Idiopathic Ventricular Fibrillation

14

Masayasu Hiraoka and Tetsuo Sasano

Abstract

Idiopathic ventricular fibrillation (IVF) is a rare condition in which patients without major structural heart diseases develop VF and often suffer from sudden cardiac death. To date, the IVF was defined excluding other primary electrical disorders. IVF may not be composed of a single entity but contain multiple forms by clinical manifestations and possible pathogenetic backgrounds. In this chapter, IVF can be described in two groups: the early repolarization syndrome (ERS), and IVF in a narrow sense excluding ERS. ERS is characterized by elevation of J-point in inferior or lateral leads, accompanied with notch or slur in the terminal portion of QRS complex. Although early repolarization pattern is not rate in healthy subjects, some of them suffer from lethal ventricular tachyarrhythmias. The intramural discordant repolarization property may explain the pathogenesis of ERS partly, but other confounding factors also contribute to the ventricular tachyarrhythmias. The IVF excluding ERS is a very rate, and may include several different types of electrocardiographic and clinical manifestation. Several electrical abnormalities are involved in the pathogenesis of the IVF, including the abnormality in conduction of His-Purkinje system, short-coupled premature contraction, and conduction disturbance in ventricle.

Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) is a rare condition in which patients without major structural heart diseases develop VF and often suffer from sudden cardiac death (SCD). While sporadic case reports of VF developing in patients without pathological conditions of the heart have been presented in the literature, the collected case studies under the terminology of IVF appeared as several publications during late 1980s to early 1990s [1–3]. Several conditions that are now categorized as primary electrical diseases also develop VF without major cardiac structural abnormalities. These are generally excluded from IVF as a different disease entity due to its unique clinical manifestations and special pathogenic mechanism. Further, IVF may not be composed of a single entity but rather contain multiple forms with different electrocardiographic manifestations and probable causative genes.

In this chapter, IVF is divided into two groups: (A) the early repolarization syndrome (ERS) and (B) IVF in a narrow sense without ERS. Early repolarization (ER) pattern in ECG indicates the elevation of the QRS and ST-segment junction (J-point), notch and slur at the terminal portion of QRS complex. IVF excluding ERS shows no ER pattern on the electrocardiography (ECG) and develops VF events. Clinical presentations of both groups of IVF develop as a sudden onset of VF and/or aborted SCD in subjects without structural heart diseases and any known conditions that causes fatal arrhythmic events. In some cases, there is a family history of ER pattern on ECG and/or SCD. Diagnosis

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of ERS can be made in patients after the resuscitation from VF/aborted SCD with an exclusion of structural heart diseases and any other reason for fatal arrhythmic events. ECG during sinus rhythm shows ER pattern in the inferior and/or lateral leads. The prevention of SCD by antiarrhythmic drugs is not sufficiently achieved and implantable cardioverter defibrillator (ICD) implantation is the only available therapy for the SCD prevention. The mechanism of ERS is assumed to be explained by the repolarization theory based on experimental studies, but clinical and genetic proof of this concept has not fully been clarified. Other types of IVF include several different types of clinical manifestation with mostly unknown diagnostic criteria and underlying mechanisms. Some forms of IVF have a familiar inheritance and genetic backgrounds have been identified as a possible pathogenesis in the limited cases.

Early Repolarization Syndrome (ERS)

Introduction

Early repolarization syndrome (ERS) is a type of IVF, in which patients with ER pattern in ECG develop sudden attacks of VF in the absence of structural heart disease and any known causes of fatal arrhythmias. ER pattern in ECG has for a long time been considered as a benign ECG sign except for the "Osborn wave" by hypothermia [4, 5].

In 1992, Brugada and Brugada reported a unique form of IVF, now known as Brugada syndrome, where patients with J-point and ST-segment elevation (ER pattern) in V1–V3 without structural heart disease are prone to develop VF and SCD [6]. Introduction of Brugada syndrome has brought about a strong interest for ER having possible correlation or trigger for the development of fatal arrhythmias. Actually, several studies of IVF with ER pattern excluding Brugada syndrome were published as reports of a single or collected cases, suggesting a possible arrhythmogeneity of ER [7–11]. The hypothesis was challenged by the experimental study dealing with canine wedge preparations for models of ER, which were shown to be capable of developing rapid polymorphic ventricular tachycardia (PVT) [12, 13].

Clinical results supporting this hypothesis were then provided with the seminal work by Haissaguerre et al. They demonstrated a high prevalence of ER pattern in patients with IVF [14]. In their study, 206 IVF and 412 control cases were explored, and ER pattern was more frequently observed in IVF patients compared with the controls (31 % vs. 5 %, respectively). The odds ratio (OR) for the presence of ER in the IVF patients with the control was 10.9 (95 % confidence interval (CI): 6.3–18.9) after adjusting for age, sex, race and level of physical activity. Similar observations were confirmed in IVF patients with case–control studies [15, 16]. The ratio of ER pattern in patients with IVF was 42–60 %, which was significantly higher than the controls (3.3–13 %, $p < 0.05$). Figure 14.1 presents representative ECGs from one IVF patients with and without ER. Subsequently, Tikkanen et al. studied the prognostic significance of ER pattern in the general population [17]. An ER pattern in inferior leads was associated with an increased risk of cardiac death in middle-aged population.

The term "early repolarization" (ER) in 12-lead ECG has been used in cardiology for many years, but its exact definition varies widely depending on the investigators. Because of such variations, the prevalence of ER in normal population varied between 2 % and 31 % [18]. In 1976, Kambara and Phillips [19] proposed the following definition of ER: (1) end-QRS notching or slurring; (2) elevation of the ST-segment; and (3) an upward-sloping ST-segment followed by a tall, symmetrical T wave. In the clinical practice, many physicians regarded the presence of J-point and ST-segment elevation merged with positive T wave, as ER being a benign ECG sign.

Therefore, definition of ER and its terminology has not yet achieved a general consensus. Recently, Macfarlene et al., have proposed a unified definition of ER to assist future studies [20]. According to their consensus paper, ER is present if all of the following criteria are met:

(i) There is an end-QRS notch or slur on the down-slope of a prominent R-wave. A notch should lie entirely above the baseline. The onset of a slur must also be above the baseline. (A notch and slur should occur on the final 50 % segment of the QRS complex).
(ii) The peak of J point is ≥ 0.1 mV in two or more contiguous leads of the 12-lead ECG, excluding lead V1 to V3.
(iii) QRS duration is <120 ms.

If the ST-segment is upward sloping and followed by an upright T wave, the pattern should be described as "ER with ascending ST segment".

If the ST-segment is horizontal or downward sloping, the pattern should be described as "ER with a horizontal or descending ST segment".

Clinical Presentation of ERS

ERS refers to the patients with IVF showing ER pattern on the ECG in inferior and/or lateral leads. It is important to recognize that ERS and ER patterns in ECGs should be separated from each other, since an ER pattern itself is mostly a benign ECG finding. Clinical diagnosis of ERS can be made in specific patients who were resuscitated from cardiac arrest due to VF, or PVT, and with a 12-lead ECG demonstrating ER pattern during sinus rhythm. At the same time, it is absolutely necessary to exclude structural heart diseases and other primary electrical disorders including

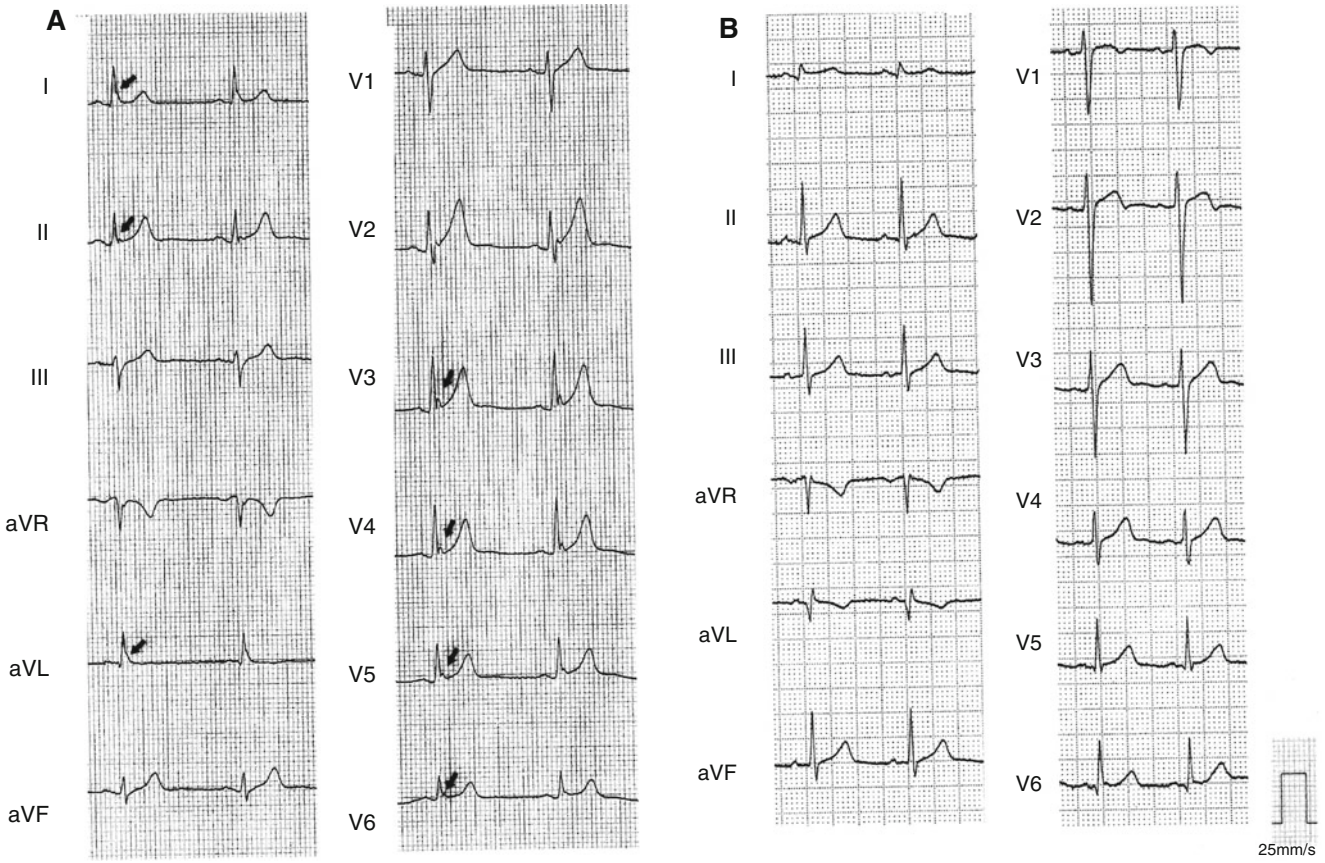

Fig. 14.1 Representative electrocardiograms (ECGs) of the IVF patients with ER (panel A) and without ER (panel B) (Panel A: ERs were recorded in both lateral and inferior leads. Panel B: ER was not observed in any lead (Reproduced by permission from Sekuguchi et al. [60]))

long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome (see the details in the individual sections of this book).

The most difficult diagnostic dilemma is to differentiate the malignant ER from benign ER in subjects showing this particular ECG sign in the inferior and/or lateral leads. The prevalence of the ER pattern in the inferior and/or lateral leads has been reported to be in a range of 3–24 % in the general population [21, 22]. The prevalence varies considerably depending on age, sex, race, and physical activity. Most of these subjects are asymptomatic without developing VF events. While clinical implications of ER pattern in asymptomatic subjects are not clear, it is assumed that the presence of ER pattern triples the risk of VF. Despite of this increase, the overall risk is still negligible because IVF itself is a rare disorder. Adler et al. have estimated that the risk of developing IVF in an individual younger than 45 years is 3:100,000. The risk increases to 11:100,000 when a J-point elevation is present [23]. A meta-analysis estimated absolute difference of subjects with ER pattern by seven cases of arrhythmic death per 100,000 subjects per year [24]. Although the presence of an ER pattern increases relative risk of VF, the absolute risk is still very low.

Clinical Diagnosis and Differential Diagnosis

ERS usually develops with sudden and unexpected onset of syncope and/or aborted SCD due to life-threatening ventricular arrhythmias, VF/PVT. A diagnosis of ERS can be confirmed in resuscitated patients after VF who show an ER pattern in their ECGs, while other causes of arrhythmic events are excluded (Figs. 14.2 and 14.3). Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/ Asia Pacific Heart Rhythm Society (APHRS) expert consensus statement has provided recommendations for ERS diagnosis [25] (Table 14.1). A diagnostic definition is stated as "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 in a patient resuscitated from otherwise unexplained VF/PVT". A highly possible case and definition of ER pattern are also described.

Other features of clinical manifestations have been presented in various reports on an observational basis with only limited numbers of cases. Thus, definite diagnostic criteria for ERS and risk stratification has not been achieved in general consensus at present time, but physicians should follow the HRS/EHRA/APHRS expert consensus recommendations to make a diagnosis.

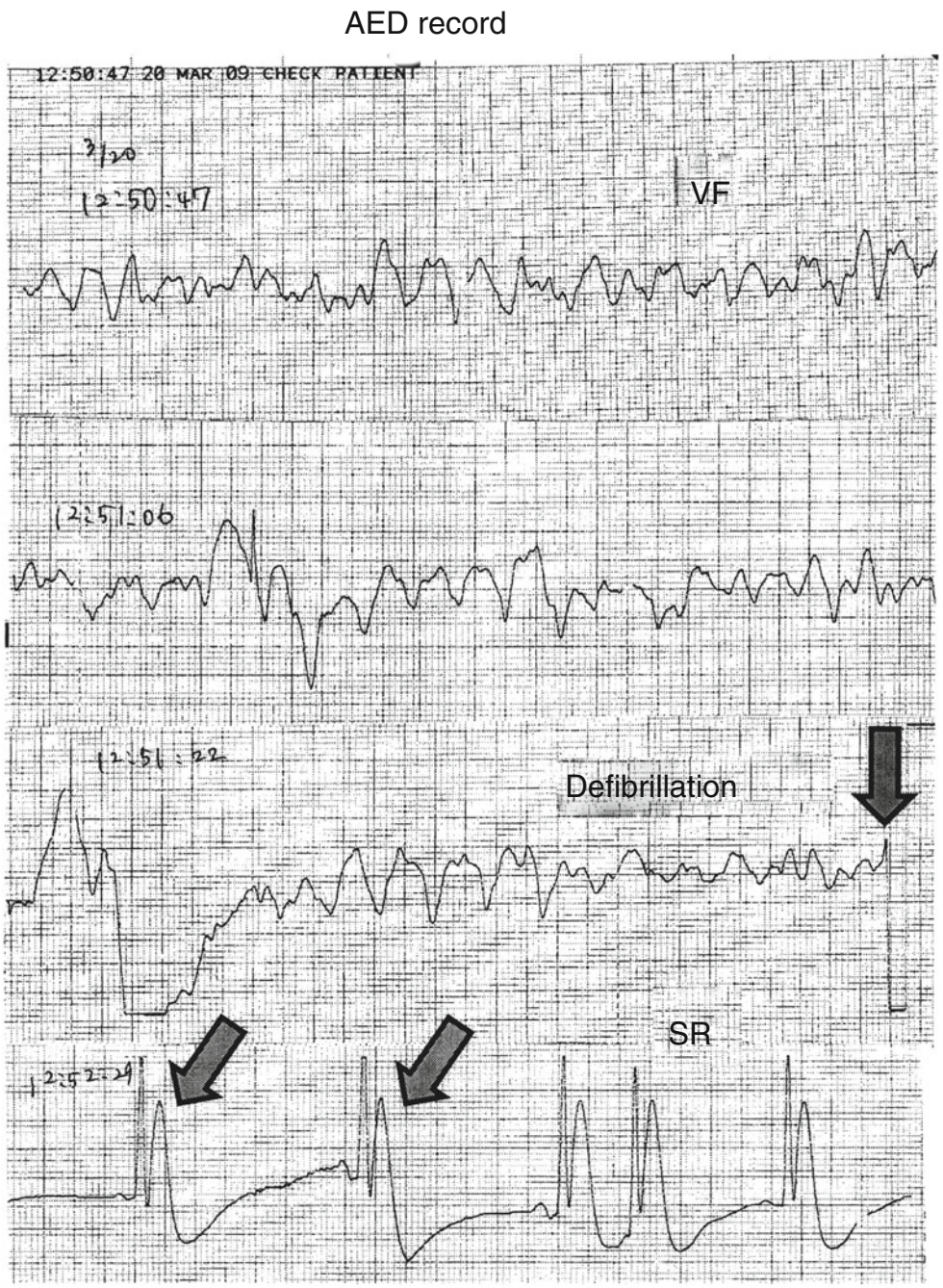

Fig. 14.2 VF and giant J-wave in sinus rhythm after defibrillation (ECG recorded by automated external defibrillator (AED) from 37 years old man with aborted sudden cardiac death. AED detected VF and delivered electric shock (the right corner of the third row) restored sinus rhythm with giant J-wave (the bottom row). He was shown to have no structural heart disease by various cardiac examinations including echocardiography, coronary angiography, and pilsicainide provocation test for Brugada syndrome)

In addition, the following findings may help with the diagnosis in suspected cases or an atypical manifestation in clinical practice:

ERS has a male predominance. The mean age of the first VF episode is 35–43 years [14–16, 26, 27]. VF attacks are more likely to develop during sleep than during physical activity [14]. In patients with ERS, the amplitude of a J-point elevation increases with slow heart rate and after a pause [27] (Fig. 14.4). VF is usually triggered by short-long-short sequence and a short-coupled extrasystole initiates the arrhythmic events [28]. Circadian variation of the J-point elevation often occurs in association with the vagal tone [26]. Increased vagal tone augments and sympathetic stimulation by isoproterenol attenuates the amplitude of the J-point elevation [27]. Sodium channel blockers also attenuate the J-point elevation [27, 29–31]. The amplitude of ER increases prominently just before VF episodes [11, 14, 16, 28]. This is recognized as a hallmark of the disease. A global appearance of a J-point elevation on 12-lead ECG was suggested to develop within 30 min of VF storms [16]. Such J-point elevation may completely disappear within weeks after VF events [27]. Dynamic manifestation of the J-point elevation in

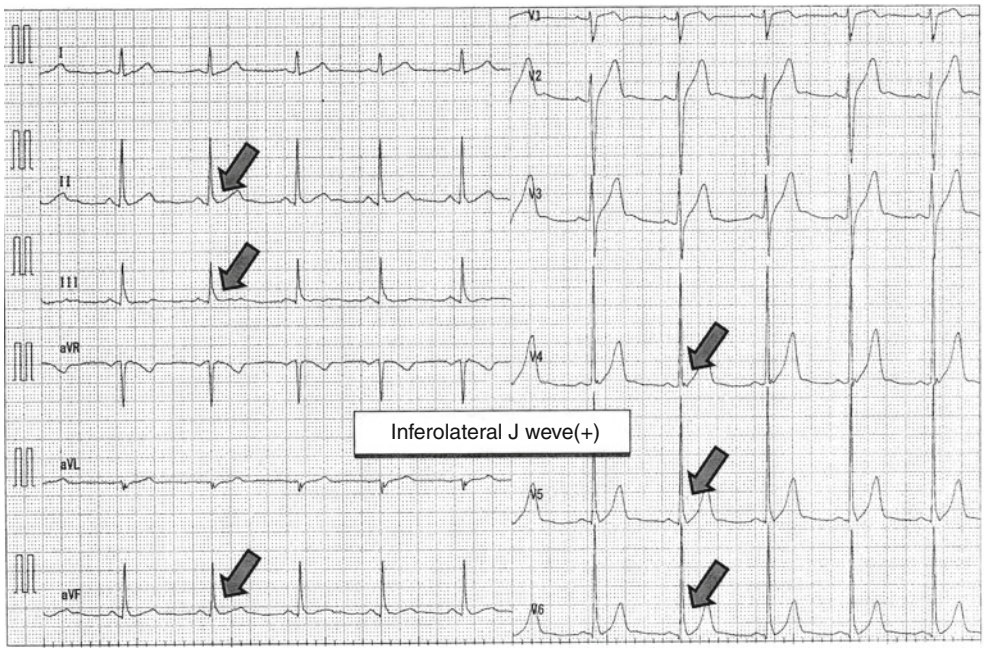

Fig. 14.3 Twelve-lead ECG with inferolateral ER (ECG was recorded from the same patient in Fig. 14.2 on admission. ERs (arrows) were observed in the inferior (II, III, aVF) and lateral (V3–V6) leads)

Table 14.1 Early repolarization diagnosis

1.	ER syndrome is diagnosed in the presence of J-point elevation ≥1 mm ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT
2.	ER syndrome can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
3.	ER pattern can be diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

ECG electrocardiogram, ER early repolarization, VF ventricular fibrillation, SCD sudden cardiac death
(Reproduced by permission from Priori et al. [25])

malignant cases of ERS might be in contrast to rather stable expression of ER pattern in healthy individuals [17, 32, 33]. The magnitude of the J-point elevation may have some prognostic significance. Either slurred or notched J-point elevations ≥0.2 mV is relatively rare in the general population and appears to be associated with an increased risk [17]. A horizontal or descending ST segment following J-point elevation is associated with a worse outcome in the general population [32]. This ECG pattern also gives information in distinguishing IVF patients from matched controls and is probably a key sign to differentiate malignant form from benign ER patterns [33].

Signal averaged ECG demonstrated that late potentials were frequently positive and were concordant with the time of VF events in ERS patients, but no such correlation was found in IVF cases without ER or controls [26]. The repolarization parameters (T-wave alternans and QT dispersion) were not different between IVF patients with and without an ER pattern. Electrophysiologic study (EPS) was not an effective method to assess the risk of ERS patients. Inducibility of VF was low (34 %) in patients with a history of VF and was not different in IVF patients with or without ER pattern [14]. The results of a multicenter study to determine the role of EPS in risk stratification of ERS patients with a recent history of VF showed a low (22 %) inducibility and a low prediction rate (33 %) for VF recurrence in EPS-positive cases [34]. Therefore, the current programmed stimulation protocol does not enhance risk stratification in patients with ERS.

Differential diagnosis is to exclude any form of structural heart diseases to develop life-threatening ventricular arrhythmia and electrolyte imbalance, especially hypokalemia. Primary electrical diseases should be excluded by unique clinical manifestations depending on each disorder and genetic screening (Refer to each section).

Clinical Therapy

Table 14.2 presents the therapeutic interventions for ERS patients according to the HRS/EHRA/APHRS expert consensus recommendations [25]. The table indicates medical treatment and indication for ICD implantation. It also stresses that ICD implantation is not recommended for asymptomatic patients with an isolated ER pattern on ECG.

Electrical storm is relatively common after ICD implantation in patients with ERS. The acute use of isoproterenol was effective for the suppression of recurrent VF and VF storms.

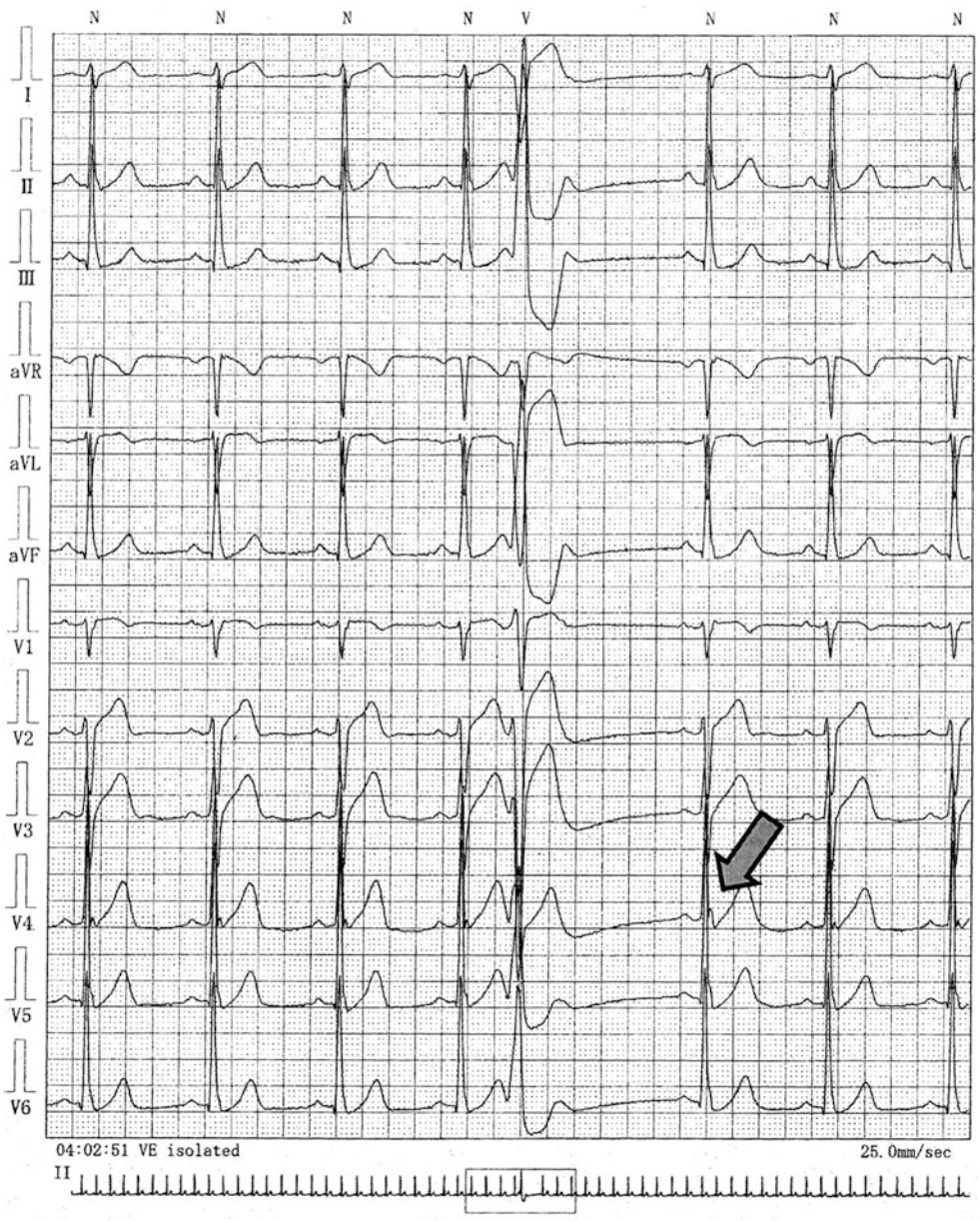

Fig. 14.4 Pause-dependent augmentation of ER (ER was augmented in a beat (arrow) following a long pause after premature ventricular contraction (recorded from the same patient shown in Fig. 14.2))

Table 14.2 Early repolarization therapeutic interventions

Class I	1. ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest
Class IIa	2. Isoproterenol infusion can be useful in suppressing electrical storms in patients with a diagnosis of ER syndrome
	3. Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome
Class IIb	4. ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation >1 mm in two or more inferior or lateral leads
	5. ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained sudden death with or without pathogenic mutation
Class III	6. ICD implantation is not recommended asymptomatic patients with an isolated ER ECG pattern

ICD implantable cardioverter defibrillator
(Reproduced by permission from Priori et al. [25])

Isoproterenol is typically initiated at 1.0 μg/min, targeting a 20 % increase in heart rate or an absolute heart rate >90 bpm, titrated to hemodynamic response and suppression of recurrent ventricular arrhythmia [25]. Quinidine together with ICD implantation was suggested for long-term suppression of VF recurrences during the chronic phase [16, 29]. A small series of case study demonstrated that the combination of cilostazol and bepridil was shown to suppress VF recurrences and to attenuate the amplitude of the J-wave in patients with ICD implantation [35].

The clinical implications for asymptomatic subjects with ER pattern in ECG are not clear. While the presence of ER pattern is associated with times the risk of developing VF, the absolute risk is still negligible in the general population [24, 36]. Based on these population studies and clinical observations, middle-aged subjects with an ER pattern on the ECG, especially those with a high amplitude (≥0.2 mV) J-point elevation and horizontal/descending ST segment, should pay attention to risk reduction for long-term basis, especially on the occasions of acute coronary events [37].

The Mechanism of ER Pattern and Early Repolarization Syndrome

The genesis of J-wave or ER pattern on the ECG was proposed by the group of Antzelevitch et al. based on animal experiments using the canine ventricular wedge preparations [12, 13]. The proposed mechanism explains the genesis of a J-wave which is formed by the transmural voltage gradient during the early repolarization phase due to different action potential configurations between the epicardium and endocardium. The action potential of the epicardial cells exhibits a prominent notch at the early phase of repolarization and that of endocardial cells lacks such notch. The voltage gradient caused by the presence and absence of the notch between the epicardial and endocardial action potentials produces the J-wave configuration on ECG. The differences in action potential configurations are brought by the membrane current distribution: epicardial cells are rich in the transient outward potassium current (I_{to}), but the endocardial cells have least development of I_{to} [38]. Conditions that augment or reduce I_{to} could modify the manifestation of the J-wave on ECG. When I_{to} was augmented or changed the current kinetics by exposure to hypothermia, slow heart rate, application of the calcium and sodium channel blockers, or I_{to} agonist such as NS5806, epicardial action potential notch, and J-wave were augmented. Reduction of I_{to} by the application of I_{to} blockers such as 4-aminopyridine, quinidine, or premature stimulation caused parallel changes of decrease in the notch and J-wave [12, 39]. With further increase in I_{to}-mediated notch, some area of epicardial action potentials become markedly abbreviated while those of other area and endocardium are not much shortened, which provide the development of "phase-2 reentry" and initiate PVT/VF.

Antzelevitch and Yan [40] proposed the terminology of "J-wave syndrome". This concept is based on several lines of observations suggesting that arrhythmias associated with ER pattern in the infero-lateral leads, like Brugada syndrome, hypothermia, and acute ST-segment elevation myocardial infarction are mechanistically linked to abnormalities in the manifestation of It_o-mediated J-wave. Although ERS and Brugada syndrome differ with respect of the lead location and the magnitude of abnormal J-wave manifestation, they can be considered to represent a continuous spectrum of phenotypic expression that the authors propose the term "J-wave syndrome". They divide J-wave syndrome into three types: type 1, displaying an ER pattern predominantly in the lateral leads, is prevalent among healthy male athletes and rarely seen in VF survivors; type 2, displaying an ER pattern predominantly in the inferior or inferolateral leads, is associated with a higher level of risk; type 3, displaying an ER pattern globally in the inferior, lateral, and right precordial leads, is associated with the highest level of risk for the development of malignant arrhythmias and is often associated with VF storms. This terminology may not be widely accepted since it includes both benign and malignant forms.

The concept of the repolarization theory can explain the experimental results and support some clinical observations. There are, however, several problems left un-clarified. For example, contiguous myocardial cells exhibit fairly good electrical couplings among individual cells so that different action potential configurations are prone to be averaged and a steep voltage gradient is not likely to exist between the epicardium and endocardium, or among adjacent cells in the epicardial regions [41]. There may be an additional factor necessary to create the observed conditions in the limited region of the inferior or lateral wall of the ventricle, such as myocardial fibrosis. Second, the I_{to} current is composed of different genetic subunits that exhibit fast and slow current kinetics: the fast component is formed by *Kv4.2 (KCND2) + Kv4.3 (KCND3)* and the slow one by *Kv1.5 (KCNA4)*. Their expression and the combination differ in different cardiac regions and species [42]. It is not known whether the candidate genes for I_{to} current in human heart, especially their distribution at the inferolateral wall, is similar to canine ventricle or not. Clinically, if the heterogeneity of repolarization caused by I_{to} is the mechanism for developing VF in patients with ERS, it is still difficult to explain why the risk of arrhythmic death is so low (7 cases per 100,000 subjects per year), while an ER pattern in the general population is common (3–24 %) [21–24]. Electrophysiologic, genetic, and clinical documentations to prove the repolarization theory as an actual mechanism for ERS await further study.

Molecular Diagnostics and Molecular Genetics

Familiar ER pattern in ECG has been reported to have an autosomal dominant inheritance with incomplete penetrance.

Population-based studies also suggested some degree of inheritance of ER pattern in the general population [43, 44]. Genetic background to ER has been suggested by observations in subjects of a common family history of SCD with ER and IVF [14, 45], but the familiar inheritance of malignant ER pattern has not clearly been demonstrated.

A 14-year-old girl with IVF-showing ER pattern on the ECG and frequent episodes of VF was found to have a mutation in the *KCNJ8* gene, encoding *Kir6.1*, – the pore-forming subunit of the cardiac ATP-sensitive potassium (K.ATP) channel. The mutation identified in this girl, which was not found in 382 healthy controls, had the substitution of highly conserved serine residue at amino acid position 422 of the channel by leucine, *Kir6.1*-S422L [46]. Subsequently, *Kir6.1*-S422L was defined as a rare variant rather than mutation, and it was also found in sporadic cases of ERS. Electrophysiologic studies of the *Kir6.1*-S422L-mutant coexpressed with the *SUR2A* subunit in COS cells demonstrated an increase in the K.ATP channel current [47, 48]. No familiar inheritance of ERS was documented in these sporadic cases. Furthermore, a case of a homozygote mutation of *Kir6.1*-S422L was found in a Ashkenazi Jewish boy, who had no significant ECG abnormalities and no clinical symptoms, while the heterozygous father presented with a subtle J-point elevation. The study also demonstrated high frequency (~4 %) of *Kir6.1*-S422L in Ashkenazi Jews without ER pattern or ERS as compared to European, Middle Eastern non-Jewish, and non-Ashkenazi Jews (<0.25 %) [49]. The results suggest that this rare variant may not represent a sole pathogenic mechanism but require an additional modifier for the clinical manifestation of ERS.

Mutations in the L-type Ca channel genes, including *CACNA1C, CACNB2B,* and *CACNA2D1* [50] as well as loss-of-function mutations in *SCN5A* [51] have also been reported in patients with ERS, but inheritance is not clearly identified. Because of a high prevalence of ER pattern in the general population, ER may be caused by polygenic basis influenced by non-genomic factors as well. A recent genomewide association meta-analysis in three independent populations of European ancestry found eight loci associated with ER, the strongest association being found with SNPs located at the *KCND3* genes, which encode I_{to} channel (*Kv4.3*) coding gene [52]. These observations need further confirmations in other populations.

Family Screening and Follow-up in Relatives

There are currently no recommendations to screen the families of individuals with asymptomatic ER pattern on the ECG. No provocation tests are available to diagnose concealed ER in family members of ERS patients. Therapeutic recommendation by the HRS/EHRA/APHRS consensus statement uses the term "strong family history" [25]. There is no clear definition of this term, but it is typically chosen when more than one family member is affected, deaths occur at an early age and a first-degree relative is affected.

Summary

ERS is a specific type of IVF, which is a very rare but highly malignant disease. Diagnosis can be made in resuscitated patients after having VF showing a J-point elevation in the inferior and/or lateral leads during sinus rhythm, after exclusion of major structural heart diseases or primary electrical disorders. Treatment should be directed to protect recurrence of VF and SCD by implantation of an ICD. Isoproterenol infusion is effective for suppressing VF events during acute phase and VF storms. Quinidine may be useful in patients with ICD implantation for preventing recurrent VF events. The mechanism and genetic background of ERS have not been fully clarified.

Take Home Message

- ERS is a very rare but potentially highly malignant disease.
- ERS should be considered in anyone resuscitated from VF showing ER pattern in inferior and/or lateral leads of a standard 12-lead ECG during sinus rhythm and a strong family history of juvenile unexpected sudden death, without potential other causes.
- One always must think about ERS in the following:
  - Aborted cardiac arrest or SCD of unknown origin.
  - The presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG during sinus rhythm.
  - A strong family history of juvenile unexplained sudden death.
- No recommendation to screen the families of individuals with asymptomatic ER pattern on the ECG.

Idiopathic Ventricular Fibrillation Without ER Pattern

Idiopathic ventricular fibrillation (IVF) without ER pattern on the ECG is characterized by spontaneous VF in the absence of structural heart disease and in the absence of known electrical disorders. IVF cases are diagnosed and studied only after the resuscitation from the cardiac arrest with exclusion of structural heart diseases and primary electrical disorders. While incidences of IVF without ER are quite rare, scattered descriptions of small numbers of IVF patients have been presented in the literature without achieving a definite and uniform clarification of clinical characterization, genetic background, and diagnostic criteria/risk stratification of arrhythmic events. There are several clinical

forms of IVF, which may be caused by different pathogenic mechanisms.

IVF Related with His-Purkinje Conduction Disturbances

Recently, several reports described that the conduction disturbances in the His-Purkinje system were involved in the mechanism of IVF. In the latter part of this chapter, we focus on His-Purkinje conduction disturbance and its involvement in IVF.

Deletion of Irx3 in Mouse Model

The Iroquois homeobox (Irx) family is an iroquios homeoboxtranscription factor, which contains a highly conserved DNA-binding homeodomain and Iro motif in Drosophila and vertebrates. The *IRX* gene family has six subtypes forming two clusters (*IRX* 1, 2, and 4 on chromosome 13 and *IRX* 3, 5, and 6 on chromosome 16 in human) [53]. The *Irx* family genes were expressed in heart during mouse development [54–56]. Among them, it was reported that *Irx3* was selectively expressed in subendocardial layer in the ventricles and plays a critical role in generating the His-Purkinje system. Zhang et al., reported that a genetic deletion of *Irx3* in mice resulted in the disruption of the fast conducting system through the His-Purkinje network [57]. The Purkinje cells express Connexin-40 (Cx40) rather than Connexin-43 (Cx43), dominantly expressed in working ventricular myocytes. The conductance of Cx40 is larger than Cx43, which explains the faster conduction through the Purkinje network. The deletion of *Irx3* resulted in the reduced expression of Cx40 in the His-Purkinje system.

Following study utilizing *Irx3* knockout mouse identified that the deletion of *Irx3* showed not only ventricular conduction disturbance but also ventricular tachyarrhythmias [58]. Ventricular tachyarrhythmias were not seen in a baseline condition, but evoked by physical exercise, sympathetic activation, or acute myocardial infarction. *Ex vivo* electrophysiological study using optical mapping showed that delayed conduction at the right ventricular outflow tract (RVOT) at baseline, and the administration of isoproterenol-induced atrioventricular block, followed by nonsustained VT (Fig. 14.5). The findings suggested that these stimulations increased the discrepancy in conduction between impaired His-Purkinje system and intact myocardium.

Irx3 Mutation-related with IVF

Koizumi et al. further performed genetic screening in *IRX3* from 130 IVF cases including Brugada syndrome, short QT syndrome, and ERS and found two novel point mutations in VF cases (R421P and P485T) [58]. For the functional analysis of these mutations, they generated identical mutations

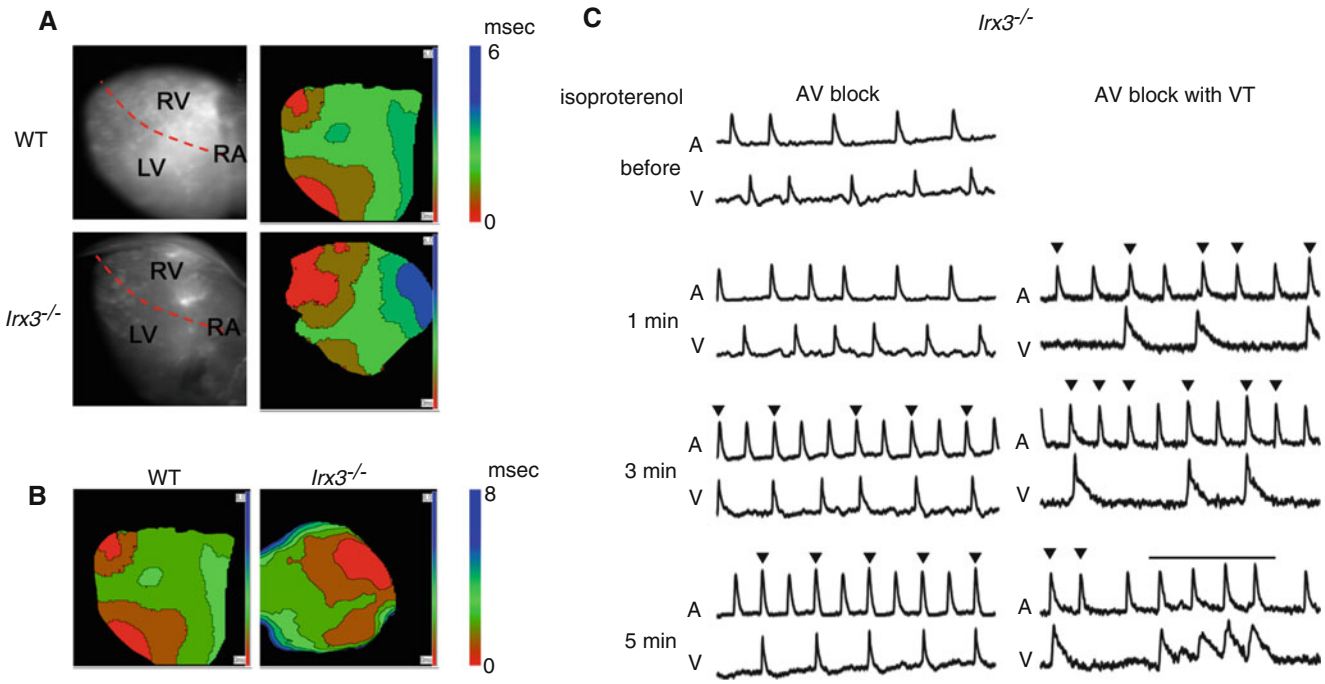

Fig. 14.5 *Ex vivo* optical epicardial mapping and arrhythmia development in Irx3$^{-/-}$ mice (Panel A: Representative optical epicardial mapping in WT and Irx3$^{-/-}$ mice in basal condition. Panel B: Representative optical epicardial mapping in WT and Irx3$^{-/-}$ mice after isoproterenol application. In Irx3$^{-/-}$ mice, epicardial breakthrough occurs from the base of the right ventricle and propagates to the apex; the propagation of depolarization became markedly slow. Panel C, AV block and AV block with nonsustained VT occurred after administration of isoproterenol. Reverse triangles indicate atrial action potential without following ventricular action potential. Solid bar indicates nonsustained VT (Reproduced by permission from Koizumi et al. [58])

using murine *Irx3* and transfected wild-type and mutated *Irx3* into HL-1 murine atrial cells or neonatal mouse ventricular myocytes. Transfection of wild-type *Irx3* increased the expression of *Cx40* and *SCN5A*, but the transfection of these two mutated *Irx3* showed significantly reduced expression of *Cx40* and *SCN5A*. Thus, these mutations contributed to the conduction disturbance in the His-Purkinje system.

The intriguing feature of these cases is that they suffered VF during physical activity. One case with the *Irx*-R421P mutation had a Brugada-type ECG but suffered syncope while he was ice-skating. Another case had syncope during commuting. These findings indicate that IVF associated with *Irx3* mutation had a different clinical manifestation than Brugada syndrome.

Although the physiological phenotype of *Irx3* knockout mouse was evident, the precise molecular mechanism linking *Irx3* mutation and conduction disturbance to IVF has not been fully elucidated. Since *Irx3* did not directly bind to the promotor region of *Cx40*, other unknown molecules should be involved in the regulation of *Cx40* expression. In addition, two mutations found in IVF cases were not in the already known functional domains (TALE-homeobox domain and Iro domain). Thus, the mechanism explaining reduced expression of *Cx40* in these two mutations is still under investigation.

Other IVF-related with Conduction Disturbance

Accumulation of the several observational studies has indicated an additional possibility of the involvement of the His-Purkinje system in IVF. One phenotype is the association of right bundle branch block (RBBB). Aizawa et al. investigated 87 cases diagnosed as IVF, excluding Brugada syndrome and catecholaminergic polymorphic VT, and found 10 of 87 patients (11.5 %) had complete RBBB and the incidence was much higher than in the age and sex comparable controls (1.37 %) [59]. There were no differences in ECG parameters except QRS duration.

The Japanese Idiopathic Ventricular Fibrillation Study (J-IVFS) summarized 64 IVF cases excluding Brugada syndrome [60]. Out of 64 cases, 24 cases had ER pattern. In remaining 40 patients, nine cases (14 %) had an abnormal axis deviation and/or RBBB, indicating conduction disturbance (CD). They classified IVF cases into ER(+) group, ER(−)CD(−) group, and ER(−)CD(+) group. The ER(−)CD(+) group consisted of five males and four females – lower proportion of male than ER(+) group. The ER(−)CD(+) group also had longer PR interval and QRS duration than the groups of ER(−)CD(−) and ER(+)CD(−). Two studies indicated about 10 % of IVF patients showing ventricular conduction disturbances, but no specific ECG parameters were noted in the rest of IVF cases. VF was initiated with short-coupled premature ventricular contractions (PVCs) in some cases. Inducibility of VF by EPS was low in both types. There were no indications for familiar pattern of IVF with or without RBBB in two studies. No risk stratification was available so far and drug treatment for the prevention of SCD was not effective. Isoproterenol infusion was proven effective for the treatment of VF storms in some cases. ICD implantation was the only therapeutic option for the prevention of SCD.

Haissaguirre et al., described short-coupled PVCs originating from the distal Purkinje fibers as the main triggering factor for VF in IVF patients [61]. The PVCs had different morphologies and were mapped in several locations of the Purkinje system, including the anterior right ventricular region and large areas of the lower half of the left ventricular septum. The PVC origins were eliminated by catheter ablation and 89 % of patients were free of VF events during the follow-up of 24 ± 28 months.

In contrast to the IVF cases with *IrxX3* mutation, both reports indicated the prevalence of exercise-induced ventricular tachy-arrhythmias was low, which suggested that the IVF related with RBBB might have a different mechanism compared with the *Irx3* deficiency.

Short-coupled Variant of Torsade de Pointes

Another type of IVF probably having association with the Purkinje system is the PVT initiated by short-coupled PVT. Leenhardt et al., described a unique from of idiopathic ventricular tachyarrhythmias in young adults and called "short-coupled variant of torsade de pintes (TdP)" [62]. The unique feature of this arrhythmia was the development of TdP under normal QT interval, in contrast to frequent association with QT prolongation in congenital and acquired forms of long QT syndrome. The TdP was initiated by PVCs of short coupling interval (245 ± 28 ms), and one-third of these patients had a family history of sudden death. Approximately 70 % of patients with short-coupled variant of TdP degenerated into VF. In the following year, similar characteristics of patients were reported [63] and the term "Short-coupled variant of TdP" could be well recognized as a specific form of PVT/VF. This form of arrhythmias was prevalent mainly in females. The initial clinical presentation of the patients was often syncope, and the type of arrhythmia was not inducible by EPS. The arrhythmia was partially suppressed by verapamil, but the drug could not prevent SCD and ICD implantation was the only option for the prevention of SCD. Recent several studies were motivated to treat the triggering PVCs from the Purkinje system in patients with PVT/VF by catheter ablation, and the ablation achieved a freedom from VF recurrences during the follow-up of short- and long-term basis [61, 64, 65].

The underlying molecular mechanism of short-coupled variant of Tdp has not been elucidated yet. A recent case report, however, indicated that point mutation in ryanodine receptor 2 (*RyR2*-H29D) was related with PVT [66]. In contrast to the

RyR2 mutation associated with catecholaminergic polymorphic VT, this case had short-coupled PVCs and PVT at rest. The *RyR2*-H29D mutation converted *RyR2* to a leaky channel. This may explain some part or the principal mechanism of short-coupled variant of TdP.

IVF Related to Over-expression of DPP6

Studies dealing with a large cohort of familiar IVF in the Netherlands were conducted to clarify a pathogenic mechanism and risk stratification for asymptomatic patients in the affected family members. Alders et al., performed a genome-wide haplotype-sharing analysis for the identification of the responsible gene in three Dutch families in which multiple individuals died suddenly or were resuscitated from cardiac arrest at young age [67]. They identified a haplotype, on chromosome 7q36, that was conserved in these three families and was also shared by 7 of 42 independent IVF patients. The shared chromosomal segment harbors part of the dipeptidyl-aminopeptidase-like protein 6 (DPP6) gene, which encodes a putative component of the I_{to} in the heart [68]. Clinical evaluation of 84 risk-haplotype carriers and 71 noncarriers revealed no ECG or structural parameters indicative of cardiac disease. Penetrance of IVF was high; 50 % of risk-haplotype carriers experienced aborted SCD before the age of 58 years. Their study also demonstrated a 20-fold increase in *DPP6* mRNA levels in the myocardium of carriers as compared to controls. From these results, they propose *DPP6* as a gene for IVF and increased *DPP6* expression as the likely pathogenic mechanism. Despite of the finding of an association between familial IVF and a risk haplotype on chromosome 7q36, identification of asymptomatic patients at risk of IVF remains challenging, and no clinical parameters to guide treatment have been defined [69–71].

Further study by Xiao et al., explored the link between the overexpression of *DPP6* and the pathogenesis of IVF [72]. According to the results, baseline ECG was normal in *DPP6* risk-haplotype carriers. Ventricular arrhythmias manifested as short-coupled PVCs that sometimes initiated PVT. PVCs consistently displayed LBBB morphology with superior/left axis, suggesting a lower RV origin. The short-coupling intervals of PVCs under normal QT interval along with relatively narrow QRS complexes suggested an origin in the Purkinje system, as observed by Haissaguerre et al., [59] in 25 % of their IVF patients. In one patient undergoing ablation for repeated VF storms after ICD implantation, RV pace mapping produced a morphology similar to that of PVCs. Radiofrequency ablation was applied at a site with early diastolic Purkinje fiber potentials in the anterior lower RV. Neither VF nor typical morphology of PVCs recurred during the 43-month follow-up.

While I_{to} density was similar in Purkinje fiber and ventricular muscle, their tetraethylammonium (TEA) sensitivity and slow recovery from inactivation were different between the I_{to} in two tissues [73, 74]. In nondiseased human heart, the expressions of *DPP6* and neuronal calcium sensor-1 (NCS-1) were rich in Purkinje fiber, while K^+ channel interacting protein type 2 (KChIP2) was rich in ventricular muscle, which indicated different β-subunit compositions of the I_{to} channel in two tissues. Heterologous expression of *Kv4.3* in Chinese hamster ovary cells demonstrated that coexpression of *DPP6* and *NCS-1* (to mimic Purkinje I_{to} composition) enhanced I_{to} compared to *Kv4.3/NCS-1* and recapitulated kinetic/pharmacologic properties of Purkinje I_{to}. Overexpression of *DPP6*-enhanced and knockdown of *DPP6*-suppressed native Purkinje fiber I_{to}. A mathematical model of cardiac Purkinje fiber action potentials showed that I_{to} enhancement can greatly accelerate the repolarization of Purkinje fiber action potential. From these results, the authors suggest that a *DPP6*-mediated Purkinje fiber early repolarization might be a novel molecular mechanism for some forms of IVF. While the suggested mechanism is related to the ER of the Purkinje fibers, further clarification is mandatory whether it represents a subset of ERS limited to the conduction system, or other additional mechanism that may be involved in the clinical manifestation of IVF.

Possible Gene Mutations for Other Types of IVF Without ER Pattern

Genetic screening of Japanese IVF patients disclosed a mutation in the human cardiac sodium channel α-subunit gene (*SCN5A*) in a symptomatic IVF patient who did not exhibit typical Brugada ECG and showed rate-dependent RBBB [75]. A novel *SCN5A* missense mutation, S1710L, was identified and its channel function studied by heterologous expression system revealed markedly reduced current due to accelerated current decay, negative shift of steady state inactivation, and positive shift of activation (Fig. 14.6). Genetic screening of his family members was refused, and therefore, cosegregation studies could not be performed.

Valdivia et al., reported loss-of-function mutation of the *SCN3B*-encoded sodium channel β3 subunit [76]. A 20-year-old healthy male suddenly lost consciousness while playing basketball and the emergency team found him in VF. After resuscitation from VF, his ECG showed epsilon wave in the right precordial leads without inverted T wave. Cardiac examinations, including echocardiography and cardiac CT scan, did not reveal any structural abnormality of the heart, and hence, he was diagnosed as IVF. Mutation analysis disclosed a missense mutation V54G in *SCN3B*, which was absent in 800 references alleles. His mother was an asymptomatic gene-mutation carrier and exhibited a J-point elevation in her ECG. Functional analysis of HEK293 cells expressing *SCN5A* coexpressed with *Navβ3*-V54G revealed markedly decreased peak sodium current density, with positive shift of activation and negative shift in inactivation compared to wild type, resulting in loss-of-function

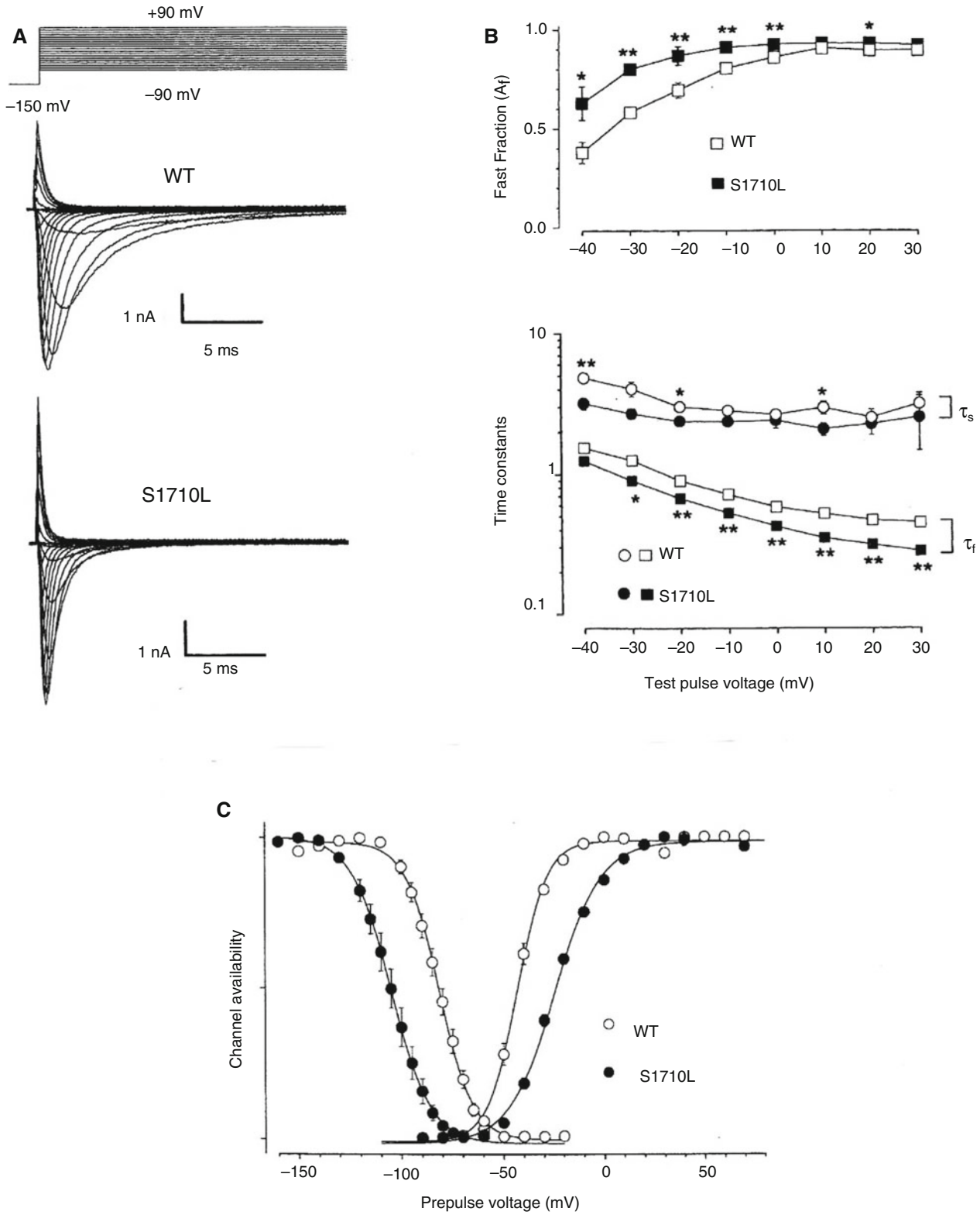

Fig. 14.6 Whole-cell current and its analysis obtained from HEK-hβ1 cells transfected with either WT or S1710L sodium channel (A: Whole-cell current records obtained from HEK cells transfected with either WT or S1710L sodium channel. Current was recorded from a holding potential of −150 mV stepped from –90 mV to +90 mV for 20 ms in 10 mV increments. Current decay is faster in S1710L than WT. B: The time course of inactivation was fit with a two exponential function. Af at the upper panel indicates the fraction of fast inactivation component. τf and τs at the lower panel indicate fast and slow the time constant of fast and slow inactivation components, respectively. C: Voltage dependence of steady-state inactivation and activation. S1710L current shows negative shift of inactivation and positive shift of activation compared to WT (Reproduced by permission from Akai et al. [75]))

by *Navβ3*-V54G. Immunocytochemistry and confocal microscopy demonstrated that *Navβ3*-V54G caused an *SCN5A*-trafficking defect. The results of the two reports may indicate that dysfunction of cardiac sodium channel due to gene mutations of main and/or auxiliary subunit is responsible for the pathogenesis in some forms of IVF.

Marsman et al., sought the genetic defect in a family with IVF manifesting in childhood and adolescence [77]. They characterized a family with a history of VF and SCD without electrocardiographic and echocardiographic abnormalities at rest. Two siblings died suddenly at ages of 9 and 10 years, and another two were resuscitated from cardiac arrest with documented VF at ages 10 and 16 years. Exome sequencing identified a missense mutation, F90L in the *CALM1* gene-encoding calmodulin in two resuscitated cases and one SCD victim. The functional analysis of this mutation was not available. The mutation was found in the mother and another sibling both being asymptomatic. Exome sequencing may be a strong tool to identify the genetic defect in families with a small numbers of affected individuals.

Summary

IVF without ER pattern in ECG may include several different types of electrocardiographic and clinical manifestation. They show either no specific ECG sign, ventricular conduction disturbance, or short-coupled variant of TdP with normal QT interval. Ventricular tachyarrythmias in most of these cases are initiated by short-coupled PVCs without QT prolongation. Diagnosis of IVF can be made only after resuscitated from VF events excluding structural heart disease and primary electrical disorder. No risk stratification is available at present time and ICD implantation is the only option to prevent SCD.

Take Home Message

- IVF without ER pattern in ECG is a very rare but potentially highly malignant disease.
- IVF without ER pattern in ECG should be considered in anyone resuscitated from VF showing no specific ECG pattern, RBBB, or short-coupled variant of TdP with normal QT interval in a standard 12-lead ECG, without potential other cause.
- Family history of juvenile unexpected sudden death
- One always must think about IVF without ER pattern in ECG in the following case:
  - Aborted cardiac arrest or SCD of unknown origin.
  - Short-coupled PVCs with normal QT interval precede the initiation of PVT.
  - A strong family history of juvenile unexplained sudden death.

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