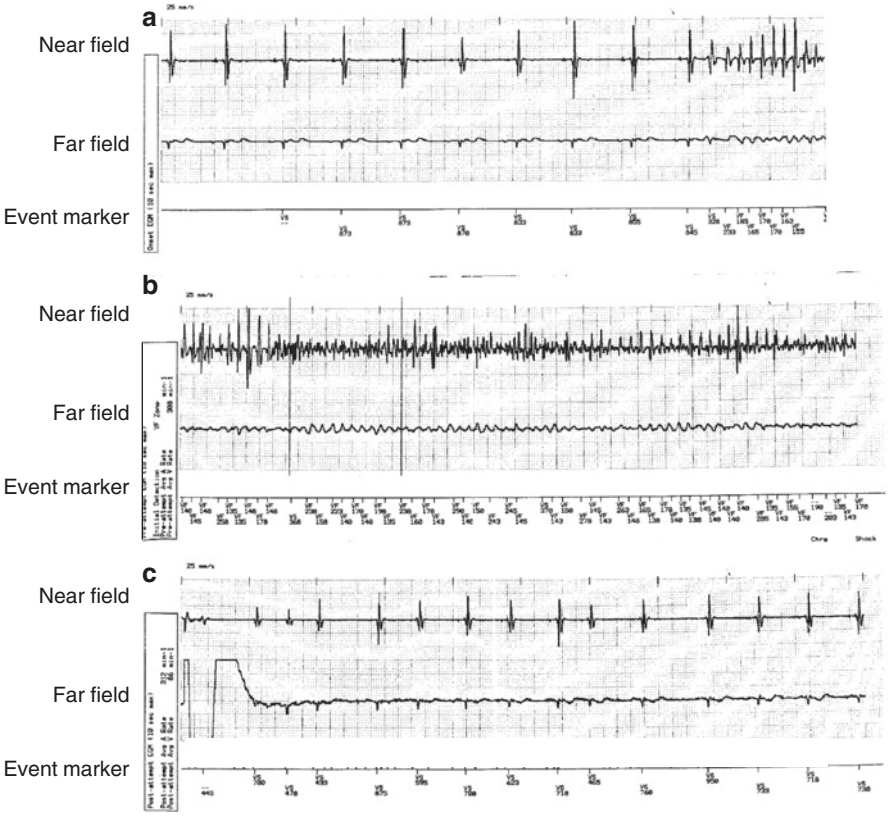

Fig. 8.2 Stored electrogram (EGM) during a ventricular fibrillation (VF) episode in a patient with idiopathic VF and early repolarization (same patient as in Fig. 8.1). The near field is an EGM recorded between the tip and ring electrodes of the right ventricular lead, and the far field is that between the tip electrode and the ICD generator. (**a**) Onset of VF. VF was induced by a premature ventricular contraction (PVC) with a short coupling interval (328 ms). (**b**) An EGM during VF. Rapid ventricular excitation was observed in the near-field EGM. The minimum cycle length that was detected by an ICD during VF was 135 ms (see event marker). However, the actual cycle length of the near-field EGM appears to be much shorter (approximately 40 ms at the minimum) than that detected by an ICD. (**c**) Termination of VF. The first shock (30-J biphasic waveform) from an ICD successfully terminated VF. The *square* wave at the beginning of this panel (near-field EGM) indicates an artifact of shock delivery

Aizawa et al. assessed the circadian pattern of VF occurrence in non-Brugada-type idiopathic VF using data derived from ICDs. They found that the presence of J waves (ER) in patients with idiopathic VF resulted in a higher nocturnal (midnight to 6:00 AM) incidence of VF [41–43]. This finding suggests that ERS may have a similar electrophysiological substrate to Brugada syndrome.

In some patients with ERS, a long-short initiating sequence of VF and pause-dependent J wave magnification were described [10, 42]. A detailed analysis of retrievable data from ICDs in patients with ERS at the timing of VF development

may contribute to revealing the electrophysiological mechanism and determining effective intervention from ICDs (e.g., stabilization of the RR interval by cardiac pacing) to prevent occurrence of VF in the future.

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Chapter 9
Acute and Chronic Pharmacological Therapy for ERS

Naohiko Takahashi, Hidekazu Kondo, and Tetsuji Shinohara

Abstract In patients with early repolarization syndrome (ERS), pharmacological therapy may be necessary in patients with frequent delivery of shocks from implantable cardioverter-defibrillator (ICD) due to ventricular fibrillation (VF). In cases of electrical storm, intravenous isoproterenol infusion has been shown to be most effective. Isoproterenol seems to be effective in restoring the action potential dome in the epicardium, because it markedly increases I_{Ca} secondary to elevation of intracellular levels of cyclic AMP. It is also effective by indirect suppression of I_{to} due to its ability to increase the heart rate. Following acute phase, oral quinidine has been reported to prevent the recurrence of VF. Quinidine is a class I antiarrhythmic agent. However, it potently blocks I_{to}, leading to the restoration of the action potential dome, a normalized ER, and prevents the occurrence of VF. An alternative therapy may be the administration of cilostazol and its combination with bepridil.

9.1 Introduction

Early repolarization syndrome (ERS) is related to endo-epicardial transmural electrical gradients [1, 2]. Such gradients are attributable to the transmural differences found in the distribution of the transient outward potassium current (I_{to}) and lead to the development of ventricular fibrillation (VF) as a result of phase 2 reentry [1, 2]. An implantable cardioverter-defibrillator (ICD) should be implemented as a requirement for patients presented with at least one episode of VF. However, frequent delivery of electrical shocks from the ICD due to recurrent VF (i.e., electrical storm) remains a serious problem. In such cases, additional drug therapy may be necessary.

N. Takahashi, M.D., Ph.D. (✉) • H. Kondo, M.D., Ph.D. • T. Shinohara, M.D., Ph.D.
Department of Cardiology and Clinical Examination, Faculty of Medicine, Oita University,
1-1 Idaigaoka, Yufu, Oita 879-5593, Japan
e-mail: takanao@oita-u.ac.jp

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9.2 Case Presentation

Herein, we present a case of inferolateral ERS [3]. A 38-year-old man experienced sudden syncope early in the morning. Responding firemen confirmed the VF, which was defibrillated by direct-current shock. For secondary prevention, an ICD was implanted in the patient. Following discharge, the patient suffered from frequent ICD shock due to VF during the midnight hour to early in the morning. He was readmitted to the hospital, where the VF was documented by an electrocardiogram (ECG) monitor (Fig. 1). The terminal QRS notching (J wave) (Fig. 1a, arrow) gradually became prominent from 5:00 PM to 2:00 AM in association with the reduction in heart rate (Fig. 1b, c, arrows). Premature ventricular contractions (PVCs) with short coupling intervals started to appear at 3:00 AM (Fig. 1d), leading to the development of VF at 3:30 AM (Fig. 1e). In this case, the responses of J waves to several cardiovascular agents were separately assessed (Fig. 2). Intravenous (IV) injection of propranolol (Fig. 2a) or verapamil (Fig. 2b) accentuated the J waves, whereas isoproterenol eliminated the J waves (Fig. 2c). Procainamide had no influence on the J waves (Fig. 2d), whereas disopyramide eliminated the J waves (Fig. 2e). Furthermore, atrial pacing at 120 bpm using an ICD generator also eliminated the J waves (Fig. 2f).

As an adjunctive drug therapy to prevent recurrent VF, cilostazol 200 mg/day was prescribed and then increased to 300 mg/day, which was effective in suppressing the VF. The patient, however, complained of intolerable palpitations due to sinus tachycardia. The addition of bepridil at a dose of 200 mg/kg reduced the resting heart rate from 96 to 84 bpm. Bepridil was later reduced to 150 mg/day. After the combination of cilostazol and bepridil was administered, there was no recurrent of VF. Five years later, a replacement of the ICD generator was needed, and cilostazol had to be discontinued due to its potent antiplatelet effects. An appropriate ICD shock due to VF was observed early in the morning on the following day after discontinuation of cilostazol. J waves in the inferior and lateral leads were disclosed (Fig. 3a) and then disappeared after resumption of cilostazol (Fig. 3b). After receiving cilostazol again, the patient suffered an ICD shock only once, and this was due to a spontaneous VF that occurred 3 years later.

9.2.1 Initial Reports

After the initial report of ERS by Haïssaguerre et al. in 2008 [4], they reported the efficacy of antiarrhythmic drugs in recurrent VF associated with inferolateral ER in 2009 [5]. They investigated all patients with more than three episodes of VF (multiple) including those with electrical storms (≥3 VF in 24 h). Successful oral antiarrhythmic drug was defined as the elimination of all recurrences of VF with a minimal follow-up period of 12 months. It was reported that electrical storms occurred in 16 patients. Of these patients, 11 were treated with beta-blockers, 9 with a combination of lidocaine/mexiletine, and 3 with verapamil; however, all were found to be unresponsive, while amiodarone was partially effective in 3 out of 10 patients. In contrast, isoproterenol infusion invariably suppressed electrical storms in 7 out of 7

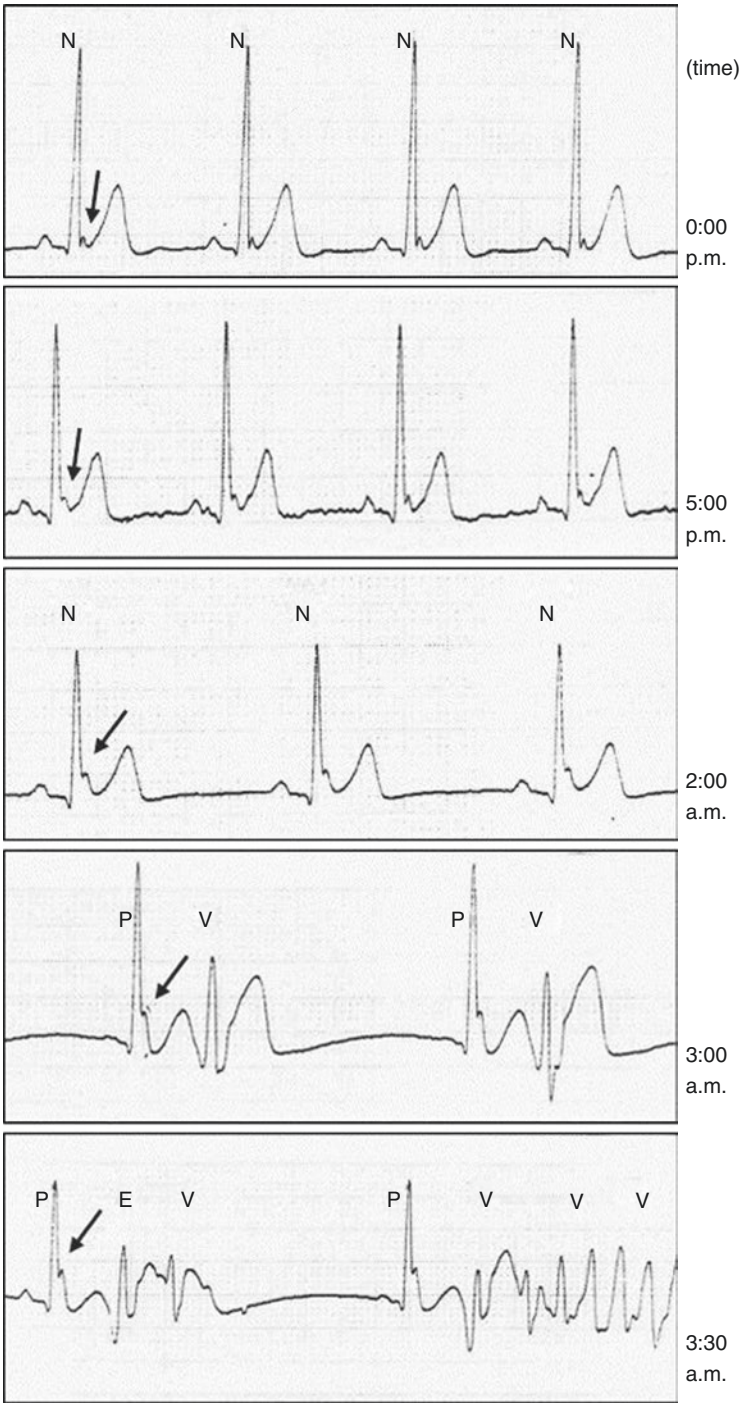

Fig. 1 Panel of ECG monitor recordings upon patient admission to the hospital up to the development of ventricular fibrillation (Figure adapted with permission [3])

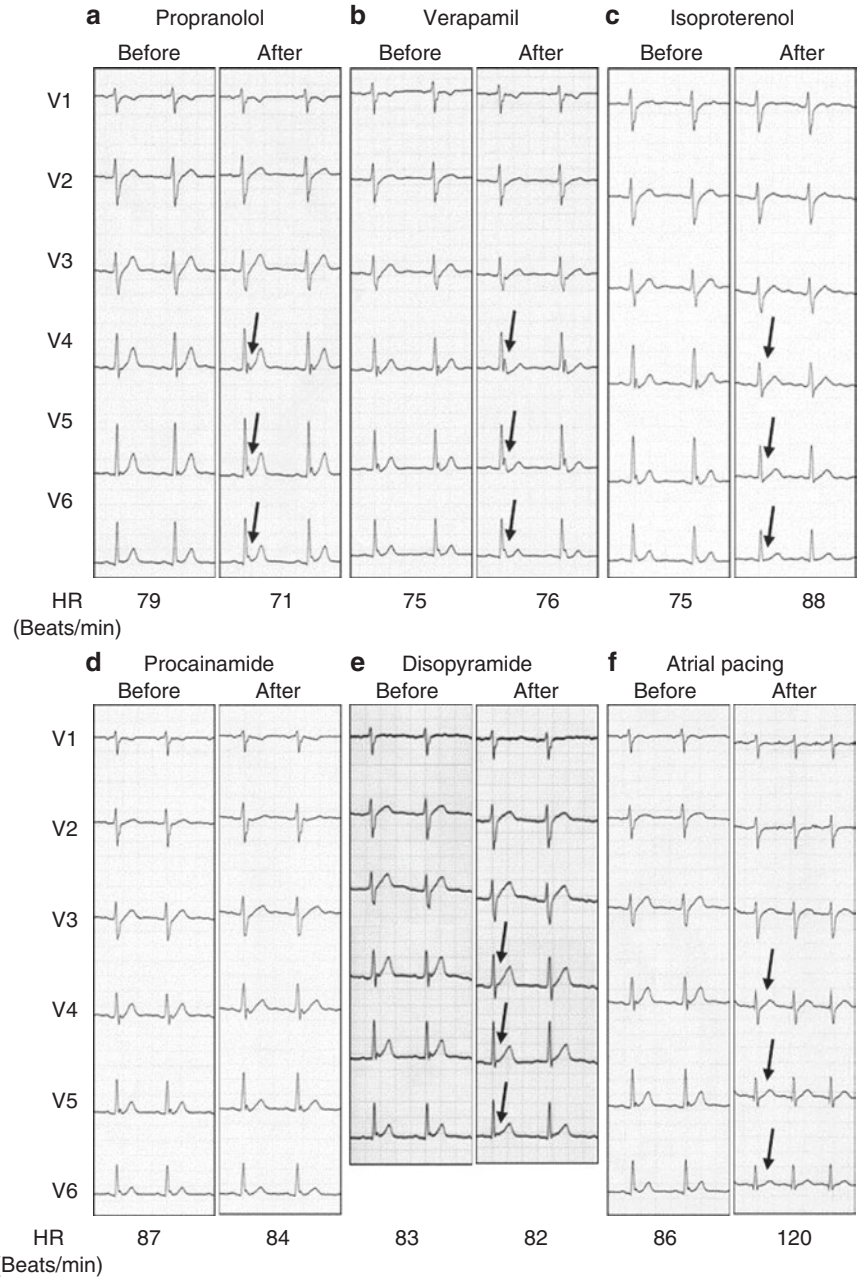

Fig. 2 Response of the J waves to drugs and atrial pacing. (**a**) Propranolol; administered at 2.0 mg via IV. (**b**) Verapamil; administered at 5.0 mg via IV. (**c**) Isoproterenol; administered at 0.01 μg/kg/min via IV. (**d**) Procainamide; administered at 400 mg via IV. (**e**) Disopyramide; administered at 50 mg via IV. (**f**) Atrial pacing (90 bpm). HR = heart rate (Figure adapted with permission [3])

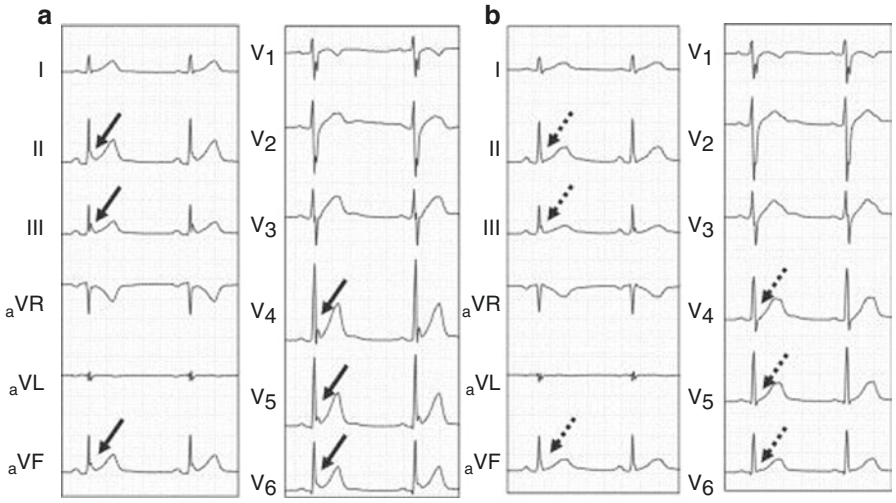

Fig. 3 Modifications in 12-lead ECGs caused by discontinuation and reinitiation of cilostazol. (**a**) Two days after cilostazol discontinuation. *Solid arrows* indicate accentuation of the J waves. (**b**) Three days after cilostazol reinitiation. *Dotted arrows* indicate elimination of the J waves (Figure adapted with permission [10])

patients. During the long-term follow-up, oral antiarrhythmic drugs were poorly effective in preventing recurrent VF. That is, the administration of beta-blockers (2 of 16 patients), verapamil (0 of 4 patients), mexiletine (0 of 4 patients), amiodarone (1 of 7 patients), and class 1C antiarrhythmic drugs (2 of 9 patients) each resulted in recurrent VF. On the other hand, quinidine successfully prevented VF recurrence in 9 of 9 patients. In addition, these investigators reported that quinidine eliminated ER and restored a normal electrocardiogram [5].

9.2.2 Insights of Suppressive Effects of Isoproterenol and Quinidine

ERS shares characteristics of the ionic and cellular basis with Brugada syndrome (BrS) [1, 2, 6]. In fact, drugs representing suppressive effects on VF in patients with BrS have been shown to suppress VF in patients with ERS [4, 5]. ER is hypothesized to be due to an outward shift in the balance of the membrane ionic currents at the end of phase 1 and phase 2 of the action potential, in which an outward current is mainly due to activation of I_{to} and the inward current is mainly due to the activation of calcium current (I_{Ca}) and an continuous component of sodium current (I_{Na}) [1, 2]. The net outward shift of this current balance leads to the loss of the dome at phase 2 of the action potential, especially in the epicardium (Fig. 4a). These changes produce a marked voltage gradient in the membrane potential between the

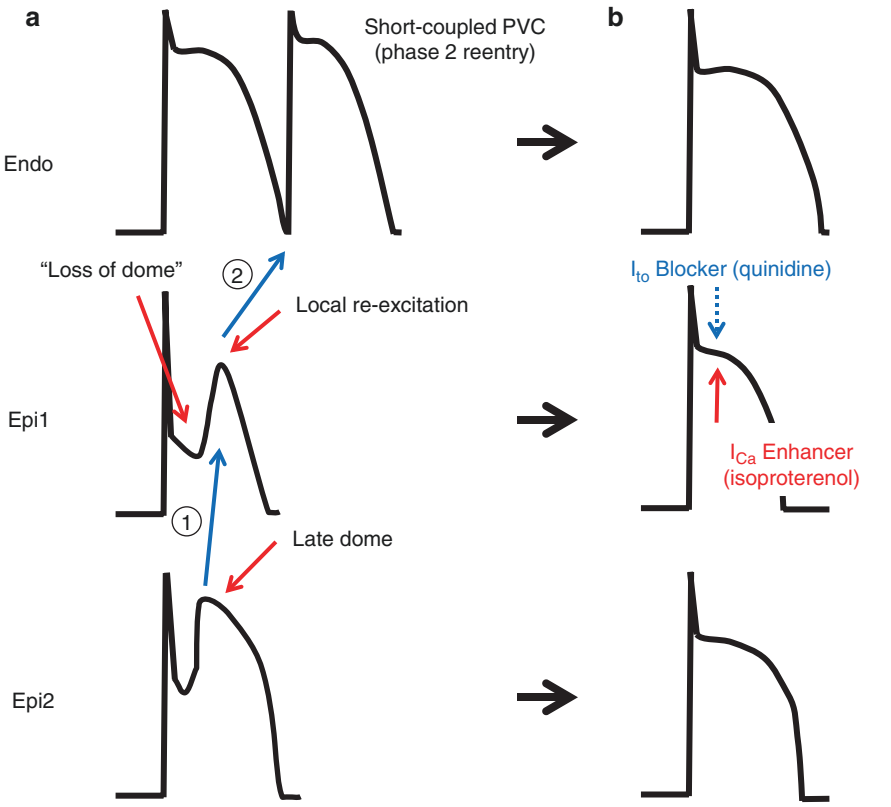

Fig. 4 Scheme of phase 2 reentry and the effects of isoproterenol and quinidine. (**a**) Late action potential dome of Epi2 causes local re-excitation in Epi1. Such an electrical activity electronically generates short-coupled premature ventricular contraction (PVC) in the endo (phase 2 reentry). (**b**) Agents that enhance I_{Ca} (i.e., isoproterenol) and I_{to} blockers (i.e., quinidine) have been shown to be effective in preventing loss of dome and phase 2 reentry

endocardial and epicardial sides during phase 2 (a change corresponding to the characteristic ER pattern). A variety of pathophysiologic conditions and pharmacologic interventions that either increase the membrane outward currents or reduce the inward currents should produce a loss of the action potential dome in the ventricular epicardium and facilitate the occurrence of VF [1, 2, 6]. Agents that augment I_{Ca} (i.e., isoproterenol) and I_{to} blockers (i.e., quinidine) may be effective in preventing a loss of the action potential dome and phase 2 reentry (Fig. 4b), leading to the suppression of VF recurrence in patients with ERS. Isoproterenol seems to be effective in restoring the action potential dome in the epicardium, because it markedly increases I_{Ca} secondary to elevation of intracellular levels of cyclic AMP. Quinidine is a class I antiarrhythmic agent. However, it potently blocks I_{to},

leading to the restoration of the action potential dome, a normalized ER, and prevents the occurrence of VF. The kinetics of I_{to} are unique, that is, they exhibit a slow recovery from inactivation. Accordingly, a slow heart rate and a long pause augment I_{to}. Conversely, I_{to} is reduced following acceleration of the heart rate. Isoproterenol, therefore, may be effective by indirect suppression of I_{to} due to its ability to increase the heart rate.

9.2.3 Cilostazol

Cilostazol, a phosphodiesterase type III inhibitor, is used primarily as a strong antiplatelet agent, but it has been shown to increase I_{Ca} and modestly increase the heart rate of an individual [7, 8]. All of these effects were secondary to an increased level of cyclic AMP caused by the inhibition of phosphodiesterase type III activity [7]. It is reasonable to believe that cilostazol has antiarrhythmic efficacy for preventing VFs in patients with ERS, since it increases in the ventricular myocyte and decreases I_{to} by increasing the heart rate, which again was secondary to increased I_{Ca} in the sinus node. Cilostazol is also effective in preventing VF in patients with BrS [9, 10]. The favorable action of cilostazol is attributed to enhanced I_{Ca} followed by restoration of the action potential dome (phase 2) and subsequent abolition of nonuniform repolarization and indirect suppression of I_{to} due to increased heart rate. Therefore, cilostazol may be useful in preventing the occurrence of VF, an event often encountered in patients with ERS [9].

9.2.4 Bepridil

Bepridil is a calcium channel antagonist with lidocaine-like rapid kinetic blocking effects of the sodium current [11]. Moreover, bepridil blocks most types of potassium currents, including I_{to} [11]. In addition, bepridil has been shown to prolong the sinus cycle length by reducing the slope of phase 4 in a concentration-dependent manner [12], leading to a reduction in heart rate during sinus rhythm. Bepridil was reported to be effective in reducing the frequency of VF episodes in patients with idiopathic VF, including BrS [13]. Recently, Katsuumi et al. reported the efficacy of bepridil to prevent VF in the severe form of ERS [14]. Bepridil was administered in three patients who had multiple recurrence of VF, including two patients with electrical storm, and was observed as being highly effective. Prior to bepridil, quinidine and isoproterenol failed to control arrhythmias in one of the three patients. The administration of quinidine was discontinued due to the gastrointestinal side effects observed in another patient. Interestingly, bepridil prolonged the QT interval but did

not augment the ER pattern in any of the patients. In three patients, the combination of bepridil with intravenous administration of isoproterenol was shown to be effective as an acute treatment. The administration of bepridil was continued and was effective even after the discontinuation of isoproterenol [14].

9.2.5 Combination of Cilostazol and Bepridil

Our group demonstrated the efficacy of the combination of cilostazol and bepridil in patients with BrS and ERS [10]. Cilostazol alone was sufficient to prevent VF recurrence; however, palpitations due to sinus tachycardia were frequently intolerable by the patients. Several candidates were considered to reduce their heart rates, such as beta-adrenergic receptor blockers and/or calcium channel antagonists, which however offset the favorable effects of cilostazol to increase intracellular concentrations of cAMP. Although the suppression effects on I_{Ca} by bepridil may be unfavorable, the suppression effects on I_{to} must be favorable to reduce the transmural electrical gradient. Cilostazol-induced palpitations due to sinus tachycardia were attenuated with the combination of bepridil [10]. We thereby proposed that a combination of cilostazol and bepridil may be effective in suppressing VF recurrence in some cases of ERS. This combination should therefore be utilized as an alternative therapy, particularly in patients who cannot be treated with quinidine [10].

9.2.6 Accidental Hypothermia-Induced VF

Accidental hypothermia is known to induce the J wave on ECG. In 1953, Osborn experimentally reported the presence of broad positive deflections originating from an elevated J point in dogs that were subjected to hypothermia and developed spontaneous VF [15]. However, an effective way to control VF induced by hypothermia is unclear. We recently encountered a case of accidental hypothermia demonstrating J waves. A 67-year-old woman was transferred to the emergency room in our hospital for a depressed level of consciousness and anasarca. Her core body temperature was 25.6 °C, and heart rate was 20 bpm. A 12-lead ECG was recorded following intravenous injection of atropine, which revealed a junctional rhythm and a significant J wave evident in I, II, and V2–V6 leads (Fig. 5, solid arrows). Interestingly, the amplitude of the J wave immediately after a long RR interval of 1620 ms was attenuated (Fig. 5, dotted arrows), which is in contrast to the response of the J wave observed in patients with ERS. In this report, the patient did not develop VF. There was another case report from Japan, in which infusion of isoproterenol was effective in suppressing the electrical storm in a patient with severe accidental hypothermia [16]. A 69-year-old man with severe hypothermia (core body temperature: 27.5 °C)

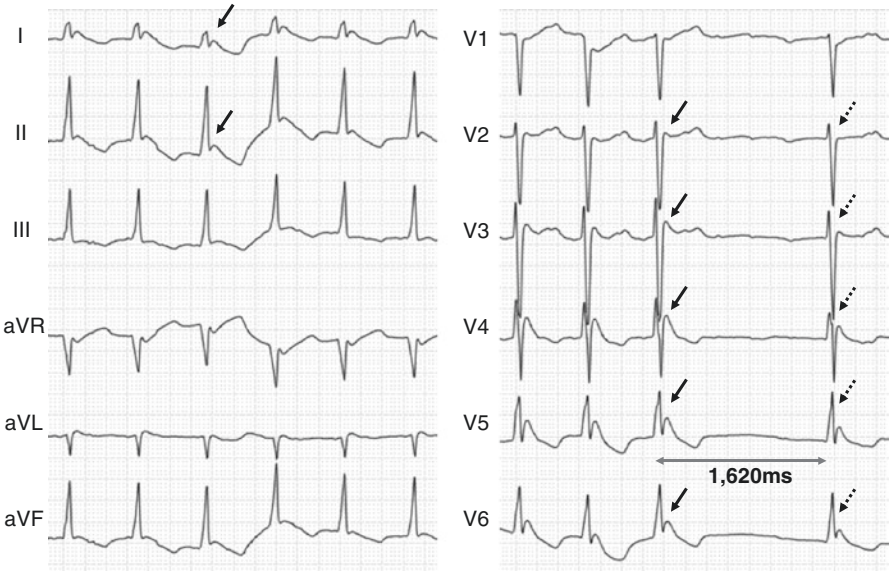

Fig. 5 Twelve-lead ECG in a patient with severe hypothermia. A significant J wave is evident in the I, II, and V2–V6 leads (*solid arrows*). The amplitude of the J wave immediately after a long R-R interval of 1620 ms was attenuated (*dotted arrows*)

and circulatory collapse developed VF. The 12-lead ECG revealed atrial fibrillation and a significant J wave visible in all leads. After isoproterenol infusion at a rate of 0.02 μg/kg/min was started, the magnitude of the J wave was significantly decreased in all leads. There were no further episodes of VF observed in the patient. Similar to our case, the ECG monitor showed augmentation of the J wave immediately following a short R-R interval [16]. Taken together, it can be postulated that isoproterenol may be effective in preventing accidental hypothermia-induced VF and in attenuating J waves, despite the concept that the kinetics of the J wave in response to heart rate was distinct from those observed in patients with ERS.

9.3 HRS/EHRA/APHRS Expert Consensus Statement

Three medical societies representing electrophysiology in North America, Europe, and Asia Pacific area, the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society, provided clinical diagnosis, risk stratification, and management of patients affected by inherited primary arrhythmia syndromes [17]. In this statement, on ER therapeutic interventions, many attempts were done for the indication of ICD. In the section of class IIa, it is stated that quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ERS [17].

9.4 Conclusion

Although evidence for this matter is insufficient to date, intravenous injection of isoproterenol is effective for the recurrence of VF, especially electrical storm, in patients with ERS. After an acute phase, oral quinidine may be effective to prevent recurrent VF. An alternative therapy may be the administration of cilostazol and its combination with bepridil to patients with ERS.

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