Inherited Arrhythmias: Brugada Syndrome and Early Repolarisation Syndrome

14

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Abstract

In this chapter a detailed overview on Brugada syndrome and the early repolarisation syndrome is presented. These two disease entities are associated with malignant arrhythmias and sudden death in otherwise healthy young adults and even children. We discuss their history, clinical perspectives (including patient characteristics and epidemiology), the pathway to the diagnosis, pathophysiological mechanisms (including genetic associations) and review clinical risk stratification and treatment. With this chapter we aim to provide a thorough insight in the knowledge base that has developed in these entities in the past decades and we specifically included current debates and uncertainties that are relevant to daily practice and influence our judgements. Undoubtedly our understanding of these syndromes will continue to develop and influence the management of patients and their families in the coming years. Relevant topics for future research in these syndromes are likewise provided. We sincerely hope that this chapter is of practical use for al health care professionals and researchers in this field and that it will contribute to a better understanding and care for affected patients and their families.

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14.1 Introduction: Brugada Syndrome

The brothers Pedro and Josep Brugada described the Brugada syndrome as a distinct clinical entity in 1992. In their initial publication, they reported eight patients with a specific ECG pattern (Fig. 14.1) and repeated episodes of aborted sudden cardiac death [1]. The contemporary concept of Brugada syndrome is a disorder characterized by sudden cardiac death at relatively young age, with familial segregation, an apparent absence of gross structural abnormalities or ischemic heart disease, and specific electrocardiographic characteristics [2, 3]. Sudden cardiac death is caused by fast polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) that typically occur in situations associated with an increased vagal tone. In some patients with Brugada syndrome, fever or drugs provoke the electrocardiographic characteristics and the life-threatening arrhythmias. Brugada syndrome is characterized on the electrocardiogram (ECG) by ST segment elevation directly followed by a negative T-wave in the right precordial leads and in leads positioned one or two intercostal space higher (Fig. 14.2), also referred to as a coved type Brugada ECG [4–6] or type 1 Brugada ECG [3]. This specific ECG hallmark typically fluctuates over time, and in some patients it may only be elicited after provocation with class 1A or class 1C antiarrhythmic drugs [7, 8].

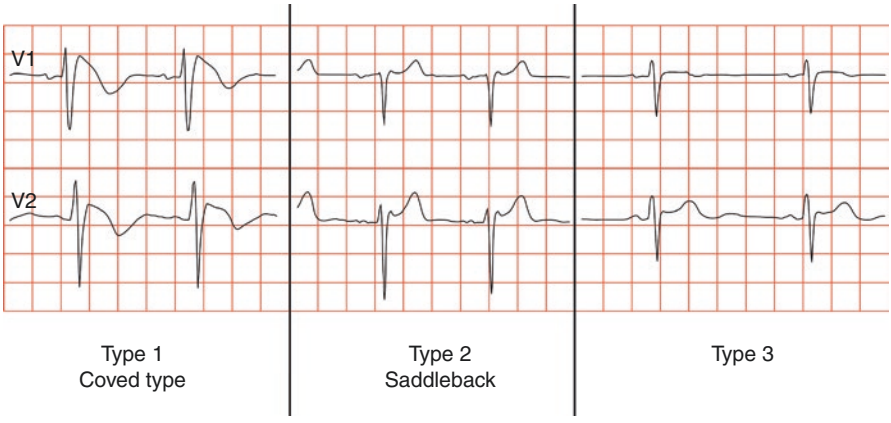

Fig. 14.1 ST segment morphologies recognized in Brugada syndrome: type 1, 2 and 3 (type 2 and 3 also recognized as type 2 only)

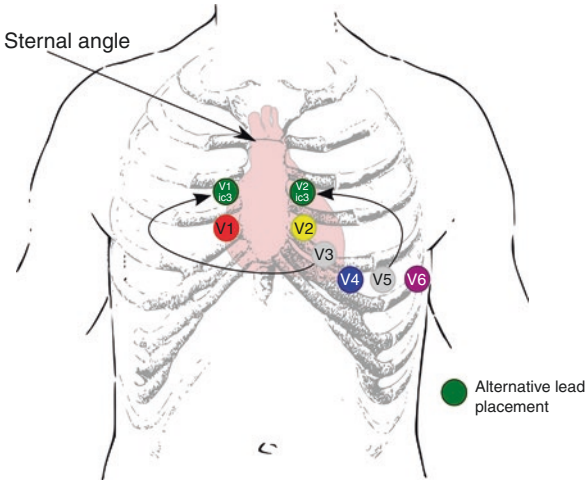

Fig. 14.2 Placement of the ECG leads in Brugada syndrome. For use in practice, V3 and V5 are often relocated from their original positions to V1 in the 3rd intercostal space (V1ic3) and in V2ic3. They may even be placed in the 2nd intercostal space (V1ic2, V2ic2)

In retrospect, the type 1 Brugada ECG was described as early as 1953 in three otherwise healthy patients who presented with atypical substernal discomfort or for routine medical testing [9]. One year later, ten more patients were described with ST elevation in the right precordial leads, including again clear-cut type 1 ECGs, without apparent heart disease and lack of events during follow-up [10]. Furthermore, 3 years before the publication of Brugada and Brugada in 1992, the characteristic Brugada ECG has been described in one out of six cases of VF without apparent heart disease [11].

In the late 1970s and 1980s in the United States, unexplained nocturnal death was reported in many refugees from East and Southeast Asia, mainly men [12]. This pattern of sudden death during sleep was already known for many centuries in Japan by the name Pokkuri (sudden unexpected death at night), and it was often prayed for as to end life without pain and suffering [13]. In the Philippines the same phenomenon is known as Bangungut (moaning and dying during sleep), in northeast Thailand as laitai (died during sleep), and in Laos as non-laitai (sleep death) [14, 15]. When studied, a considerable number of these patients displayed a Brugada-type ECG [14].

Different genes have been associated with Brugada syndrome since its description. First, in the late 1990s, cardiac sodium channel (*SCN5A*) mutations were documented in Brugada syndrome patients [16, 17]. Studies using heterologous expression in Xenopus oocytes demonstrated that these mutations resulted in loss-of-function of the cardiac sodium channels. Well over 300 *SCN5A* mutations associated with Brugada syndrome have been described [18], but *SCN5A* mutations are present in only 15%–30% of clinically diagnosed cases. Some Brugada-'mutations' have been found in control populations as well or were not proven to segregate with the phenotype, challenging their pathogenicity [19–23]. Second, the gene which encodes for the glycerol-3-phosphate dehydrogenase 1-like protein (*GPD1L*), was correlated with Brugada syndrome in a single large family [24, 25]. In their report,

London et al. report a reduction of sodium current in human embryonic kidney (HEK) cells expressing the mutated *GPD1L* gene versus wild-type controls, alike the *SCN5A* mutations linked with Brugada syndrome [26]. Third, loss-of-function missense mutations in the genes encoding for the L-type calcium channel (*CACNA1C*, *CACNB2* and *CACNA2D1*) were reported in Brugada syndrome patients [27, 28]. Additionally, in a subset of these patients carrying a calcium channel mutation, the heart rate corrected QT interval appeared to be shorter than normal. Finally, in rare cases mutations in *SCN1B*, *SCN2B*, *SCN3B, SCN10A*, *KCND3*, *KCNE3*, *KCNJ8*, *ABCC9*, *TRPM4*, *SLMAP, MOG1*, *PKP2*, FGF12, and *HCN4* have been associated with Brugada syndrome [29–43].

Notwithstanding the identification of as yet unknown genetic mutations and pathophysiologic mechanisms, clinical decision making in Brugada syndrome remains a daunting task. Implantation of an implantable cardioverter defibrillator (ICD) is the generally accepted therapy for the prevention of sudden death in patients affected by Brugada syndrome [44–48]. Oral therapy with quinidine may also prove valuable [49–55]. Importantly, risk stratification in asymptomatic patients is heavily debated, as it is still unclear how to correctly identify the large number of patients who will not develop life-threatening arrhythmias and how to prevent overtreating patients with ICD-therapy and its own associated morbidity and mortality [48, 56, 57].

14.2 Clinical Presentation

14.2.1 Epidemiology

The prevalence of the Brugada ECG is estimated at 1/2000 [58]. This is quite similar to long QT syndrome with an estimated prevalence of 1/2000 [59], but less than hypertrophic cardiomyopathy with a prevalence of 1/500 [60]. The exact prevalence of Brugada-like ECGs is difficult to estimate partly because the specific ECG pattern typically fluctuates over time and can be intermittently concealed [61, 62]. Furthermore, many patients with a spontaneous or inducible Brugada ECG are asymptomatic, and therefore will not come under medical attention and will remain without diagnosis. Also higher placed right precordial leads will often not be purposely used. The prevalence of the spontaneous Brugada syndrome ECG also seems to vary between different regions in the world (Fig. 14.3). Brugada syndrome would be most prevalent in East and Southeast Asia, particularly Japan, Thailand, and the Philippines, where it is part of the sudden unexplained (nocturnal) death syndrome (SUDS or SUNDS), which has been described as a major cause of death among young men [14, 92, 93]. In Europe, Brugada syndrome is also quite extensively described [20, 44, 94]. In the northern part of Europe [70] as well as in the United States [90] its prevalence seems to be lower. The worldwide prevalence of the spontaneous type 1 Brugada ECG from current prevalence studies (Fig. 14.3) is 0.05 ± 0.14% and of the type 2–3 ECG this is 0.17 ± 1.38% (n = 437,190).

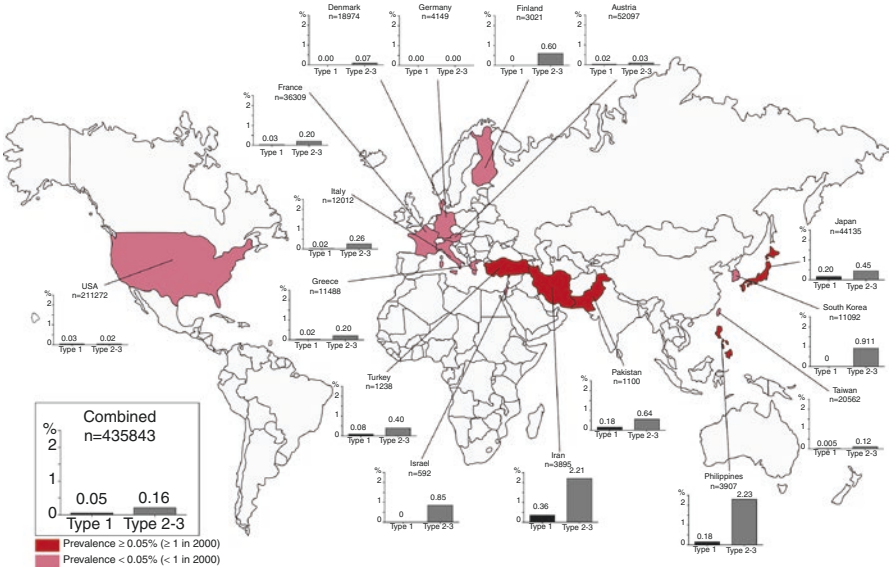

Fig. 14.3 Combined prevalence data of the spontaneous Brugada syndrome ECG in different parts of the world from 2000 to 2012. Bars represent mean prevalence in percentages. Only reports in English were considered. Prevalence studies in adolescents or children [63–65] were discarded for this figure. As the type 1 ECG was only recognized after the first consensus report [3], prevalence in two studies was acknowledged as type 1 only [66, 67], a coved type ECG was acknowledged as type 1, a saddleback or suspicious ECG as type 2–3. It should be noted that the populations studied and the methods used vary importantly. This figure is similar to [58]. Austria [68], Denmark [69], Finland [70], France [71, 72], Germany [73], Greece [74], Turkey [75], Israel [76], Iran [77], Italy [78], Japan [66, 79–83], Pakistan [84], Philippines [85], South Korea [86, 87], Taiwan [88], USA [67, 89–91]

14.2.2 The Patient

Malignant arrhythmic events can occur at all ages, from childhood to the elderly [1, 95, 96] with a peak around the fourth decade [2] of life. To our knowledge, the youngest patient clinically diagnosed with Brugada syndrome was 2 days old, [97] and the oldest 85 years old [98]. It has been estimated that Brugada syndrome is responsible for 4–12% of all sudden cardiac deaths and up to 20% of sudden cardiac deaths in patients without apparent structural heart disease [99]. However, these estimations have not been verified and may well be overestimating the true casualties due to Brugada syndrome. Still, Brugada syndrome may also be a cause of sudden infant death syndrome (SIDS) [95, 100]. Some patients present with palpitations or dizziness, but increasingly the clinical scenario is the detection of a Brugada ECG in an asymptomatic individual [72, 94, 101]. In a meta-analysis in 2007 of 1217 Brugada syndrome patients (defined by a spontaneous or inducible Brugada ECG and excluding case reports) the majority was asymptomatic (59%, range 0–80%) [102]. In a more recent meta-analysis of 1312 subjects the number of asymptomatic patients was even higher (67%) [103].

When sudden death occurs, it is most likely the result of fast polymorphic VT originating from the right ventricle/right ventricular outflow tract [104], which subsequently degenerates into VF leading to cardio-circulatory arrest. The onset of these life-threatening arrhythmias typically occurs in situations with an augmented vagal tone [105], during sleep [106], or after large meals [107, 108]. Indeed, the latter gave rise to the suggestion of the use of a "full stomach test" as a diagnostic tool [109]. Hyperthermia, particularly fever, may also provoke the ECG or arrhythmias in a subset of affected patients [55, 110–114]. Furthermore, a large number of drugs have been reported to induce Brugada syndrome, or Brugada syndrome-like ECG characteristics; for example antiarrhythmic drugs, anti-anginal drugs, psychotropic drugs, and also substances like cocaine and alcohol [2, 3, 115]. Some Brugada syndrome patients may experience agonal respiration at night, when arrhythmias are most prevalent [14, 106]. This is explained by self-terminating VT, which can provoke (recurrent) syncope [116–119]. Clinical presentation with sustained monomorphic ventricular tachyarrhythmia, although quite uncommon, has also been described [120–125].

In most patients, premature ventricular complexes are scarce during 24-hour Holter monitoring, but premature ventricular complexes can occur [116] and may increase before the spontaneous onset of VF [126]. The morphology of the preceding premature ventricular contractions appears to be identical to the first beat of VF. Repetitive episodes of VF may be initiated by premature ventricular contractions of similar morphology [126]. Most premature ventricular contractions have a left bundle branch block morphology, indicating an origin in the right ventricle. There seems to be a predilection site of origin in the right ventricular outflow tract, but also extra systoles from the right ventricular free wall, septum and apex contribute and are capable of initiating VF [104]. Further confirmation of the relationship between these right ventricular extra systoles and VF was derived from a study in three Brugada syndrome patients using endocardial catheter ablation of focal triggers of VF at different sites in the right ventricle [127]. This therapy resulted in the absence of further episodes of tachy-arrhythmias during short-term follow-up. Large studies using this strategy of endocardial ablation of VF-initiating extrasystoles with long-term follow-up are lacking, however. Moreover, epicardial ablation has now emerged as a more promising treatment [128].

Although the most impressive ECG characteristics in Brugada syndrome are the changes in the right precordial leads, other ECG abnormalities are frequently occurring. Supraventricular arrhythmias, mainly atrial fibrillation, are very common with a prevalence between 10 and 39% [129–132]. Supraventricular arrhythmias were found to be more prevalent in patients who had an indication for ICD for either symptoms or inducible VT/VF during electrophysiological study [133, 134]. Importantly, atrial arrhythmias may often lead to inappropriate ICD shocks [47, 48, 56, 57, 134, 135].

For a syndrome that inherits as an autosomal dominant trait with equal transmission to both genders, there is a striking male to female ratio of 4 to 1 [102, 103, 136]. Testosterone is probably a contributor to this gender disparity; surgical castration of two Brugada syndrome patients for prostate cancer normalized their ECGs [137],

and testosterone levels in Brugada syndrome patients were found to be higher when compared to controls [138]. Sex hormones were suggested to modulate potassium and calcium currents during the repolarisation phase of the action potential [139]. Where testosterone may shorten the action potential duration [140], oestrogen may lengthen action potential duration [141]. Furthermore, a different distribution of certain ionic currents, particularly I_{to}, in males versus females may contribute [140]. Whether a difference in, for example, structural changes (fibrosis) may also play a role is uncertain.

14.3 Electrocardiography and Diagnosis

14.3.1 The Brugada ECG

Since its description in 1992, the signature sign of Brugada syndrome is its characteristic ECG [1, 44]. Patients with a spontaneous Brugada ECG and symptoms are considered to be at a high risk for sudden death secondary to VT/VF [44, 46, 94, 103, 136]. The electrocardiographic manifestation of Brugada syndrome is typically dynamic and may often be concealed. The latter has important consequences for risk stratification and follow-up of these patients, as patients with dynamic ECGs can still be at risk for future arrhythmic events [107, 142, 143]. Furthermore, the ECG may be influenced or elicited by hyperthermia and drugs.

The diagnosis of Brugada syndrome requires the demonstration of the "type 1" ECG pattern (Fig. 14.1) [2, 3, 144]. Since 2013, this type 1 Brugada ECG consists of ≥2 mm J point elevation in at least one of the right precordial leads (V1 and V2), in the standard 4th, or in the 3rd or 2nd intercostal space, gradually descending into a negative T-wave (also known as a "coved type" morphology of the ST-T segment). While between 2002 and 2013, V3 was also included but higher right precordial leads were not included in the consensus criteria (although they were increasingly used by many expert centres in the world). In some patients, the Brugada syndrome type 1 ECG is exclusively diagnosed in the leads positioned in the 3rd or 2nd intercostal space [5, 6, 145]. The reason why the characteristic Brugada ECG can be found in different intercostal spaces is most probable due to varying positions of the right ventricular outflow tract [146]. Importantly, with the higher placement of the V1 and V2 leads (Fig. 14.2), sensitivity increases and there do not seem to be false-positive test results [147]. Also the prognosis of patients with a spontaneous type 1 morphology exclusively in the leads positioned in the third intercostal seems to be similar to patients with a spontaneous type 1 morphology in V1 and V2 [148]. However, large prospective and long-term follow-up studies in the use of higher placed V1 and V2 are still lacking.

The type 1 ECG may be spontaneously present or provoked by drugs or hyperthermia. In the first and the second consensus report, the definite diagnosis of Brugada syndrome required, in addition to the type 1 ECG, either documented VT or VF, a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, syncope, inducibility of VT/VF with programmed electrical

stimulation, or nocturnal agonal respiration [2, 3]. In the third consensus report in 2013, these additions were abandoned and only the ECG pattern, in the absence of an alternative diagnosis ('phenocopy'), was regarded sufficient for the diagnosis of Brugada syndrome.

Previously, there were two other ECG patterns recognized in Brugada syndrome, a type 2 and a type 3 ECG, although they are not considered to be specific and, importantly, not diagnostic (Fig. 14.1). Since 2013, these both ECG patterns have been renamed to type 2 patterns. This can be a "saddleback" appearance; consisting of ≥2 mm J elevation followed by a descending ST segment that does not reach the baseline and then giving rise to a positive or biphasic T-wave or a type 3 Brugada ECG with the morphology of a type 1 or saddleback ECG with ≥2 mm J elevation but characterized by a smaller magnitude of the ST elevation (≤1 mm) [144, 149]. Due to its typical dynamic nature, the type 1 ECG can change from and to a type 2 or normal ECG spontaneously or under influence of hyperthermia or drugs. Interestingly, the magnitude of ST elevation does not differ between Brugada syndrome patients with or without a *SCN5A* mutation [22]. As discussed earlier in this chapter, many drugs and substances are capable of inducing a type 1 ECG in patients with Brugada syndrome. For clinical purposes this knowledge is used as a diagnostic tool to evoke a type 1 ECG in patients suspected of Brugada syndrome who do not display a spontaneous type 1 ECG, for example, in case of symptoms (syncope, aborted sudden cardiac death) or as part of familial screening for Brugada syndrome. For this purpose, sodium channel blockers such as ajmaline, flecainide, pilsicainide, or procainamide are mostly used (Table 14.1) [2, 3]. The diagnostic accuracy of drug challenge in patients suspected of Brugada syndrome is higher with the use of ajmaline over flecainide, while equally safe [150]. Safety of drug challenges for Brugada syndrome is ensured when the test is performed using continuously 12-lead ECG monitoring, with cardioverter defibrillators and advanced cardiac life support close at hand and discontinuation of the test when a type 1 ECG is obtained, when ventricular extra systoles or VT develops or when the QRS duration increases more than 30% [3]. As a type 1 ECG is associated with ventricular arrhythmias, drugs or substances associated with a type 1 ECG need to be avoided in patients diagnosed with Brugada syndrome (Table 14.2). Particular attention should also be given to general anesthesia in Brugada syndrome patients [151–155].

Table 14.1 Drugs used for provocation of the Brugada ECG

Drug	Dosage (mg/kg)
Ajmaline	IV 1
Flecainide	IV 2
Procainamide	IV 10
Pilsicainide	IV 1

Notes: IV denotes intravenously. Ajmaline administration particularly differs between studies/centres (e.g., bolus every minute versus continuous administration, total dose in 5 min versus 10 mg/min up to maximal dose). Flecainide may be administered over 10 min or also as 10 mg/min. Flecainide is often maximized at 150 mg. Procainamide and pilsicainide are more routinely administered over 10 min

Table 14.2 Drugs known to induce Brugada or Brugada-like ECGs and arrhythmias

Anti-arrhythmic drugs	
1	To be avoided by Brugada syndrome patients
	Ajmaline, allapinine, ethacizine, flecainide, pilsicainide, procainamide, propafenone
2	Preferably avoided by Brugada syndrome patients
	Amiodarone, cibenzoline, disopyramide, lidocaine, propranolol, verapamil, vernakalant
Anesthetics	
1	To be avoided by Brugada syndrome patients
2	Bupivacaine, Procaine, Propofol Preferably avoided by Brugada syndrome patients Ketamine, Tramadol
Psychotropic drugs	
1	To be avoided by Brugada syndrome patients
	Amitriplyline, clomipramine, desipramine, lithium, loxapine, nortriptyline, oxcarbazepine, trifluoperazine
2	Preferably avoided by Brugada syndrome patients
	Bupropion, carbamazepine, clothiapine, cyamemazine, dosulepine, doxepine, fluoxetine, fluvoxamine, imipramine, lamotrigine, maprotiline, paroxetine, perphenazine, phenytoin, thioridazine
Other drugs and substances	
1	To be avoided by Brugada syndrome patients
2	Acetylcholine, alcohol (toxicity), cannabis, cocaine, ergonovine
	Preferably avoided by Brugada syndrome patients
	Demenhydrinate, diphenhydramine, edrophonium, indapamide, metoclopramide, terfenadine/fexofenadine

Source: Status of www.BrugadaDrugs.org in May 2016, adapted from [115], see www.BrugadaDrugs.org

The administration of isoprotenerol, a β-receptor agonist, and/or quinidine may effectively be used to treat repetitive ventricular arrhythmias or electrical storms [50, 105, 156–159].

As mentioned earlier, hyperthermia also evokes a type 1 ECG or ventricular arrhythmias in a (large) subset of Brugada syndrome patients. Several reports revealed the presence of a type 1 ECG or episodes of arrhythmias during febrile illness, often in children [55, 113, 114, 121, 160–163]. Elevation of the core body temperature e.g. during hot baths may have a similar effect [164] and in Russia hot baths are even discouraged for Brugada patients (www.BrugadaDrugs.org/patient-letter/). It also seems that patients with a fever induced Type-1 ECG have a slightly higher risk than patients with only a drug-induced Type-1 ECG [165]. Treating fever with antipyretic agents such as paracetamol (U.S.: Acetaminophen) and/or antibiotics may prove valuable in these cases. If hyperthermia persists and arrhythmias cannot be counteracted, cooling the patient by all means may be the ultimate rescue (personal communication Dr. Pedro Brugada, ESC congress 2006).

There is a wide differential diagnosis of clinical conditions accompanied by coved-like or elevated ST segments in the right precordial ECG leads, and these should be ruled out before a conclusive diagnosis of Brugada syndrome is made (Table 14.3) [3].

Table 14.3 Differential diagnosis for ST segment abnormalities in the right precordial ECG leads

Abnormalities
Right or left bundle branch block, left ventricular hypertrophy
Acute myocardial ischemia or infarction
Acute myocarditis
Right ventricular ischemia or infarction
Dissecting aortic aneurysm
Acute pulmonary thromboemboli
Various central and autonomic nervous system abnormalities
Heterocyclic antidepressant overdose
Duchenne muscular dystrophy
Friedreich's ataxia
Thiamine deficiency
Hypercalcemia
Hyperkalemia
Cocaine intoxication
Mediastinal tumor compressing right ventricular outflow tract
Arrhythmogenic right ventricular dysplasia/cardiomyopathy
Long QT syndrome type 3
Other conditions
Early repolarisation syndrome
Other normal variants (particularly in men)

Source: Adapted from [3]

When these conditions result in a type 1 or type 2 Brugada ECG these conditions have recently been named Brugada phenocopies [166, 167]. Relatively common causes include early repolarisation [168], myocardial infarction or ventricular aneurysms [72, 169], vasospastic angina [170, 171], electrolyte disturbances such as hyperkalemia or hypercalcemia [172–175], pericarditis or myocarditis [176–178]. The differentiation from Brugada syndrome can be made after resolution of the clinical condition (if possible), followed by performing a Brugada syndrome provocation test (e.g. using ajmaline) when the ECG turned non-diagnostic.

14.3.2 Other Electrocardiographic Characteristics

Other ECG characteristics associated with Brugada syndrome include conduction defects in the atria, conduction system, and ventricles. Frequently present are broad P-waves [145], long PQ interval [22], prolonged corrected sinus node recovery times, prolonged His-Ventricle intervals (HV), which may or may not be accompanied by prolonged Atrio-His (AH) intervals [130, 132, 134], sinus and AV node dysfunction [179], QRS axis deviation [1, 180], and broad QRS complexes [22, 145, 180]. Conduction interval prolongation is frequently associated with the

presence of *SCN5A* mutations [22]. Furthermore, *SCN5A* mutations in Brugada syndrome patients may, as in Lev-Lenègres disease, worsen the phenotypic expression of the disease with ageing and may lead to the necessity of pacemaker implantation [132, 181, 182]. Although there is some variability of the heart rate corrected QT interval (QTc), it does not seem to prolong importantly when a type 1 Brugada ECG or VF develops [1, 126, 145, 180]. This clearly distinguishes Brugada syndrome from long QT syndrome where excessive QTc prolongation is the hallmark of the disease [183]. However, overlap syndromes between Brugada syndrome and long QT syndrome (type 3) exist, based on a multidysfunctional sodium channel caused by specific *SCN5A* mutations [184–188]. Interestingly, the phenotype of one of these mutations (*SCN5A* 1795insD) shares many similarities with mouse model carrying the murine equivalent mutation (*SCN5A* 1798insD) with bradycardia, right ventricular conduction slowing, an increased vulnerability for arrhythmias and QTc prolongation [189]. Conversely, shortened QTc intervals were noted in a subset of Brugada syndrome patients with calcium channel mutations [27]. However, data regarding the calcium channel mutation and/or shortened QTc intervals are limited.

Wide S-waves in the inferior and lateral leads are frequently observed before and after a type 1 ECG develops during drug challenge, which may mirror simultaneous slowing of right ventricular activation [145, 180, 190]. This is reflected in the possible prognostic value of wide and deep S-waves in lead I as a predictor of future VT/VF events [191, 192]. S-waves ≥80 ms in lead V1 appear to be a good predictor for a history of VF [193] but a possible prognostic value is not well studied.

Signal-averaged ECGs show more variation in filtered QRS duration and late potentials in symptomatic patients [105, 107, 194–197]. Late potentials are generally regarded as delayed and disorganized ventricular activation and are related to ventricular tachy-arrhythmias [198]. Particularly in Brugada syndrome, however, other mechanisms have also been proposed: late potentials might for example represent a delayed second upstroke of the epicardial action potential, a local phase 2 reentry [99]. These latter proposals have, however, not yet been validated as primary or cooperative pathophysiologic mechanisms of late potentials in Brugada syndrome (nor in other diseases).

Like late potentials, QRS fractionation or fragmentation is regarded as a sign of delayed and disorganized ventricular activation [199]. In Brugada syndrome, QRS fractionation might also have prognostic value regarding future arrhythmic events [200, 201].

In some reports of patients who presented with VF, ST elevation in the inferior and/or lateral leads has been described in the absence of electrolyte disturbances, hypothermia, or myocardial ischemia [202–207]. In a French family, different *SCN5A* mutation carrying family members displayed either inferior or right precordial coved-type ST segment elevation [208]. At present it still remains uncertain if these patients have the same characteristics as has been described in patients with solely right precordial coved-type ST segments.

14.4 Pathophysiology and Genetics

14.4.1 Arrhythmia Mechanisms

Ventricular arrhythmias in Brugada syndrome often originate from ventricular extra systoles in the right ventricle, which subsequently initiate polymorphic VT or VF. The exact pathophysiology behind Brugada syndrome is, however, still not clear and there might be different electrophysiological mechanisms involved. It seems that an increased vulnerability of the ventricles is present before the onset of VF. The coupling interval (i.e., the timing) of the premature ventricular complex, for example, may be important. In most electrophysiological studies, short coupled extra systoles (<200 ms) were necessary to induce VF while the coupling interval of the first premature ventricular complex of spontaneous VF is often (far) more than 300 ms [105, 126, 201]. There might also be a relation between the vulnerability of the ventricle and the preceding RR interval following for example an extra systole, which may augment ST elevation and eventually degenerate into VF [209]. Notwithstanding the associated risk for sudden cardiac death of a type 1 ECG, it is not necessary for arrhythmias in Brugada syndrome, as was shown in Holter and ICD recordings documentation suggesting that there might be distinct—albeit possibly related—electrophysiological mechanisms involved. Moreover, a substantial number of patients with spontaneous type 1 ECGs will never have any symptoms [9, 10, 210].

14.4.2 The Coved ST Segment

Ever since the first descriptions of Brugada syndrome, authors have been investigating possible mechanisms for this characteristic ECG feature [1, 8, 10, 211–214]. Currently, there are two theories explaining the pathophysiology underlying the Brugada syndrome: the repolarisation and the depolarization hypothesis [215]. Yan and Antzelevitch have developed the repolarisation hypothesis in canine right ventricular wedge preparations [216]. This hypothesis has attracted most support in the first 15 years after the description by the Brugada brothers in 1992. In this canine model, simultaneously measured epicardial and endocardial electrograms showed loss of action potential dome in the epicardium only when the wedge preparation was exposed to a potassium channel opener (pinacidil) or a combination of a sodium channel blocker (flecainide) and acetylcholine. This resulted in a transmural dispersion of repolarisation with different lengths of action potentials across different cardiac layers, ST segment elevation on the ECG and it created a vulnerable window for (‘phase 2’) re-entry to occur between these layers and degenerate into ventricular tachyarrhythmias. Isoprotenerol, 4-aminopyridine, and quinidine were able to restore this loss of action potential dome, normalize the ST segments, and prevent the ventricular arrhythmias. This model resolves around a heterogeneous expression of the transient outward potassium current I_{to}. This current seems to be expressed to a higher degree in the canine epicardium compared with the endocardium [217], in

the right ventricle more than in the left ventricle [218], and in males more than in females [140], resulting in a higher susceptibility for I_{to} augmentation over other currents and a consequential higher risk for ventricular tachyarrhythmias. Relative augmentation of I_{to} would be enhanced by sodium current (I_{Na}) reduction, either by a loss-of-function sodium channel mutation or sodium channel blockade. Furthermore, reduction of the calcium current (I_{Ca}) and augmentation of the ATP-driven potassium current ($I_{K\text{-}ATP}$) would give similar effects [211].

The second hypothesis explaining the coved-type morphology resolves around a depolarization disorder [219] and is now regarded as the leading hypothesis. In this hypothesis, conduction slowing or conduction delay in the right ventricular outflow tract (RVOT) causes the type 1 morphology in the right precordial leads. Most evidence for this model is derived from clinical studies [105, 128, 180, 190, 195–197, 220–223]. The slowing of conduction originates in concert with subtle structural abnormalities (fibrosis, see below) [224]. Furthermore, conduction slowing in concordance with these structural abnormalities will create the vulnerability for re-entrant activation in the right ventricle and give rise to ventricular extra systoles and VT/VF (Fig. 14.4). The marked conduction slowing in atria and ventricles, which is seen during drug challenges with sodium channel blockers and in *SCN5A* mutation carriers particularly, further supports this model [145, 215, 227]. However, as with many diseases, it may be that Brugada syndrome is not explained by one single mechanism [219, 228]. The final common pathway of a spontaneous or inducible coved-type ECG and the vulnerability for ventricular arrhythmias may be started by distinct but cooperative mechanisms and may require tailored risk stratifications and treatment. Moreover, cooperative pathophysiological mechanisms such as structural myocardial abnormalities and gene–gene interactions are probably important modifiers or risk.

14.4.3 Structural Changes

The consensus criteria for Brugada syndrome recommend the exclusion of gross structural myocardial derangements in conjunction with the documentation of a type 1 ECG (see section Electrocardiography and Diagnosis) before a conclusive diagnosis of Brugada syndrome can be made [2, 144]. This reflects the initial hypothesis that Brugada syndrome is an electrical disease involving cardiac ion channel abnormalities and thus requires the absence of structural changes as opposed to, for example, hypertrophic cardiomyopathy. This issue has, however, been debated. Similarities between Brugada syndrome and arrhythmogenic (right) ventricular cardiomyopathy were early on suggested by many centres, even starting before the sentinel paper of the Brugada brothers in 1992 [11, 229, 230]. Biventricular endomyocardial biopsies in 18 Brugada syndrome patients showed myocarditis, cardiomyopathy-like changes, or fatty infiltration in the right ventricle of all patients (without a control group) [231]. Furthermore, in 8 out of these 18 patients (45%) there were similar findings in the left ventricle. Both magnetic resonance imaging (MRI) and echocardiography were negative in all patients. Interestingly, patients

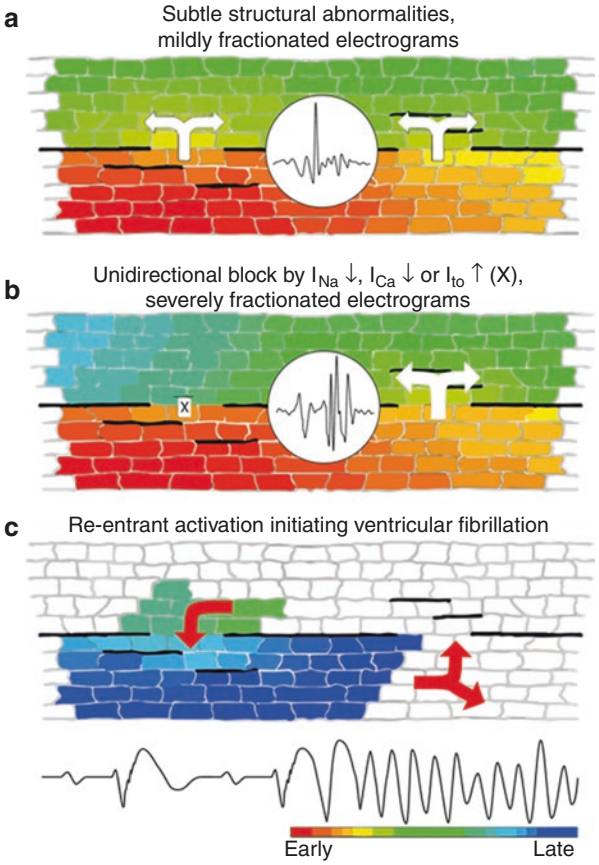

Fig. 14.4 This illustration (adjusted from the illustration of Hoogendijk et al.[225] with permission) shows the induction of re-entrant arrhythmia by current-to-load mismatch in myocardium containing two isthmuses due to subtle structural abnormalities (fibrosis). (**a**) During normal conditions, the redundancy in excitatory current makes conduction successful over both isthmuses and there is no re-entrant activation. Local electrograms will show mild fractionation. (**b**) Reduction of the cardiac sodium current (INa) or L-type calcium current (ICa) or an increase of the transient outward current (Ito) lowers the excitatory current and can cause unidirectional conduction block depending on the local geometry of the myocardium. Here, activation is blocked (X) at the left but not at the right isthmus. Local electrograms will show severe fractionation. (**c**) The asymmetrical distribution of the structural discontinuities at the left isthmus makes conduction in the opposite direction successful, and activation re-enters the proximal myocardium, causing re-entry, which in turn can initiate ventricular fibrillation. The coved type ECG, including fractionation, before the onset of the arrhythmia can be appreciated and is caused by excitation failure in adjacent myocardium in the right ventricular outflow tract [225, 226]. Ablation therapy [128] is targeted at the fractionated electrograms to close the gaps/isthmuses, and thereby resolving the excitation failure (coved type ST segments) and the substrate for re-entrant activation and ventricular fibrillation. Colours depict activation time; black indicates fibrous tissue between myocardial cells

with fatty infiltration and cardiomyopathy-like changes all had a *SCN5A* mutation. In another report, right ventricular fibrosis and epicardial fatty infiltration was documented in the explanted heart of a *SCN5A* mutation carrying Brugada syndrome patient who experienced intolerable numbers of ICD discharges (up to 129 appropriate shocks in 5 months) [232]. This patient also had no clinically detected cardiac structural abnormalities many years before transplant. In an elegant collaboration between different centres with detailed post-mortem and biopsy material analysis again fibrosis, connexion-43 and conduction abnormalities were found in concert [224]. In a study using endocardial mapping it was noted that Brugada syndrome patients showed increased (although still modest) electrogram fractionation and abnormal conduction velocity restitution, both also related to structural changes [190]. Finally, the sentinel report of Nademanee and co-workers on epicardial ablation of the substrate of Brugada syndrome showed complex fractionated electrograms at the RV outflow tract, with ablation terminating the substrate and ECG characteristics of Brugada syndrome [128]. The fractionated electrograms also appeared to coincide with areas of fibrosis [224]. These reports suggest that there are cooperative functional and subclinical structural derangements in Brugada syndrome, which may be enhanced by mutations in the sodium channel. In support of this hypothesis, mice and human data illustrate that *SCN5A* mutations may lead to impressive fibrosis accompanied by conduction disturbances, mainly in the right ventricle, which worsens with ageing [233–236]. Interestingly, a meta-analysis into risk stratification for ventricular tachyarrhythmias did not find an increased risk for patients carrying a *SCN5A* mutation [136]. The uncovering of *PKP2* mutations characteristic for arrhythmogenic (right) ventricular cardiomyopathy in patients with Brugada syndrome (and leading to decreased sodium current) further strengthened the association between structural abnormalities and Brugada syndrome [29, 237]. Fibrosis is probably underdetected in clinical practice as the clinical modalities to assess structural cardiac changes (echo, CT and MRI) are incapable of detecting mild or diffuse abnormalities although mild derangements have been noted [238–242].

14.4.4 Genetics of Brugada Syndrome

SCN5A mutations have been identified in about 15–30% of patients [20, 22]. Although efforts in screening 16 putatively associated genes identified another ion channel (the calcium channel), this still only resulted in a mutation diagnosis in 24% of patients [27]. When Brugada syndrome is present in children however, the amount of uncovered mutations, specifically *SCN5A* mutations, can be considerably higher [243].

The first mutation in Brugada syndrome patients was identified in a collaborative effort of clinics in Europe and the United States in 1998 [16]. A loss-of-function mutation in the *SCN5A* gene, encoding the pore-forming α-subunit of the human

cardiac sodium channel protein (Nav1.5) was present in three out of six families with Brugada syndrome. Mutations leading to loss of sodium channel function can lead to a variety of disorders [244, 245]: Brugada syndrome (OMIM 601144), (progressive) cardiac conduction defects also known as Lev-Lenègres disease (OMIM 113900) [246], sick sinus syndrome (OMIM 608567) [247], Sudden infant death syndrome (OMIM 272120) [95, 100], and dilated cardiomyopathy associated with conduction defects and arrhythmias (OMIM 601154) [248]. In combination with other (atrial-specific modifier) genes, a loss-of-function defect may cause atrial standstill [249]. Mutations leading to a gain of function of the channel may cause long QT syndrome type 3 (OMIM 603830) [250] and also sudden infant death syndrome (OMIM 272120) [251, 252]. As mentioned earlier, certain mutations in the cardiac sodium channel gene may lead to combined phenotypes of loss-of-function and gain-of-function mutations, also referred to as an overlap syndrome [184–187]. *SCN5A* promoter polymorphisms in a haplotype variant may lead to variability in phenotypic expression as was shown in a study demonstrating slower cardiac conduction with a gene-dose effect in patients of Asian origin [253]. The same holds for common *SCN5A* polymorphisms or the combination of different *SCN5A* mutations that may modulate the expression of the mutant gene(s) and disease [254–257].

Loss-of-function cardiac calcium channel mutations have been demonstrated in Brugada syndrome patients [27]. These mutations involved the L-type calcium channel encoded by *CACNA1C* for the pore-forming Cav1.2 α1 subunit, and *CACNB2* for the Cavβ2b subunit involved in channel activation modulation of the α1 subunit. Mutations in the *GPD1L* gene have also been linked to Brugada syndrome in a single family [24, 25] and associates with reduced sodium current. This gene probably does not contribute more than 1% in Brugada syndrome [258, 259].

Exon mutations or duplications in the *SCN5A* gene and a large number of other candidate genes (Caveolin-3, Irx-3, Irx-4, Irx-5, Irx-6, Plakoglobin, Plakophilin-2, *SCN1B*, *SCN2B*, *SCN3B*, *SCN4B*, *KCNH2*, *KCNQ1*, *KCNJ2*, *KCNE1*, *KCNE2*, *KCNE3*, *KCND3*, *KCNIP2*, *KCNJ11*, and *CACNA2D1*) have been investigated in *SCN5A* mutation-negative Brugada syndrome patients with little success [27, 258]. Nevertheless, also mutations in several of these and other genes (*SCN1B*, *SCN2B, SCN3B*, *SCN10A, CACNA2D1, KCND3, KCNE3, KCNJ8, ABCC9, TRPM4*, *SLMAP, MOG1*, *PKP2*, FGF12, and *HCN4*) have finally been associated with Brugada syndrome [28–43]. It should, however, be acknowledged that in many of these reports segregation with the phenotype was not investigated or documented. In addition, variants in all these genes, except *SCN5A*, were also identified in equal numbers, in control patients or in existing next-generation sequencing data cohorts [40, 260]. This importantly challenges the pathogenicity and thus the association with Brugada syndrome of many of these rare genetic variants [23, 40, 260]. Recently it has actually been suggested that Brugada syndrome is not a monogenetic disease but an oligogenetic disease [261], where a (small) number of genetic hits together give rise to the clinical phenotype.

Interestingly, a study revealed common gene expression levels in Brugada syndrome patients irrespective of the culprit gene [262]. This expression pattern involved not only cardiac sodium channel and its subunits, but also potassium channels and calcium channels.

Typically for Brugada syndrome, and other Mendelian disorders, is an incomplete penetrance and variable expression of the disease [263]. Hence, not all mutation carriers are affected by the same degree and will thus not require the same treatment. Even so, the importance of diagnosing mutation carriers with little or no phenotypic expression of the disease is important because they still have a 50% chance of transmitting the genetic defect to their offspring, who in turn may be seriously symptomatic at young age. It is, however, not clear whether presymptomatic genetic testing in children of Brugada syndrome patients is to be advised [264]. As symptomatic Brugada syndrome is rare in children, risk stratification is imperfect, and treatment may do more harm than good (see also the section on Clinical Decision Making), the consequences of a positive test result of presymptomatic genetic testing should be carefully considered [243].

14.5 Clinical Decision Making

14.5.1 Risk Stratification

After diagnosing Brugada syndrome, risk stratification for future ventricular arrhythmias is mandatory. The prognosis and risk stratification of Brugada syndrome patients is, however, debated. Risk for future ventricular arrhythmias is generally accepted to be high in patients who are known to have already experienced life-threatening ventricular arrhythmias, that is, patients with a history of aborted sudden cardiac death. Syncope, dizziness or nocturnal agonal respiration can also be caused by ventricular arrhythmias and are thus often regarded as high-risk features. However, the assumption that these symptoms are indeed arhythmogenic in origin can be erroneous and other causes of these symptoms should also be sought.

A meta-analysis combined a history of sudden cardiac death and/or syncope as representative for a history of ventricular arrhythmias and found a relative risk (RR) of 3.34 [95% confidence interval (CI) 2.13–4.93] for the combined event of sudden cardiac death, syncope, or ICD shock during follow-up [136]. Also male gender, RR 3.47 (95% CI 1.58–7.63), and a spontaneous type 1 ECG versus a drug-induced type 1 ECG, RR 4.65 (95% CI 2.25–9.58), were positively associated with the occurrence of the combined events (sudden cardiac death and/or syncope) during follow-up. A family history of sudden cardiac death, *SCN5A* mutation, or inducible ventricular arrhythmias during electrophysiological study was not associated with events during follow-up in that meta-analysis. Importantly, these risk factors are probably not independent.

As the majority of Brugada patients are asymptomatic but can experience ventricular arrhythmias in the future, there is a dire need for reliable risk stratification in these patients. The role of the inducibility of ventricular arrhythmias during electrophysiological study in this matter has long been debated [2, 3, 46, 94, 265, 266]. A meta-analysis in 2007 to assess its prognostic role was not able to identify a significant role with regard to arrhythmic events during follow-up [102]. In a combined effort of 14 centres in France and Japan, it was shown that 45% of the 220 studied Brugada syndrome patients received an ICD following inducibility of ventricular

arrhythmias during electrophysiological study whilst being asymptomatic [47]. In this study there was an 8% rate of appropriate shocks for ventricular arrhythmias during >3 years follow-up, and a relatively low (2 to 5 times lower) rate of appropriate shocks in asymptomatic patients compared to the patients with syncope or aborted sudden cardiac death. There were no other factors (like a spontaneous type 1 ECG) apart from a clinical history of syncope or aborted sudden cardiac death predicting appropriate shocks. Of importance, approximately 20% of patients in each group suffered from inappropriate shocks during follow-up. In a follow-up study in 2013 [48], the number of asymptomatic patients implanted with an ICD because of inducibility had grown to 87%, notably some in combination with other risk factors such as a spontaneous type 1 ECG. Interestingly, the number of patients who had already experienced a cardiac arrest and were inducible was lower (53%) than the number of patients who were asymptomatic and were inducible (87%). Again, inducibility could not be identified as a useful parameter to separate the patients who will and who will not progress to arrhythmias during follow-up. Importantly, ICD-complications, including fatal events, did occur in these patients with a primary prevention ICD. This notwithstanding, being asymptomatic at inclusion, still associated with about 1% of appropriate ICD interventions per year. Whether all these patients were indeed saved from a sudden death will never be known [267] but probably some of these events (if not a considerable number), would have been terminated spontaneously without sudden death. Importantly, programming longer detection intervals and higher cut-off rates for VF also seems to reduce inappropriate shock rates without compromising ICD safety [48, 268]. In 2016, another meta-analysis on inducibility was published, also including data from earlier studies [103]. In this paper, in contrast to earlier studies, additive value of inducibility to symptoms and presenting ECGs was found. Still it should be noted that 527 out of 1312 patients (40%) was inducible, while 65 patients (5%) experienced events (5 with sudden cardiac arrest and 60 with ICD shocks, 21 of whom being asymptomatic at presentation) during a median follow up of 38 months.

Non-invasive risk stratification has been attempted in relatively small cohorts of patients and yielded the strongest predictive value in spontaneous changes in the right precordial ST segments [107, 142, 143]. A standard cardiology workup including echocardiogram, 24-hour Holter, and an exercise test may be valuable to exclude differential diagnoses and to assess baseline conditions. There could be added value in 24-h 12-lead Holter monitoring as a number of patients with spontaneous type-1 ECGs will be uncovered [61, 62]. Thorough cardiac imaging using MRI or CT does not seem to add significant clinical value at present, unless arrhythmogenic right ventricular cardiomyopathy needs to be excluded.

A summary of the current literature on risk stratification in patients who did not yet experience a cardiac arrest, suggests that symptoms likely to be related to ventricular arrhythmias in combination with a spontaneous type-1 ECG identifies the patients at highest risk for future life-threatening arrhythmic events. Conversely, as asymptomatic patients without a spontaneous type-1 ECG have a (very) low risk of experiencing these arrhythmias, and the currently available treatment option (ICD implantation) may do more harm than good [56, 57], they should be identified as

low risk. The combination of several characteristics to assess the risk profile is probably very worthwhile, and has been suggested [269, 270]. Undoubtedly, risk stratification should be re-evaluated in all patients during long-term follow-up using up-to-date consensus criteria.

14.5.2 Treatment

The most effective therapy to treat ventricular arrhythmias in Brugada syndrome is an ICD. Patients may, however, still experience intolerable numbers of ICD shocks, up to 150 a day [121], as an ICD does not lower the vulnerability of the heart for ventricular arrhythmias and ICDs are often programmed to quickly react—probably also treating VT/VF episodes that would have terminated spontaneously [267]. In some patients in earlier days, heart transplantation has been considered to be the only remaining option to diminish VT/VF events [271]. Cardiologists should carefully weigh possible benefits versus possible harm, quality of life, and costs of ICDs, as event rates are generally low and complications (in particular inappropriate shocks) are high in this population [47, 48, 57]. ICD implantation in the young specifically denotes several battery replacements, re-implantations over many decades, increased morbidity and even ICD-related mortality [48]. Still, in individual cases it might be considered to also implant an ICD in Brugada patients who are considered to have a low risk profile but who have an intolerable and uncontrollable anxiety that severely diminishes their quality of life and impairs their daily activities e.g. because they have lost a family member due to sudden cardiac death.

Acute lowering of the vulnerability of the heart for ventricular arrhythmias may be accomplished by treating hyperthermia (e.g., cooling, antipyretics, antibiotics), correcting electrolyte disturbances, and the administration of quinidine and/or isoproterenol [55, 110, 157, 160, 162]. Further chronic oral treatment with quinidine or several other agents may also prove valuable [50, 52, 272–279]. Excluding differential diagnoses in case of acute events is still mandatory as tachyarrhythmias not due to Brugada syndrome may display a devastating response on isoproterenol [280].

All patients with Brugada syndrome should receive a list of avoidable drugs and substances, including a number of antiarrhythmic drugs (particularly several class Ia & Ic drugs), psychotropic drugs (e.g. tricyclic antidepressants and lithium), anaesthetics (e.g. bupivacaine and propofol) and substances like cocaine, and excessive use of alcohol; see www.BrugadaDrugs.org [115]. Of note, some of these drugs, particularly propofol have been used frequently without untoward events. Still, the increased risk for arrhythmias should be recognized and be anticipated on. Furthermore, patients should be instructed to obtain an ECG in case of fever at least once (and if negative maybe every 5 years or so) to assess whether their form of Brugada syndrome is hyperthermia sensitive.

Special interest has emerged in the last years for ablation therapy to prevent (or even cure?) ventricular arrhythmias [127, 128, 281–283]. Especially the epicardial approach with ablation of late and fractionated electrograms of the right ventricular outflow tract seems to be very promising with abolition of inducibility, resolution of

the characteristic ECG and a diminishing of recurrent episodes of VT/VF [128]. A randomized trial is currently prepared and should provide the first results around 2020 [284].

Long-term follow-up is mandatory in all Brugada syndrome patients. Symptomatic patients will have more frequent visits, but also asymptomatic patients should be seen with regular intervals for reassessment of the risk for arrhythmic events and genetic counselling in case of children. Genetic counselling should be advised for all adult patients.

14.6 Future Research

The knowledge and awareness of Brugada syndrome will continue to increase. In the first years after the description in 1992, many severely symptomatic patients were recognized, which led to the notion that Brugada syndrome is a malignant disease that is hard to manage [1, 44]. However, many asymptomatic patients have now been diagnosed and one of the great challenges for the future is to develop reliable risk stratification for arrhythmic events in this group of patients [144, 285]. Risk stratification and treatment in the paediatric population affected with Brugada syndrome, although limited in numbers, should also receive our continued attention. The pathophysiology of the ventricular arrhythmias and the coved-type ECG in the right precordial leads has been and will continue to be a major area of research. Although many animal and computer models are available, detailed descriptions of human data will continue to be important and will guide therapeutic interventions. Finally, further characterization of the (potentially complex) genetic origin of Brugada syndrome will help to identify those silent carriers, and their offspring, who might be at risk and may clarify the complicated genotype–phenotype relationship in Brugada syndrome patients.

14.7 Early Repolarisation Syndrome

14.7.1 Introduction

Already in 1936, in the era of the string galvanometer, common variations at the end of the QRS complex and the early ST segment were described. Shipley and Hallaran (Cleveland Ohio) noted in their study of 200 healthy men and women between the age of 20 and 35 (i.e. before the possible onset of significant coronary artery disease), and with a normal physical examination, in up to 44% percent of traces slurring or notching of the terminal QRS occurred [286]. In the same paper, ST-elevation was noted in up to 25% of males and up to 16% in females. In the years thereafter, also in 12-lead ECGs and in vectorcardiograms, ST-elevation, notching and slurring was found to be a frequent finding in apparently healthy individuals, particularly in young and athletic individuals and in those from African descent [287–291]. The term ‘early repolarisation’ to describe (common) inferolateral ST-elevation has

been attributed to Grant, Estes and Doyle in their 1951 paper on the 12-lead ECG and vectorcardiogram [292, 293]. In later years, some authors even used the statement early repolarisation *syndrome* to describe this normal variant with ST-elevation, notching or slurring in the inferolateral leads [294, 295]. Currently we use early repolarisation *syndrome* only for those patients with an early repolarisation *pattern* in conjunction with a history of otherwise unexplained malignant ventricular arrhythmias [144].

Although considered a benign variation for decades [293, 294, 296], also because of its frequent occurrence in the young and healthy, since the 1990s several case reports of 'idiopathic' ventricular fibrillation with the presence of inferolateral ST elevation were published [202, 205, 297]. In 2008 the interest in early repolarisation, including notching and slurring, truly pivoted with the near simultaneous publication of two cohort studies investigating an association between the occurrence of malignant ventricular arrhythmias and an inferolateral early repolarisation pattern. Haïssaguerre and colleagues from 22 centres reviewed 206 case subjects who were resuscitated after cardiac arrest due to idiopathic ventricular fibrillation and compared these patients to 412 matched control subjects without obvious heart disease [298]. It appeared that an elevation of the QRS–ST junction of at least 0.1 mV from baseline in the inferior or lateral leads, manifested as QRS slurring or notching, was more frequent in case subjects (31 vs. 5%, $p < 0.001$). In a very comparable study, albeit with lower numbers, almost simultaneously published by Rosso and colleagues from three centres [299], 45 patients with idiopathic ventricular fibrillation were compared to 124 matched control subjects. Again, J-point elevation, particularly in the inferior and lateral extremity leads, was more common among cases (42 vs. 13%, $p = 0.001$). One year later, in 2009, a large community based study of 10,864 middle-aged subjects also noted an association between ST-elevation in the inferior leads and an increased risk of death due to cardiac causes [300]. Since then, many more papers have been published on the association between early repolarisation and an increased risk for cardiac events [301–304].

Still, in the AHA/ACC/HRS 2009 consensus statement on ECG interpretation, early repolarisation was continued to be described as 'a statement that is used frequently to characterise a normal QRS-T variant with J-point elevation' [305]. In 2011, two distinguished electrocardiographists even labelled the statement early repolarisation (and its accomplice 'J-wave') to be inappropriate and confusing [306]. In 2013, in the HRS/EHRA/APHRS consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, the diagnosis of early repolarisation *syndrome* was reserved for those subjects who actually were resuscitated from otherwise unexplained ventricular fibrillation or polymorphic ventricular tachycardia in the presence of J-point elevation ≥0.1 mV in ≥2 contiguous inferior and/or lateral leads [144]. The early repolarisation *pattern* could be diagnosed with the same criteria but in the absence of (a strong suggestion of) malignant arrhythmias [144]. However, ongoing debate on nomenclature and definitions of early repolarisation led to the establishment of another consensus statement by many of the previous mentioned authors and specifically included terminal QRS notching or slurring *without* the need for ST-segment elevation [307].

A genetic basis for the early repolarisation syndrome is still under investigation and is currently suggested by anecdotal observations of an increased familial appearance of the early repolarisation pattern in concert with otherwise unexplained sudden deaths [308, 309]. In search for genetic variants in one severely affected patient, a *KCNJ8* gene variant was uncovered in a candidate gene approach including 21 genes [310]. However, in the same study an additional 156 early repolarisation syndrome patients were also tested for variants in *KCNJ8*, but this analysis failed to identify more proof of an association of early repolarisation syndrome with genetic variants in *KCNJ8*. In other candidate gene approach studies, variants in *KCNJ8* (the same variant), *CACNA1C*, *CACNB2*, (both unsuccessfully tested in the previous *KCNJ8* study) and *CACNA2D1* were documented as possible susceptibility genes for early repolarisation syndrome [28, 41]. However, in a subsequent study this specific *KCNJ8* variant (S422L) was found to be actually very common in Ashkenazi Jews, and not apparently associated with early repolarisation, not even in a homozygous boy [311]. In 2015 however, in the ESC guideline on ventricular arrhythmias, it was still claimed that no clear evidence of familial transmission of the early repolarisation syndrome exists [312]. This is mainly due to the relatively frequent occurrence of these variants in patients or cohorts without signs of early repolarisation syndrome.

The treatment of early repolarisation syndrome, in line with the 2013 consensus statement, is particularly aimed at preventing sudden death from recurrent malignant arrhythmia by a secondary prevention ICD implantation. During electrical storm isoproterenol can be useful in patients with a diagnosis of early repolarisation syndrome, while quinidine can be useful for secondary prevention of malignant arrhythmias in these patients [144, 313].

14.7.2 Clinical Presentation

14.7.2.1 Epidemiology

The prevalence of the early repolarisation pattern in the general population has been estimated at 1–13% but increases to 15–70% when studying cases of idiopathic ventricular fibrillation [298–301, 303, 314–317]. Differences in the prevalence of early repolarisation are mainly due to the type of population studied and the definition of early repolarisation that is used. Also, studies have shown that the early repolarisation pattern is intermittently present [315], which challenges the determination of its exact prevalence. Even though no clear regional differences in its prevalence have been observed, as for example have been seen in the Brugada syndrome, the early repolarisation pattern is more prevalent among blacks than in whites [318]. One study observed a higher prevalence of early repolarisation in aboriginal Australians compared to white Australians [319]. A rather high prevalence of the early repolarisation pattern has also been reported in a Japanese cohort of atomic-bomb survivors [301].

Early repolarisation is further predominantly found in the paediatric population, in males, young physically active individuals and in athletes [320]. In the athletes, case-control studies have estimated the prevalence of the early repolarisation

pattern between 10 and 90% [321], and also here it is thought that the early repolarisation pattern is a most often a benign variant and associated with a low risk of arrhythmic events. It has been hypothesized that early repolarisation is influenced by hormonal factors since its prevalence is higher in the paediatric population. Furthermore, after puberty its prevalence increases (16–25%) in male subjects and decreases in female subjects (11–4%) [322, 323].

14.7.2.2 The Patient

Only an extremely small minority of the patients with the early repolarisation pattern will ever experience any symptoms of the early repolarisation *syndrome* (i.e. ventricular fibrillation), this is partly due to the high prevalence of the early repolarisation *pattern* in the young and healthy [321]. The early repolarisation pattern may be intermittently present and is can be modulated by vagal tone, heart rate and drugs [313, 316, 324, 325]. The Valsalva manoeuvre may unmask the early repolarisation pattern on the ECG. However, the sensitivity of the test is low (45%), and evidence relies predominantly upon one study [308]. Disappearance of the pattern may occur during exercise and infusion of isoproterenol [325].

Before the onset of VF, an increase in the amplitude of early repolarisation, can be seen as compared to baseline values [298, 326, 327]. For example, in the study of Haïssaguerre the J-point amplitude increased from 2.6 ± 1 to 4.1 ± 2 mm ($P < 0.001$) before the onset of VF [298]. This initial increase in the amplitude of the ERS may be subsequently followed by a ventricular ectopic beat with a short coupling interval that initiates ventricular fibrillation. It appears that this ectopy preceding VF most often arises from the left ventricle inferior wall [298]. In a follow-up study of IVF patients, patient with ERS had a higher risk for future cardiac events (41 vs. 23%) (HR 2.1; 95% confidence interval (CI), 1.2–3.5; $P = 0.008$) compared to those without ERS [298].

In the general population, the early repolarisation pattern has also been linked to an increased risk of cardiac events. A community based prospective study [300], analysed 10,864 Finnish subjects with a mean age of 44 ± 8 years old. In this study, patients with a J-wave amplitude of ≥0.1 mV in the inferior leads carried an increased risk of death from cardiac causes (adjusted relative risk (RR) 1.28, confidence interval (CI) 1.04–1.59) and this relative risk rose even further in patients with a J-wave amplitude of >0.2 mV in the inferior leads (adjusted RR 2.98; 95% CI 1.85–4.92) and from arrhythmia (adjusted RR 2.92; 95% CI 1.45–5.89). In another population-based prospective study including 1945 patients [303], the presence of an early repolarisation pattern was associated with cardiac and all-cause mortality, especially in those of younger age (35–54 years old) and male sex (hazard ratio 2.65; 95% CI 1.21–5.83). An inferior early repolarisation pattern further increased cardiac mortality (hazard ratio 3.15; 95% CI 1.58–6.28) for both sexes and particularly in male subjects between 35 and 54 years of age (hazard ratio 4.27; 95% CI 1.90–9.61). Important in this respect is that there seems to be a time dependent risk over very long follow-up (up to 20 years). Whether the early repolarisation pattern was still present before the event and what the association is with comorbidities like, e.g., ischaemic heart disease, is uncertain however.

Other studies have shown that the presence of the early repolarisation pattern may be a modulator of risk for sudden death in the setting of comorbidities. Tikkanen et al. studied the association between early repolarisation and risk of sudden death during an acute coronary event [328]. In this case-control study including 432 cases with a mean age 66 ± 11 years they found that the risk of sudden cardiac death was increased in patients with the early repolarisation pattern (odds ratio (OR), 1.85; 95% CI, 1.23–2.80). Specifically, in those patients with an early repolarisation pattern with a horizontal/descending ST segment predicted the occurrence of sudden cardiac death (OR, 2.04; 95% CI, 1.25–3.34). After multivariate adjustments the presence of the early repolarisation pattern with horizontal/descending ST segment remained as independent predictors of sudden cardiac death. A comparable association of increased risk of cardiac events in the setting of other pathologies has been observed in patients with inherited cardiac arrhythmia syndromes. For example, in a retrospective cohort study of catecholaminergic polymorphic ventricular tachycardia (CPVT) patients, those with an early repolarisation pattern were at increased risk for arrhythmic events when compared to CPVT patients without early repolarisation [329]. Such an association has also been found in the long QT syndrome type 1 and type 2 [330] and in Brugada syndrome [204].

14.7.3 Electrocardiography and Diagnosis

The diagnosis of early repolarisation syndrome is made *per exclusionem*. In survivors of a cardiac arrest due to ventricular fibrillation or polymorphic ventricular tachycardia, an extensive work-up in search of a diagnosis is recommended [312]. This will often include sequential ECGs and 24-h ECG-monitoring, coronary angiography and echo, while also exercise testing, detailed ECG analysis using signal averaging or brisk standing, magnetic resonance imaging (MRI), drug provocation with sodium channel blockers and endocardial biopsies should be considered. When all these tests turn negative while at the same time a clear early repolarisation pattern is evident, a diagnosis of early repolarisation syndrome can be made [144, 331, 332].

The criteria for the early repolarisation pattern have been susceptible for discussion and are not uniform across many papers (Fig. 14.5). One consensus statement on this topic specifically includes terminal QRS notching and slurring with or without concomitant ST-elevation as essential to the early repolarisation pattern [307]. Their definition incorporates terminal QRS notching or slurring with either elevation of the QRS–ST junction (also named J-termination or ‘Jt’) of at least 0.1 mV from baseline and/or elevation of the J-peak (in the case of a notch) of at least 0.1 mV from baseline in the inferior or lateral leads. Moreover, the consensus view of that group of authors was that in the absence of terminal QRS notching or slurring, ST- or Jt-elevation alone should *not* be reported as early repolarisation [307]. This last statement could clearly be in conflict with the HRS/EHRA/APHRS

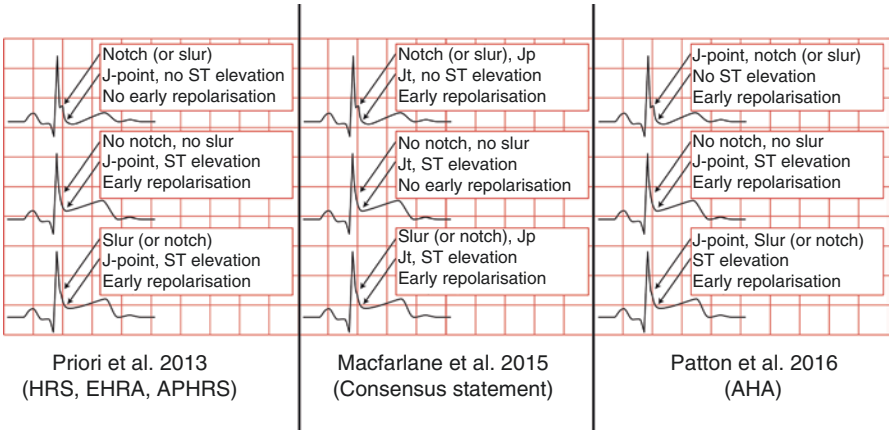

Fig. 14.5 Early repolarisation pattern examples and classification according to different statements [307, 333, 334]. Jp denotes J-peak, Jt denotes J-termination (a.k.a. QRS end or J-point). In the Patton paper the J-amplitude/ST elevation is measured at the peak of the notch or the start of the slur, instead of at the end of the QRS. In all statements, ST elevation, J-point or J-peak should be ≥0.1 mV and present in ≥2 contiguous inferior and/or lateral leads

2013 consensus statement which *only* mentions J-point elevation ≥0.1 mV in ≥2 contiguous inferior and/or lateral leads [144]. This is because the J-point is generally considered to be the QRS-ST junction or J-termination and when elevated this does not necessarily combine with a notched or slurred terminal QRS. In the 2016 AHA scientific statement yet another definition is suggested, [333] which also seems to be in conflict with the 2015 Macfarlane paper. In this 2016 AHA statement, early repolarisation includes ST- or Jt-elevation *with* or *without* notching or slurring (similar to the 2013 HRS/EHRA/APHRS statement). However, specific to this statement, the measurement of the J-elevation is performed on the peak of the notch or at the start of the slur, as opposed to the 2013 and 2015 statements.

Another important aspect of early repolarisation is the direction of the ST-segment; being either horizontal or down-sloping versus upsloping [335]. Tikkanen et al. in a follow-up paper of their earlier study, evaluated the ST-segment in athletes and in middle-aged subjects from the general population, and noted that only a horizontal or down-sloping ST-segment after terminal QRS-notching or slurring associated with an increased risk for arrhythmic death [300, 336]. Also a secondary analysis of the Rosso study showed that a horizontal or down-sloping ST-segment was more common in the subjects who suffered from idiopathic ventricular fibrillation than in the control subjects [335]. This has led to the suggestion to describe the early repolarisation pattern as either benign (upsloping) or malign (horizontal or down-sloping) [335]. This does not imply, however, that an upsloping ST-segment after a QRS notch or slur is always benign, as still about 30% of patients with early repolarisation syndrome will only show this 'benign' pattern [335, 337].

14.7.4 Pathophysiology

The pathophysiological mechanisms underlying early repolarisation syndrome are currently far from clear. The absence of a well-defined genetic substrate, the common occurrence of the early repolarisation pattern in the young and healthy, and the obligatory absence of any other known primary electrical disease or (signs of) cardiomyopathy, complicates this further. Although some authors have shared early repolarisation syndrome and Brugada syndrome under the common denominator 'J-wave syndromes' [338], others have opposed this practice [306, 339]. Whether the notching or slurring of the terminal QRS complex is actually a depolarisation or a repolarisation phenomenon is also still unclear [339–341]. Certainly there is a clear distinction between the mechanisms underlying Brugada syndrome and early repolarisation syndrome as is mirrored on the reverse reaction on different provocations and the inherent difference in the localisation of the aberrant ST-elevation. While in early repolarisation tachycardia, hyperthermia, isoproterenol and sodium blocker administration will decrease the ST-elevation, it will increase ST-elevation in Brugada syndrome [110, 180, 324, 325, 342–344]. Also, in Brugada syndrome there is evidence of conduction delay and of abnormal endocardial and particularly epicardial electrograms [22, 128, 190], while this is not the case in early repolarisation syndrome [337]. In contrast, in both Brugada syndrome and early repolarisation syndrome, an increased vagal tone is associated with ST-elevation [105, 109, 308, 337].

14.7.5 Genetics

For the comprehensive and authoritative Online Mendelian Inheritance in Man compendium, early repolarisation associated with ventricular fibrillation (OMIM 613601) still awaits confirmation of a genetic association [245]. The first study into the genetic underpinning of early repolarisation syndrome was published in 2009 by the group of Haïssaguerre et al. shortly after their pivotal 2008 paper [298, 310]. In this study, a severely affected 14-year-old female is described who suffered from >100 cardiac arrests due to ventricular fibrillation and displayed a prominent early repolarisation pattern (mostly prominent notching). Detailed genetic evaluation of many candidate genes (*KCNQ1*, *KCNE1*, *KCNH2*, *KCNE2*, *KCNJ2*, *KCNJ8*, *KCNJ11*, *ABCC9*, *KCNJ5*, *KCNJ3*, *KCND3*, *IRX3*, *IRX5*, *SCN5A*, *SCN1B*, *NCX1*, *CACNA1C*, *CACNB2*, *CALR*, *CASQ2* and *ANK2*) revealed a missense variant (p.S422L) in the *KCNJ8* gene encoding the Kir6.1 subunit of the K-ATP channel. This variant was absent in 764 control alleles from healthy controls, and, importantly, was also absent in a cohort of 156 additional early repolarisation syndrome patients. The mother of the patient did not have this same variant and the father denied testing, so no segregation analysis was available. In the year thereafter, an association with the *KCNJ8*-S422L variant was replicated by Medeiros-Domingo et al. [41]. In this study 101 unrelated patients with Brugada syndrome (n = 87) or early repolarisation syndrome (n = 14), were evaluated for *KCNJ8* variants, and in 1 Brugada patient and in 1 early repolarisation syndrome patient the same S422L variant was found (and absent in

1200 control alleles). Additional analyses showed that this variant was able to significantly increase the K-ATP current of Kir6.1, suggesting a gain-of-function mutation. However, in sharp contrast to these two studies suggestive of a pathogenic role for *KCNJ8*, and particularly for the S422L variant, in a subsequent study in Ashkenazi Jews this association was questioned [311]. The *KCNJ8*-S422L appeared to be rather prevalent in this population (4%) and was not apparently associated with an early repolarisation pattern nor syndrome, not even in a homozygous boy.

Further studies into the genetic underpinning of early repolarisation syndrome suggested a role for calcium channel mutations. Burashnikov et al. evaluated multiple candidate genes (*CACNA1C*, *CACNB2*, *CACNA2D1*, *KCNH2*, *KCNQ1*, *KCNJ8*, *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, *SCN1B*, and *SCN3B*) in a cohort of unrelated probands with Brugada syndrome (n = 162), early repolarisation syndrome or pattern n = 24) and idiopathic ventricular fibrillation (n = 19). In their patients with early repolarisation syndrome or pattern, they found mutations in *CACNA1C*, *CACNB2* (both unsuccessfully tested in the 2009 *KCNJ8* study) and *CACNA2D1*. However, these variants were still only found in single cases among many tested subjects without proof of familial segregation.

There have also been reports of other possible associated genes, particularly *SCN5A*. One report suggested loss-of-function mutations in *SCN5A* to be associated with early repolarisation syndrome in the absence of a Brugada phenotype in 3 out of 50 early repolarisation syndrome patients [345]. However, in this report there was clear evidence of conduction slowing and abnormal right precordial ST segments in these three patients, while a Brugada syndrome was not definitely excluded in the absence of potent sodium channel blockade with ajmaline or higher placed right precordial leads. Again, familial segregation was not demonstrated. In another report the *ABCC9* gene was implicated to be associated with the early repolarisation syndrome [37]. In 4 out 150 probands with either the early repolarisation pattern of syndrome or Brugada syndrome, a variant in the *ABCC9* gene was found. One of the tested variants indeed caused a gain-of-function of the K-ATP channel Kir6.1. These authors also reported that the father of one of these patients also carried the same variant and also showed the early repolarisation pattern, now indeed suggesting familial segregation.

As mentioned earlier, in the 2015 ESC guideline on ventricular arrhythmias, it is stated that no clear evidence of familial transmission of the early repolarisation syndrome exists [312]. There are, however, reports on early repolarisation in families [308, 309]. In the Nunn et al. study, family members of probands diagnosed with the sudden arrhythmic death syndrome (SADS), were evaluated and were compared to matched controls. They found that inferolateral J-point elevation was more common in SADS-relatives as compared to controls (23 vs. 11%) and suggested that this inferolateral J-point elevation may indeed be a marker of pro-arrhythmic trait or even a marker of pro-arrhythmia. In the Gouraud et al. study, the relatives of four families affected by the early repolarisation syndrome were studied. They found that an early repolarisation pattern was indeed common among family members (33–61%), and suggestive of an autosomal dominant mode of inheritance.

An inherent problem in the genetic underpinning of early repolarisation syndrome remains that the alleles from a (phenotyped) control cohort can barely cover

the extremely low incidence of the cases with a genetic variant. As long as there is no proof of genetic linkage with the phenotype a plausible genetic explanation for early repolarisation syndrome will remain a challenging issue. Illustrative to this point is that the largest study into the identification of genetic variants predisposing to the early repolarisation *pattern* did not provide supporting evidence for a genetic substrate [346]. In this study, a genome-wide association meta-analysis in 7482 subjects for the discovery stage, and in 7151 subjects for the replication stage (combined prevalence of the early repolarisation pattern 2.9–9.8%), no variants found in the discovery stage could be replicated. Combined meta-analysis results also failed to reach genome-wide significance.

14.7.6 Clinical Decision Making

14.7.6.1 Risk Stratification

Risk stratification in early repolarisation syndrome is not particularly difficult; as these patients have already experienced malignant ventricular arrhythmias resulting in cardiac arrest and resuscitation, these patients have a class I indication for secondary protection by an ICD [144]. However, the problem in risk stratification arises in those with an early repolarisation pattern. As mentioned earlier, an upsloping ST-segment is considered to be more probable benign, while a horizontal or downsloping ST-segment is considered to be more probable malignant [300, 335, 336]. This knowledge base underlies a class 2b recommendation to consider prophylactic ICD implantation in patients with a malignant early repolarisation pattern and/or in those with a previous syncope suggestive to be a tachyarrhythmia [144]. Importantly, there are currently no other parameters of risk in early repolarisation, including programmed stimulation [347]. In asymptomatic patients with an isolated early repolarisarion pattern, prophylactic ICD implantation is not recommend (class III recommendation) [144]. Whether patients with an overlap phenotype of Brugada syndrome and an early repolarisation pattern have a distinct risk profile is currently uncertain and it is advised to follow the regular risk stratification process for both.

14.7.6.2 Treatment

As mentioned earlier, secondary prevention for sudden death due to malignant arrhythmias can be established with ICD implantation. In a multi-centre study on drug therapy in early repolarisation syndrome it was documented that isoproterenol can be used to treat patients during electrical storm and that quinidine can be used to suppress recurrent arrhythmias on the long term [313]. Importantly, the other tested drugs in this cohort were ineffective to control arrhythmias and included mexiletine, verapamil, flecainide, propafenone, pilsicainide and also amiodarone (the latter seemed to be effective in 1 out of 6 patients during electrical storm though). There is currently no evidence that patients with early repolarisation syndrome should avoid specific drugs, in contrast to Brugada syndrome, Long QT syndrome and catecholaminergic polymorphic VT.

14.7.7 Future Research

Although the early repolarisation pattern has been known since the early years of electrocardiology (even before the recognition of the importance of a prolonged QT interval), the early repolarisation syndrome is a rather new entity. As mentioned earlier, we are also still struggling with the definition of the early repolarisation pattern, precluding uniformity in the research in this area. Another very important issue in the coming years will be to gain experience in the recognition of patients without symptoms but a high propensity for malignant arrhythmias in the future. These patients could be prophylactically treated with quinidine for example. However, as the early repolarisation pattern affects 5–60% and seldom up to 90% of investigated cohorts of presumably healthy individuals, and true early repolarisation syndrome is a particularly rare entity, this unmistakably is a daunting task. Lastly, although evidence for a monogenic substrate for early repolarisation syndrome is currently lacking, there will probably be genetic variants influencing the phenotype. This might possibly also have impact on screening and prophylactic treatment in the future.

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