The Brugada Syndrome

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10.1 Introduction

The syndrome of right bundle branch block, persistent ST-segment elevation, and sudden cardiac death, today better known as the *Brugada syndrome*, was described in 1992 as a new clinical entity characterized by a typical electrocardiographic pattern and a susceptibility to develop polymorphic ventricular arrhythmias in the absence of structural heart disease.[1] The description of the first eight patients was followed by other case reports[2,3] and subsequently numerous works appeared either focusing on clinical characteristics of larger populations of patients[4–7] or defining the genetic, molecular, and cellular aspects of the disease.[8–10] In recent years, major advances in clinical and mechanistic knowledge have provided very valuable information about the disease, but remaining questions still propel today a large research activity on the subject. This chapter reviews the current knowledge on clinical, genetic, and molecular features of the Brugada syndrome, and provides updated information supplied by recent clinical and basic studies.

10.2 Definition and Epidemiology

Certain ambiguities appeared in the years following the initial description of the syndrome, basically concerning the characteristic electrocardiographic hallmark and the specific diagnostic criteria. Three repolarization patterns were soon identified (Fig. 10.1)[11]: (a) *type 1* electrocardiogram (ECG) pattern, the one described in the initial report in 1992, in which a coved ST-segment elevation greater than or equal to 2 mm is followed by a negative T-wave, with little or no isoelectric separation, this feature being present in more than one right precordial lead (from V1 to V3); (b) *type 2* ECG pattern, also characterized by an ST-segment elevation but followed by a positive or biphasic T-wave, which results in a saddle-back configuration; (c) *type 3* ECG pattern, a right precordial ST-segment elevation less than or equal to 1 mm either with a coved-type or a saddle-back morphology.

Although all three patterns can be present in Brugada syndrome patients, only the type 1 ECG diagnostic of the syndrome was stated in the first consensus report of the Arrhythmia Working Group of the European Society of Cardiology[11] and subsequently confirmed in the II Consensus Conference published in 2005.[12] Both documents also held that, in order to establish the definite diagnosis of the Brugada syndrome, the type 1 ECG pattern should be documented in combination with one of the following clinical criteria: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden death (SD) at an age younger than 45 years, the presence of coved-type ECG in family members, inducibility of ventricular arrhythmias with programmed electrical stimulation, syncope, or nocturnal agonal respiration.[11,12] However, this definition should be applied with caution, especially when causative mutations have been identified and the disorder can be understood as a disease rather than a syndrome.[13,14] In this regard, our data confirm that the only presence of the characteristic type 1 ECG pattern, even with no further clinical criteria, may be associated with SD in the follow-up.[14] This attests for

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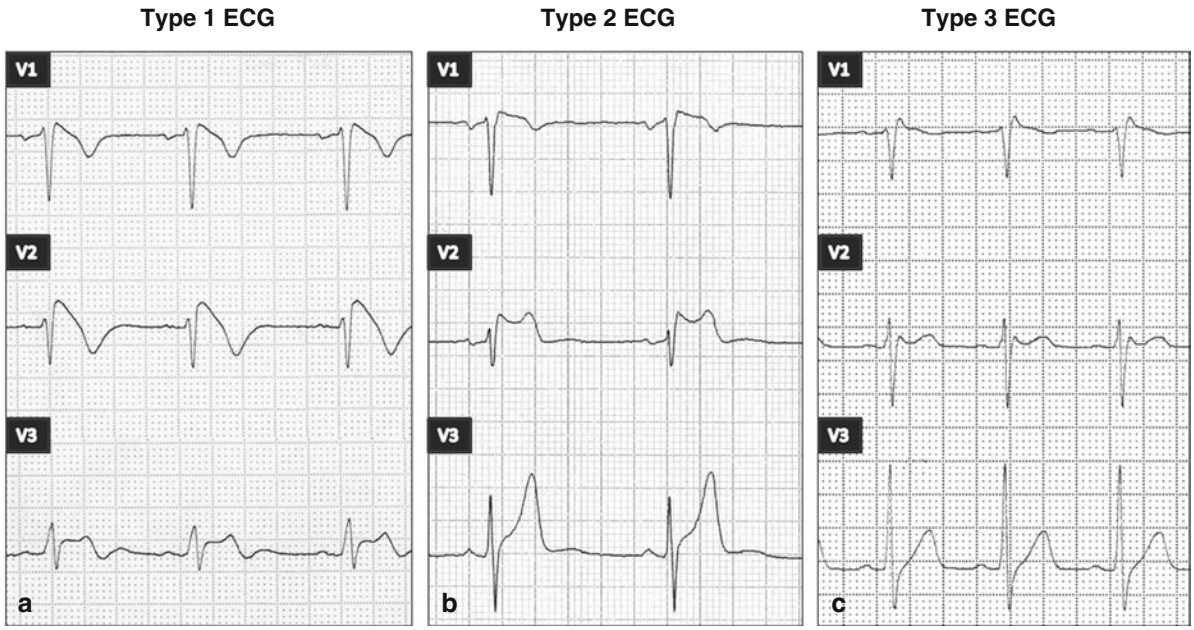

Fig. 10.1 Three different electrocardiogram (*ECG*) patterns in right precordial leads frequently observed in patients with Brugada syndrome: (**a**) type 1, also called coved-type ECG pattern, in which a descendent ST-segment elevation is followed by negative T-waves; (**b**) type 2 or saddle-back pattern, a ST-segment elevation followed by positive or biphasic T-waves; (**c**) type 3, either a coved-type or a saddle-back morphology with ST-segment elevation < 1 mm (see text for more detailed description). A type 1 ECG pattern is required to establish the definite diagnosis of Brugada syndrome

the need of following all patients even when a type 1 ECG pattern is found isolated. Moreover, these patients should be instructed not to use sodium channel blocking agents or other contraindicated medications and (high) fever should be treated promptly. First-degree relatives should be screened and have an ECG.

The Brugada syndrome is included among the so-called *channelopathies*, that is, primary electrical disorders produced by the dysfunction of a cardiac channel participating in the action potential, the electrical change favoring the development of arrhythmias. Characteristically, no underlying structural heart disease exists concomitantly. In fact, the Brugada syndrome is thought to be responsible for 4–12% of all SD and for up to 20% of SD in subjects with structurally normal heart.[12]

The *prevalence* of the Brugada syndrome has been estimated in 5/10,000 inhabitants, although this rate should be understood cautiously, first, because many patients present concealed forms of the disease, thus making it likely that the real prevalence is higher, and second, because important ethnic and geographic differences have been described.[12] For example, a type 1 ECG pattern was observed in 12/10,000 Japanese inhabitants,[15] whereas the few available data on North American and European populations point to a much lower prevalence.[16,17] In fact, the syndrome is considered to be endemic in certain Southeast Asian areas, where it has been long recognized as the sudden unexplained death syndrome (SUDS), also named *bangungot* (in the Philippines), *pokkuri* (in Japan), or *lai tai* (in Thailand), all of them known to be phenotypically, genetically, and functionally identical disorders as the Brugada syndrome.[18]

10.3 Genetics of the Brugada Syndrome

Inheritance in the Brugada syndrome occurs via an autosomal dominant mode of transmission,[12] although in some patients the disease can be sporadic, that is, absent in parents and other relatives.[19] The first *mutations* related to the syndrome were described in 1998 by Chen and coworkers, and were identified in *SCN5A*, the gene encoding the α- subunit of the cardiac sodium channel (locus 3p21, 28 exons).[8] To date, more than 100 other different mutations associated with the

syndrome have been found in the same gene.[9,18,20–23] Functional studies performed with expression systems have demonstrated, for the majority of them, a loss of function of the sodium channel that translates into a decrease in sodium current (INa). This can be achieved either through a quantitative decrease (failure in expression) or through a qualitative dysfunction (impaired kinetics) of the sodium channels (Fig. 10.2).[9,18,20–23]

Although *SCN5A* has been the only gene linked to the Brugada syndrome for almost a decade, mutations

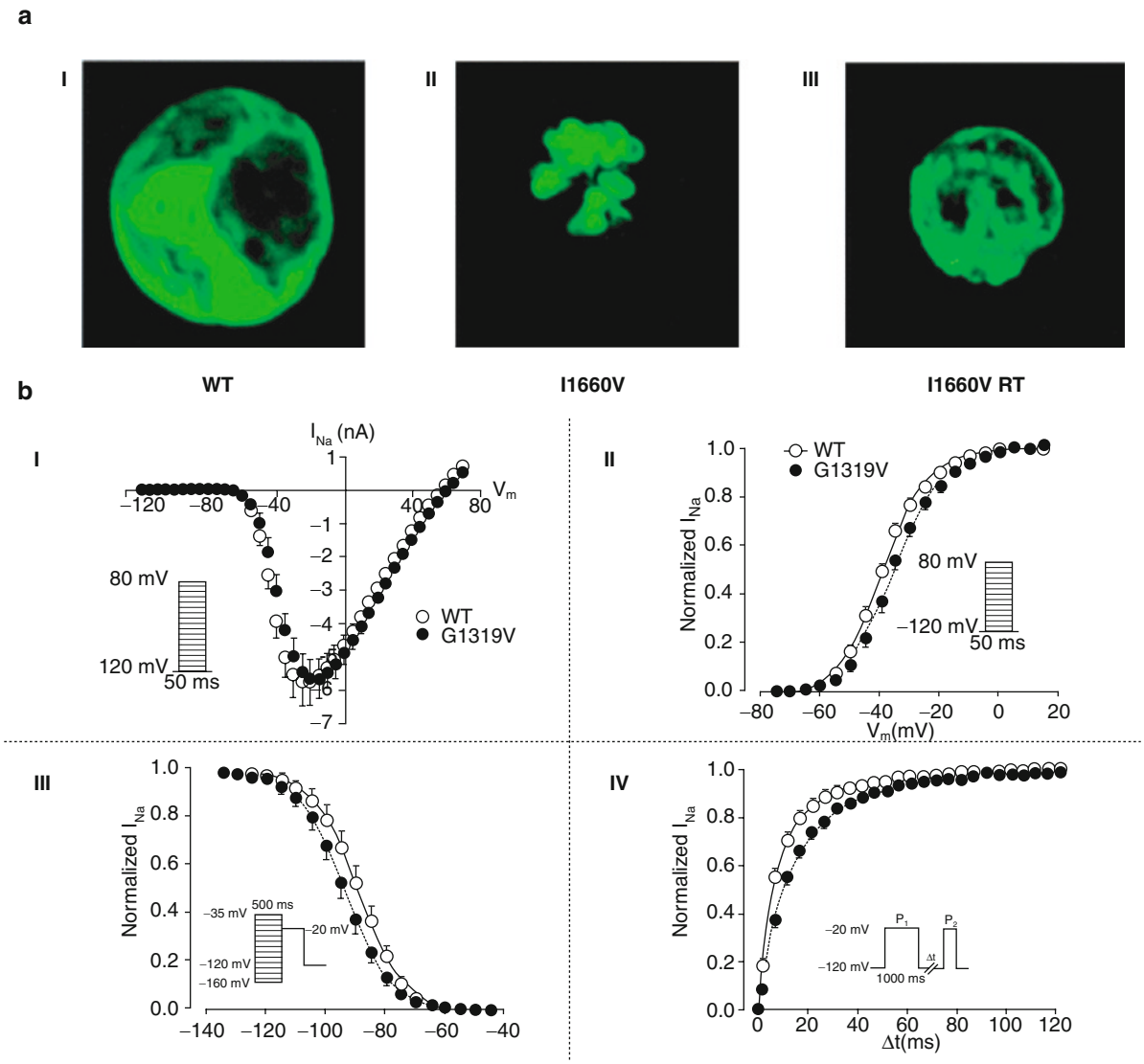

Fig. 10.2 Examples of two different mutations in *SCN5A* leading to a loss of function of the sodium (Na) channel: (**a**) Mutation I1660V, producing a trafficking defect of the Na channel, and thus a decrease of Na channels present in the sarcolemma. Mutant and WT Na channels have been expressed in TSA201 cells and tagged with green fluorescent protein. (A-I) WT channels are present both in the center and the periphery of the cell, suggesting that WT channels are manufactured in the cell center and trafficked to the cell membrane. (A-II) The fluorescence distribution of I1660V channels is essentially localized in intracellular organelles, which suggests that mutant channels are manufactured but remain trapped within the cell. (A-III) Rescue of the mutant channels by incubation at room temperature (Modified from Cordeiro et al.[21] With permission). (**b**) Mutation G1319V, which modifies the kinetics of the sodium channel. Functional studies performed in HEK-293 cells. (B-I) Maximal peak current amplitudes are similar in WT and mutant cells, indicating that the number of functional channels is similar for WT and mutants. (B-II) Voltage dependence of activation, showing a small depolarizing shift in mutant channels compared with WT channels, with no change in slopes. (B-III) Voltage dependence of steady-state inactivation, reflecting enhanced inactivation in mutant channels compared with WT. (B-IV) Recovery from inactivation, which is markedly slowed in G1319V channels (Modified from Casini et al.[22] With permission). *WT* wild type

in *SCN5A* are generally found in only 18–30% of patients,[12] this rate suggesting a genetic heterogeneity of the disease. Accordingly, in the last 2 years four other genes have been found to be linked to the Brugada syndrome. The first of them, the glycerol-3-phosphate dehydrogenase 1-like (*GPD-1 L*), was described in 2007[24] after previous identification of the locus on chromosome 3 (3p22–p24) in 2002.[25] The A280V mutation in *GPD1-L* was shown to induce a sodium loss-of-function effect by affecting the trafficking of the cardiac sodium channel to the cell surface.[24] Very interestingly, two recent reports demonstrate that mutations in genes other than those involved with sodium channel function can be responsible for some cases of Brugada syndrome. Loss-of-function mutations in the genes encoding the cardiac calcium channel Cav1.2 (*CACNA1c*) and its β subunit *CACNB2b* have been linked to a syndrome overlapping short QT and the Brugada ECG pattern.[26] On the other hand, Delpon et al. have described the first family with Brugada syndrome carrying a mutation (R99H) in the *KCNE3* gene, which encodes a beta-subunit that is thought to modulate Kv4.3 channels and be responsible for an increase in transient potassium Ito currents.[27] Together, these findings open up new lines of research, where the concept of Brugada syndrome as a pure sodium channelopathy gives way to the concept of the syndrome as an ionic imbalance between the inward and outward currents during the phase 1 of the action potential.

10.4 Pathophysiology: Cellular and Ionic Mechanisms

Experimental studies have elucidated the cellular and molecular basis for the two main characteristic features of the Brugada syndrome: the specific ECG morphology (ST-segment elevation in right precordial leads) and the susceptibility for VF and SD. Figure 10.3 represents the normal ventricular myocyte action potential and the major ionic currents involved in each one of the phases. Sodium loss-of function conditions, the most encountered disorder in *SCN5A* mutations related to Brugada syndrome,[9,18,20–23] create an *ionic imbalance* between outward and inward positive currents during phase 1.The imbalance favors cell repolarization and the appearance of a particular notch in the action potential (dashed line), which is mediated by a relative increase in the outward transient potassium currents (Ito). From Fig. 10.3, it is easy to conclude that comparable imbalances may appear either by decrease in ICaL (in calcium channel loss-of-function mutations[26]) or absolute increase in Ito (in the recently described *KCNE3* mutation[27]).

Because the Ito density is constitutionally greater in epicardium than in endocardium, the ionic imbalance underlying the Brugada syndrome is heterogeneous through the myocardial wall. This creates a *transmural voltage gradient* between epicardium and endocardium responsible for the characteristic *ST-segment elevation* on the ECG (Fig. 10.4).[28] The imbalance between outward and inward positive currents during the phase 1 sets also the basis for the development of ventricular arrhythmias in the Brugada syndrome. The proposed mechanism would be a *phase-2 reentry*, which is represented in Fig. 10.5. When the notch is such that phase 1 reaches approximately −30 mV, all-or-none repolarization can lead to a complete loss of the action potential dome. The heterogeneity of the loss of the dome among different sites within the epicardium and between the epicardium and the endocardium results in *epicardial and transmural dispersion of repolarization*, respectively (Fig. 10.5a). This substrate may facilitate the development of premature beats, by means of conduction of the action potential dome from the sites where it is maintained to the sites where it is lost (Fig. 10.5b).[10,28] Studies with high-resolution optical mapping in arterially perfused canine right ventricular preparations confirm the presence of a gradient between dome-loss regions and dome-restoration regions in the epicardium, and a subsequent development of a reentrant pathway that rotates in the epicardium and gradually involves the transmural myocardium (Fig. 10.5c).[29]

The understanding that the imbalance between inward and outward ionic currents at phase 1 defines the pathologic substrate of the Brugada syndrome entails multiple applications. First, it provides the basis for the development of experimental models, which have been successfully created by administration of potassium openers (pinacidil), the combination of acetylcholine and a sodium channel blocker (flecainide), or the administration of drugs with combined sodium channel and calcium channel blocker effect (terfenadine).[10,29,30] These interventions create a relative predominance of outward positive currents at the end of phase 1, and thus accentuate the notch. The ionic imbalance hypothesis

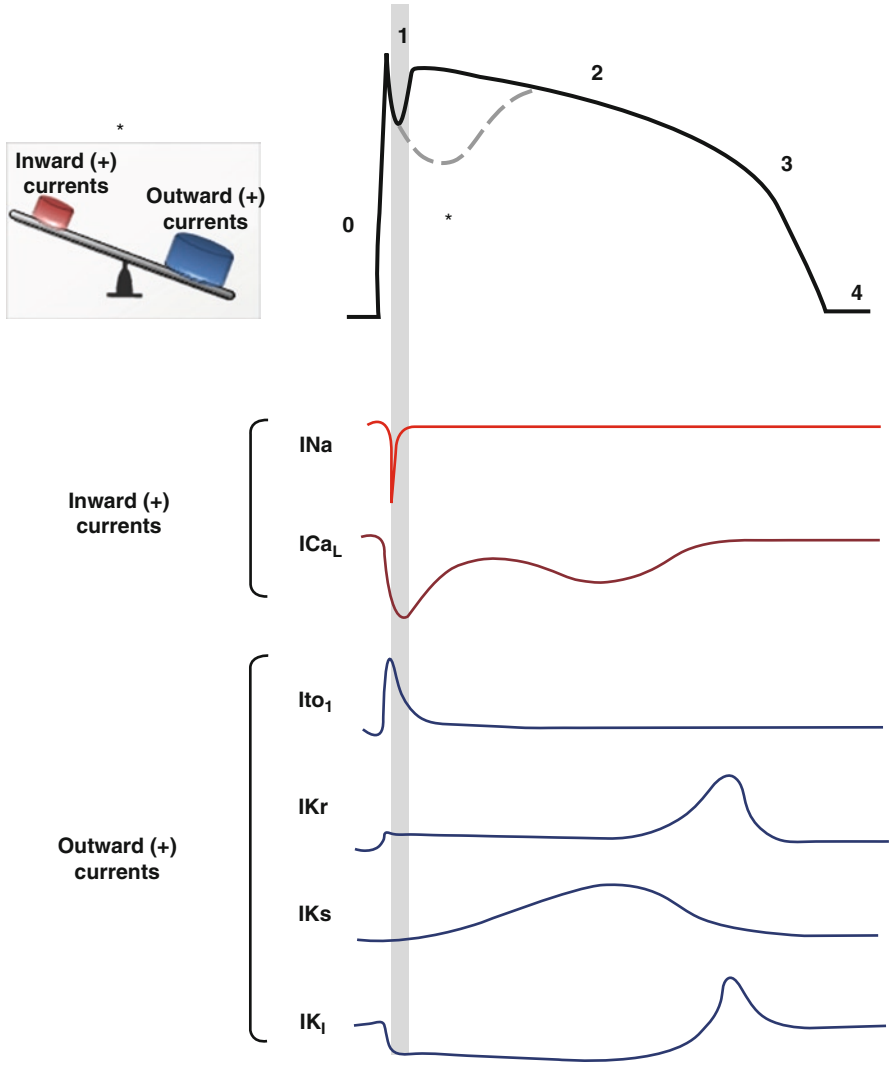

Fig. 10.3 Ventricular myocyte action potential and main underlying ionic currents. The shaded area highlights phase 1, mostly determined by the balance between INa, ICa, and Ito. When positive inward currents are impaired with respect to positive outward currents (*), the cell achieves greater degree of repolarization, and the normal dome of the action potential is lost, leading to the development of a particular notch at the end of phase 1 (dashed line). This is the mechanism that is thought to underlie the Brugada syndrome. *ICa* inward calcium current, *INa* inward sodium current, *Ito* transient outward potassium current

also explains the effects of certain modulators and certain particularities of the syndrome, such as the enhanced phenotypic expression (accompanied by an increased risk of arrhythmias) during vagal situations[31–34] (acetylcholine inhibits calcium currents whereas beta-adrenergic drugs increase them[10,35]) or the worse prognosis in men than in women affected with the disease[36] (men could have constitutionally greater Ito density than women).[37] Likewise, it appears that interventions that decrease inward positive currents (as do sodium channel blockers) could be potentially harmful in patients with Brugada syndrome by increasing ST-segment elevation and the risk of arrhythmic events, although they have been proven on the other hand notwithstanding useful for unmasking concealed forms of the disease.[38] In contrast, Ito blockers such as quinidine, which reduce the notch at the end of the phase 1, could represent a good therapeutic option for Brugada syndrome patients (see Treatment).

10.5 Clinical Manifestations of the Brugada Syndrome

Patients with Brugada syndrome usually remain asymptomatic. However, *syncope* or *cardiac arrest*, a consequence of an arrhythmic complication such as polymorphic VT or VF, has been described in up to 17–42% of diagnosed individuals.[39–42] This rate probably

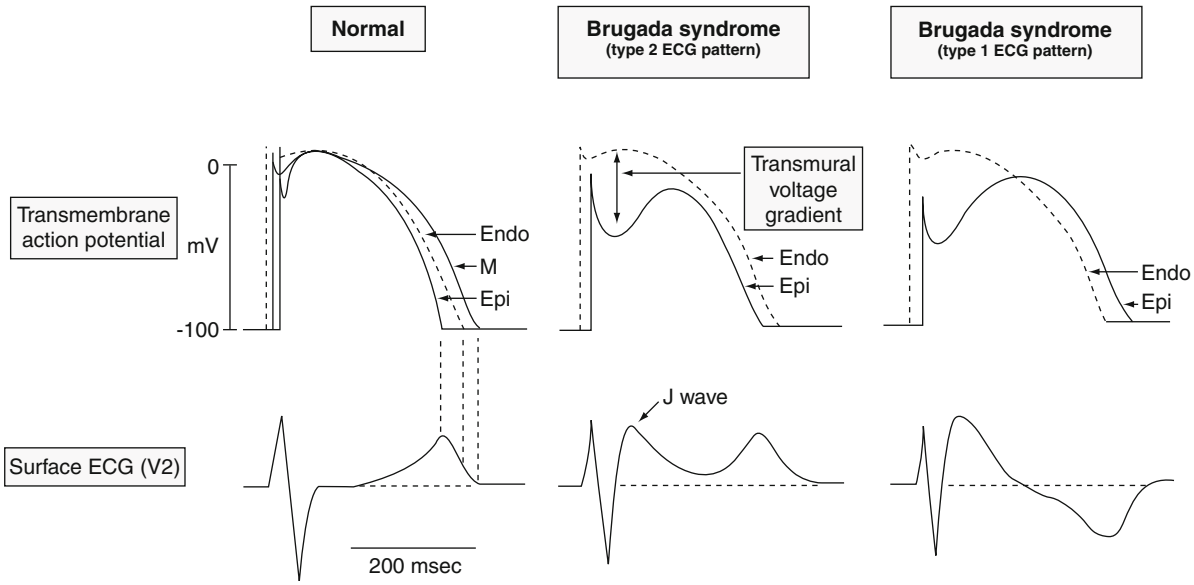

Fig. 10.4 Proposed mechanism that underlies ST-segment elevation in Brugada syndrome. The accentuated notch present in epicardium but not in endocardium gives rise to transmural voltage gradient and J-point elevation (Brugada saddle-back). Further accentuation of the notch may be accompanied by a prolongation of the action potential in epicardium, which becomes longer than in endocardium, thus leading to the development of negative T-waves in addition to the ST-segment elevation (Brugada coved-type) (Modified from Antzelevitch.[28] With permission)

overestimates the real prevalence of symptoms among Brugada syndrome patients, given that most asymptomatic patients remain underdiagnosed. The age of symptom occurrence (especially cardiac arrest) is consistently around the fourth decade of life in all the series (Fig. 10.6),[19] with no definite explanation for this observation thus far. Previous syncope may be present in up to 23% of patients who present with cardiac arrest.[40]

Up to 20% of patients with Brugada syndrome may present *supraventricular arrhythmias*[43] and thus complain of palpitations and/or dizziness. An increased atrial vulnerability to both spontaneous and induced *atrial fibrillation* (AF) has been reported in patients with Brugada syndrome.[44] Other symptoms, such as neurally mediated syncope have been also recently associated with the Brugada syndrome, but their implications on prognosis have not yet been established.[45,46]

As in the case of other sodium channel-related disorders as type-3 long QT syndrome, ventricular arrhythmias in the Brugada syndrome typically occur at rest, especially during nighttime or sleep. In a study by Matsuo et al.,[32] 26 of 30 episodes of VF documented in implantable cardioverter defibrillator (ICD) recordings of Brugada syndrome patients appeared during sleep. This finding has been confirmed in more recent series.[34] As mentioned before, the increase in *vagal tone* mediated by acetyl-choline decreases calcium currents,[10] which could favor arrhythmogenesis through a phase-2 reentry mechanism.

It is currently accepted that the clinical phenotype of the Brugada syndrome is eight to ten times more prevalent in male than in female patients.[12] Consequently, the main clinical studies published thus far include a 71–77% of men, which generally are more symptomatic as compared to women.[39–42] In fact, the observation that SD mainly occur in young men at the time of sleep has long been recognized in South-East Asia for the SUDS, where males from certain small villages used to dress in women's bedclothes since the syndrome is understood as a female spirit searching for young males at night. We recently conducted a study aimed to analyze *gender differences* in a large population of patients with Brugada syndrome.[36] The study population ($n=384$) included 272 men (70.8%) and 112 women (29.2%). General demographic characteristics were similar between male and female patients (mean age 45.8), but, at diagnosis, men presented more frequently with symptoms (syncope in 18%, previous aborted SD in 6%) than women (14% and 1% respectively, $p=0.04$). Male patients also had higher rates of

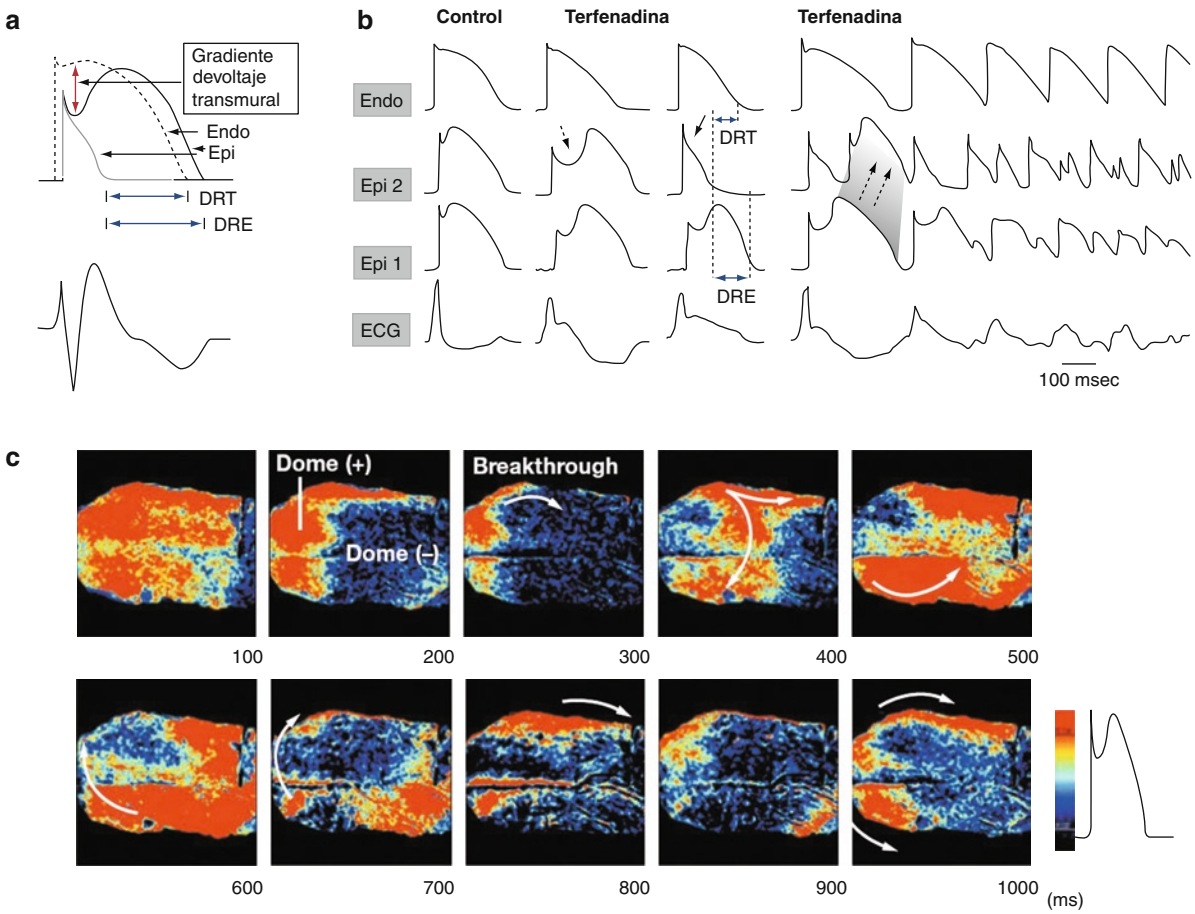

Fig. 10.5 Proposed mechanism that underlies ventricular arrhythmias in Brugada syndrome. (**a**) With a further shift in the balance of currents at the end of phase 1, all-or-none repolarization occurs and leads to a complete loss of the action potential dome (silver drawing). The arrythmogenic substrate is thought to develop when the loss of dome appears at some epicardial sites but not at others, creating both transmural dispersion of repolarization and epicardial dispersion of repolarization (*blue arrows*). At this point, a premature impulse or extrasystole can induce a reentrant arrhythmia (Modified from Antzelevitch.[28] With permission). (**b**) Simultaneous transmembrane action potentials at two epicardial sites and one endocardial site together with a transmural electrocardiogram recorded from a canine arterially perfused right ventricular wedge preparation. The administration of terfenadine (5 μM), a potent sodium and calcium channel blocker, accentuates the epicardial action potential notch (*dashed arrow*), induces all-or-none repolarization heterogeneously at the end of phase 1 (*solid arrow*), and creates epicardial transmural of repolarization (*EDR*) and transmural dispersion of repolarization (*TDR*). Propagation from the site where the dome is maintained (epicardial site 1) to the site where it is lost (epicardial site 2) results in the development of a premature beat that leads to polymorphic ventricular tachycardia by phase 2 reentry (*dashed double arrow*) (Modified from Antzelevitch.[28] With permission). (**c**) High-resolution optical mapping system with transmembrane action potentials from 256 sites simultaneously (epicardial and endocardial surface) of an arterially perfused canine right ventricular wedge preparation. Recording at the beginning of a polymorphic ventricular tachycardia. Propagation by phase-2 reentry occurs from red areas (where the dome is maintained) toward blue areas (where the dome is lost) (Modified from Shimizu et al.[29] With permission)

spontaneous type 1 ECG (47% versus 23%, $p = 0.0001$) and inducibility of VF during the electrophysiologic study (32% versus 12% $p = 0.0001$) (Fig. 10.7a).[36] Prognosis also differed between men and women. Cardiac events (defined as SD or documented VF) appeared in 31 males (11.6%) but only in three females (2.8%) during a mean follow-up period 58 ± 48 months (log-rank test $p = 0.007$). Kaplan-Meier estimate of cardiac event-free survival according to gender is represented in Fig. 10.7b.

Two main hypotheses have been proposed to explain the gender distinction, perhaps interacting with each other: the sex-related intrinsic differences in ionic currents and the hormonal influence. Di Diego and

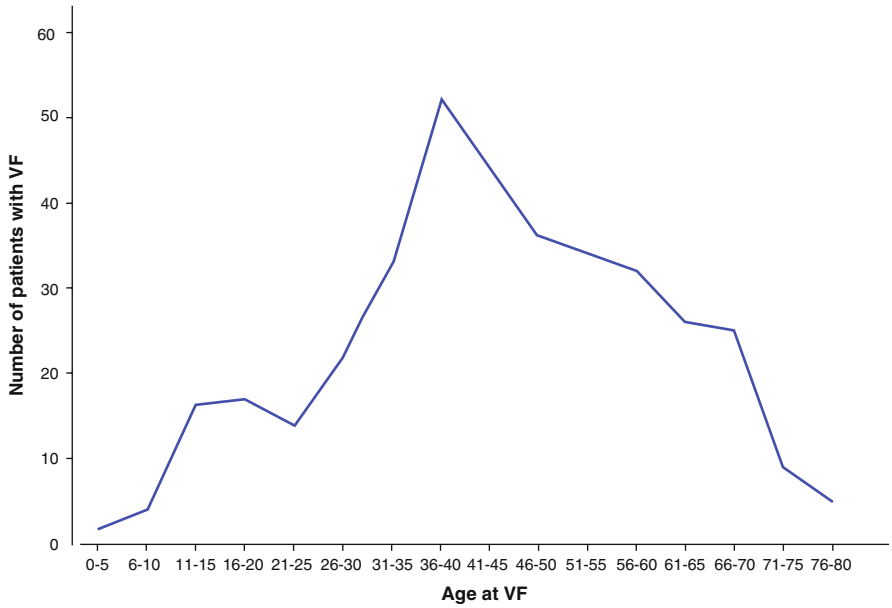

Fig. 10.6 Incidence of spontaneous ventricular fibrillation (*VF*) or sudden death (*SD*) according to age in patients with Brugada syndrome. Data from 370 updated patients of the international registry. SD or VF occurred in 120 (32.4%) patients

coworkers showed by whole-cell patch-clamp techniques that Ito density was significantly greater in male than female right ventricle epicardia of arterially perfused canine heart preparations, thus providing the basis for the greater ST-segment elevation and the higher occurrence of arrhythmias in men as compared to women.[37] Sex hormones seem also to play a role in the final phenotype. Regression of the typical ECG features has been reported in castrated men,[47] and levels of testosterone seem to be higher in Brugada male patients as compared to controls.[48] In accordance with the hormonal hypothesis, the few available data existing thus far of Brugada syndrome in childhood have not shown a difference in clinical presentation between boys and girls before the age of 16.[49]

Although three of the eight patients reported in the first description of the disease were within pediatric ages,[1] to date little information has been available on the behavior of the Brugada syndrome during *childhood*. Probst et al. recently provided data from a multicenter study including 30 Brugada patients aging less than 16 years (mean age 8 ± 5).[49] More than half ($n = 17$) had been diagnosed during family screening, but symptoms were present in 11 patients (one aborted SD and ten syncope). Interestingly, 10 of the 11 symptomatic patients displayed spontaneous type 1 ECG, and in five of them, symptoms were precipitated by *fever* illnesses. Five patients received an ICD and four were treated with hydroquinidine.[49] During a mean follow-up period of 37 ± 23 months, three patients (10% of the population) experienced SD ($n = 1$) or appropriate shock by ICD ($n = 2$). Importantly, all the three patients had presented with syncope at the time of diagnosis and displayed spontaneous type 1 ECG. The four patients under quinidine remained asymptomatic during 28 ± 24 months of follow-up.[49] Our results on 58 pediatric patients younger than 18 are in line with the ones by Probst et al.[50] In our population, six patients experienced cardiac events during a mean follow-up of 48.8 ± 48 months. Cardiac events occurred more frequently among patients with spontaneous type 1 ECG and among those with inducible VF at the EPS; but, in our series, symptoms at diagnosis were the strongest variable to predict events during follow-up.[50] Though small, these two studies suggest that:

- The Brugada syndrome can manifest during childhood.
- Symptoms in pediatric patients may appear particularly during febrile episodes.
- Symptomatic patients, especially if they present spontaneous type 1 ECG, may be at a high risk of cardiac events in a relatively short period of follow-up.
- Individuals at risk can be protected with an ICD, although *quinidine* could be a good option in certain patients, particularly the youngest.

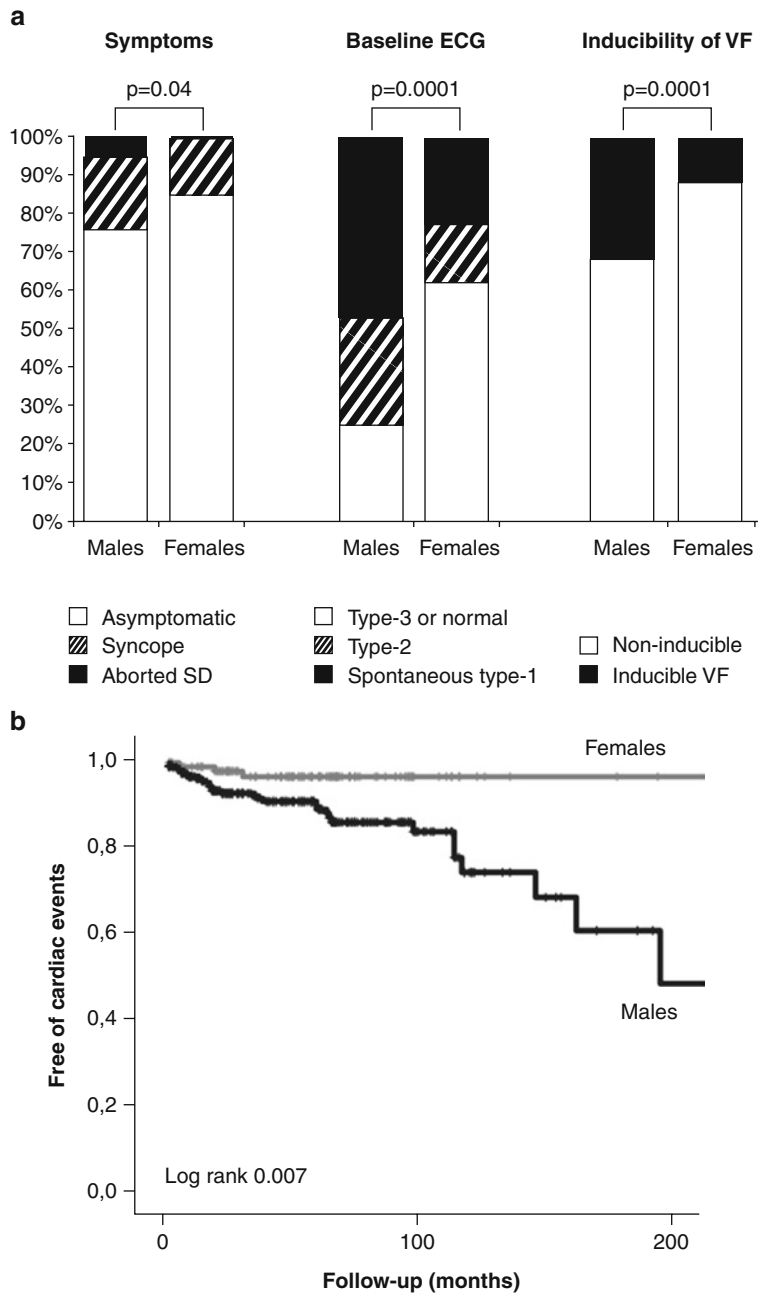

Fig. 10.7 Gender differences in clinical manifestations of Brugada syndrome. Data from Benito et al.[36] (**a**) Differences on clinical characteristics at the time of first evaluation. Males are more symptomatic, display more pathological electrocardiogram (*ECG*) at baseline and present more inducibility of ventricular fibrillation than females. (**b**) Kaplan-Meier analysis of cardiac events defined as sudden death or documented ventricular fibrillation during follow-up. A total of 31/272 males (11.6%) and 3/112 females (2.8%) experienced cardiac events during a mean follow-up period 58 ± 48 months (log-rank test $p = 0.007$). *VF* ventricular fibrillation, *SD* sudden death

10.6 Diagnosis

10.6.1 ECG Findings

As mentioned above, three types of repolarization have been described (Fig. 10.1), but only is the coved-type ST-segment elevation (type 1 ECG pattern) diagnostic of the syndrome. However, it is important to underline that the ECG typically fluctuates over time in Brugada patients, and thus can change from type 1 to type 2 or type 3 within the same individual or even be transiently normal. The prevalence of spontaneous *ECG fluctuations* was assessed in a work by Veltmann et al., including 310 ECGs on 43 patients followed during 17.7 months.[51] Among 15 patients with an initial diagnostic ECG, 14 revealed at least one nondiagnostic ECG in a median time of 12 days, while 8 out

of 28 patients with nondiagnostic ECG developed a type 1 ECG pattern in a median time of 16 days. On the basis of these results, it seems that repetitive ECG recordings may be mandatory in patients with the syndrome.[51,52]

Numerous studies have analyzed the ECG of the Brugada syndrome aiming to identify new electrocardiographic hallmarks and/or risk markers. Pitzalis and coworkers described a prolongation of the corrected QT interval (QTc) in the right but not the left precordial leads after administration of flecainide to patients with Brugada syndrome and nondiagnostic basal ECG.[53] Subsequently, other groups have correlated a QTc ≥ 460 ms in V2 to the occurrence of life-threatening arrhythmias.[54] More recently, the *aVR sign* (an R wave ≥ 3 mm or an R/q ratio ≥ 0.75 in lead aVR) has also been defined as a risk marker of cardiac events in Brugada syndrome, the prominent R-wave possibly reflecting some degree of right ventricular conduction delay and consequently more electrical heterogeneity (Fig. 10.8a).[55] In addition, *T-wave alternans*, also indicative of transmural dispersion of repolarization, has been reported in some cases after administration of sodium blockers, and associated with an increased risk for development of VF (52.9% vs 8.3%, $p < 0.001$) (Fig. 10.8b).[56] Finally, a very recent study points out that up to 11% of patients with Brugada syndrome may have a spontaneous *inferior-lateral repolarization pattern*, which also has been linked to a greater rate of symptoms (Fig. 10.8c).[57]

Cardiac conduction disturbances may be present in patients with Brugada syndrome. Both phenotypes (Brugada syndrome and cardiac conduction disorders) can be explained by a reduction in the sodium current, and have been described within the same family carrying a mutation on the *SCN5A* gene.[58] Consequently, conduction parameters (specifically PQ interval, QRS duration, and HV interval) seem to be longer among those patients with Brugada syndrome who are *SCN5A* genetic carriers (and do have a mutation in the sodium channel) as compared to non-*SCN5A* genetic carriers, in which the underlying mechanism or mutation is not identified.[59] These differences have been recently shown to accentuate progressively during follow-up.[60] In a recent study by our group, we observed that some conduction parameters such as QRS duration are increased among symptomatic patients. Indeed, in a population of 200 Brugada patients, of whom 66 (33%) presented symptoms, the optimized cut-off point of QRS in lead V2 ≥ 120 ms gave an odds ratio (OR) of 2.5 (95% CI: 1.4–4.6, $p = 0.003$) for being symptomatic.[61]

Although sinus rhythm is the most common, supraventricular arrhythmias, and especially AF, can be found in up to one third of patients with Brugada syndrome.[43,44,62] Other rhythm disorders, as bradycardia secondary to sick sinus syndrome or atrial standstill, have also been reported in association to Brugada syndrome.[28]

10.6.2 Differential Diagnosis and ECG Modulators

It is worth to note that some factors can account for an ECG abnormality that can closely resemble the Brugada ECG (Table 10.1). Importantly, some of them are conditions different than the syndrome and should be carefully excluded during the differential diagnosis, while others may induce ST-segment elevation probably when an underlying genetic predisposition is present.[19]

Modulating factors play a major role in the dynamic nature of the ECG and also may be responsible for the ST-segment elevation in genetically predisposed patients (Table 10.1). As mentioned before, sympathovagal balance, hormones, metabolic factors, and pharmacological agents, by means of specific effects on transmembrane ionic currents, are thought to modulate not only the ECG morphology but also explain the development of ventricular arrhythmias under certain conditions (see Pathophysiology: cellular and ionic mechanisms).[10,31,32,34,38,47,48,63] Temperature may be an important modulator in some patients with Brugada syndrome. Premature inactivation of the sodium channel has been shown to be accentuated at higher temperatures in some *SCN5A* mutations, suggesting that febrile states could unmask certain Brugada patients or temporarily increase the risk of arrhythmias.[64] In fact, several case reports in which fever precipitate the syndrome or an arrhythmic complication have been published in the last years.[65,66] It seems that fever would be a particularly important trigger factor among the pediatric population.[49]

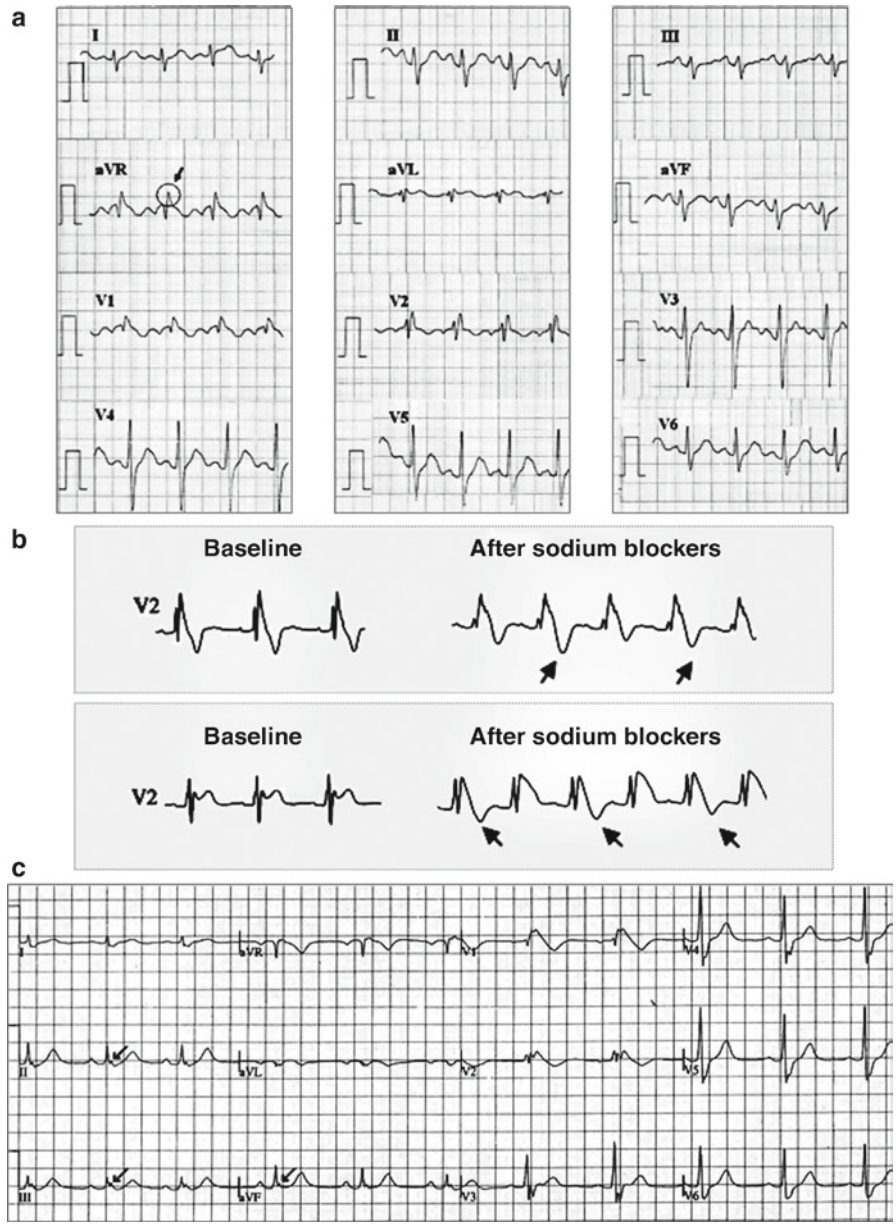

Fig. 10.8 Other electrocardiogram (*ECG*) findings that have been associated to higher risk of ventricular arrhythmias in patients with Brugada syndrome. For detailed explanation, refer to the text. (**a**) aVR sign (Reproduced from Babai et al.[55] With permission); (**b**) T-wave alternans (Adapted from Tada et al.[56] With permission); (**c**) Inferior-lateral early repolarization pattern (Reproduced from Sarzoky et al.[57] With permission)

10.6.3 Diagnostic Tools: Pharmacological Tests and Upper Right Precordial Leads

Because the ECG in the Brugada syndrome is dynamic in nature and even can be transiently normal in affected patients, pharmacological provocative tests have been used in an attempt to unmask concealed forms of the disease. Sodium channel blockers, which increase the ionic imbalance at the end of the phase 1 of the action potential by decreasing sodium currents, appear as the most attractive option.[38] *Ajmaline*, *flecainide*, procainamide, pilsicainide, disopyramide, and propafenone have been used,[12] although the specific diagnostic value for all of them has not yet been systematically studied. The recommended dose regimens for the most commonly used drugs are listed in Table 10.2. The

Table 10.1 ECG abnormalities that can lead to ST-segment elevation in V1-V3

Differential diagnosis	Genetic predisposition?
- Atypical right bundle branch block	- Hyperkalemia
- Acute myocardial infarction, especially of RV	- Hypercalcemia
- Acute pericarditis/miopericarditis	- Cocaine intoxication /Alcohol intoxication
- Hemopericardium	- Treatment with:
- Pulmonary embolism	I. Antiarrhythmic drugs:
- Dissecting aortic aneurysm	- Na channel blockers (class IC, class IA)
- Central and autonomic nervous system disorders	- Ca channel blockers
- Duchenne muscular dystrophy	- β-blockers
- Friedreich Ataxia	II. Antianginal drugs:
- LV hypertrophy	- Ca channel blockers
- Arrhythmogenic RV cardiomyopathy	- Nitrates
- Mechanical compression of RV outflow tract	III. Psychotropic drugs:
• Mediastinal tumor	- Tricyclic antidepressants
• Pectus excavatum	- Tetracyclic antidepressants
- After electrical cardioversion	- Phenothiazines
- Early repolarization, especially in athletes	- Selective serotonin reuptake inhibitors
- Hypothermia	- Lithium

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Table 10.2 Drugs used to unmask Brugada syndrome

Drug	Dosage	Administration
Ajmaline	1 mg/kg over 5 min	IV
Flecainide	2 mg/kg over 10 min 400 mg	IV PO
Procainamide	10 mg/kg over 10 min	IV
Pilsicainide	1 mg/kg over 10 min	IV

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diagnosis of Brugada syndrome can be established if a coved-type (type 1) ECG pattern appears or accentuates after the sodium blocker administration. The pharmacological test should be monitored under continuous ECG recording and should be terminated when: (1) the diagnostic test is positive, (2) premature ventricular beats or other arrhythmias develop, and/or (3) QRS widens to greater than or equal to 130% of baseline.[12]

Current data point out that ajmaline is probably the most useful drug in the diagnosis of Brugada syndrome. In a study with 147 individuals from four large families with identified *SCN5A* mutations, ajmaline provided a sensitivity of 80%, a specificity of 94.4%, a positive predictive value of 93.3%, and a negative predictive value of 82.9% for the diagnosis of Brugada syndrome.[67] These results are considerably higher than those obtained for flecainide in another study with 110 genotyped patients, in which the sensitivity, the specificity, and the positive and negative predictive values for the diagnosis were 77%, 80%, 96%, and 36%, respectively.[68] It is important to note the low negative predictive value, which should be taken into account when using flecainide, especially during genetic screening. Ajmaline and flecainide were directly compared in a study with 22 patients with confirmed Brugada syndrome who were subjected to both pharmacological tests. Although the test was positive in 22 of 22 patients after ajmaline administration, only 15 patients showed a positive response to flecainide.[69] Whole-cell patch-clamp experiments revealed that, although both of them have a sodium blocker effect, flecainide reduced Ito to a greater extent than ajmaline, thus explaining its lesser effectiveness.[69]

Given the limitations of the standard ECG, even after administration of sodium blockers, new strategies have been proposed to help in the clinical diagnosis of the Brugada syndrome. Placement of the right precordial leads in an upper position (*second or third intercostal spaces*) can increase the sensitivity of the ECG to detect the Brugada phenotype, both in the presence or absence of a drug challenge,[70,71] although whether the greater sensitivity is at the expense of a lower specificity is still uncertain. Recent data demonstrate that the presence of a type 1 ECG pattern recorded at higher intercostal spaces, even when the standard ECG is normal, can identify a subgroup of patients that behaves similarly in terms of prognosis to those with spontaneous type 1 ECG pattern at standard leads (Fig. 10.9).[72] Therefore, this strategy seems to allow the identification of a subset of patients at risk that would otherwise be underdiagnosed.

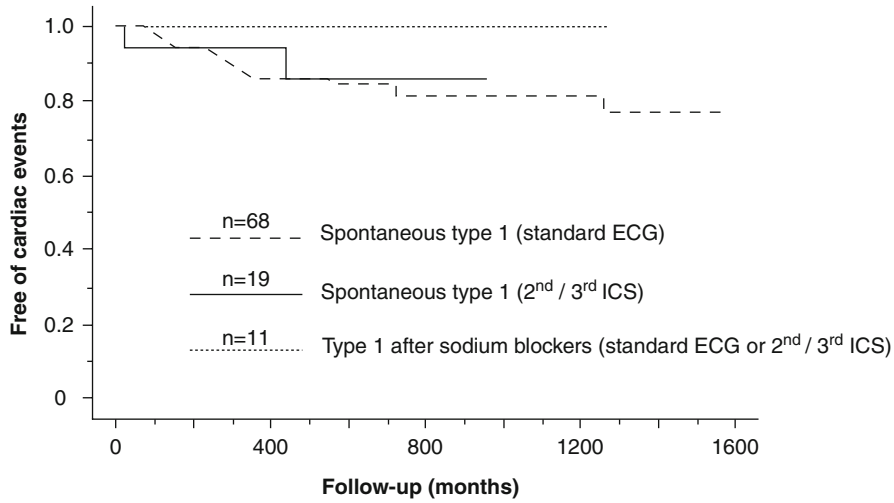


Fig. 10.9 Kaplan-Meier analysis of cardiac events (documented VF or SD) during follow-up in patients with spontaneous type 1 ECG pattern at standard leads (*dashed line*), patients with spontaneous type 1 ECG recorded only at a higher intercostal space (*solid line*), and patients with type 1 ECG pattern at standard and/or higher intercostals spaces only after receiving a sodium channel blocker (*dotted line*). No significant difference was observed in the frequency of cardiac events between the first two groups (Modified from Miyamoto et al.[72] With permission). *ECG* electrocardiogram, *SD* sudden death, *STD* standard, *VF* ventricular fibrillation

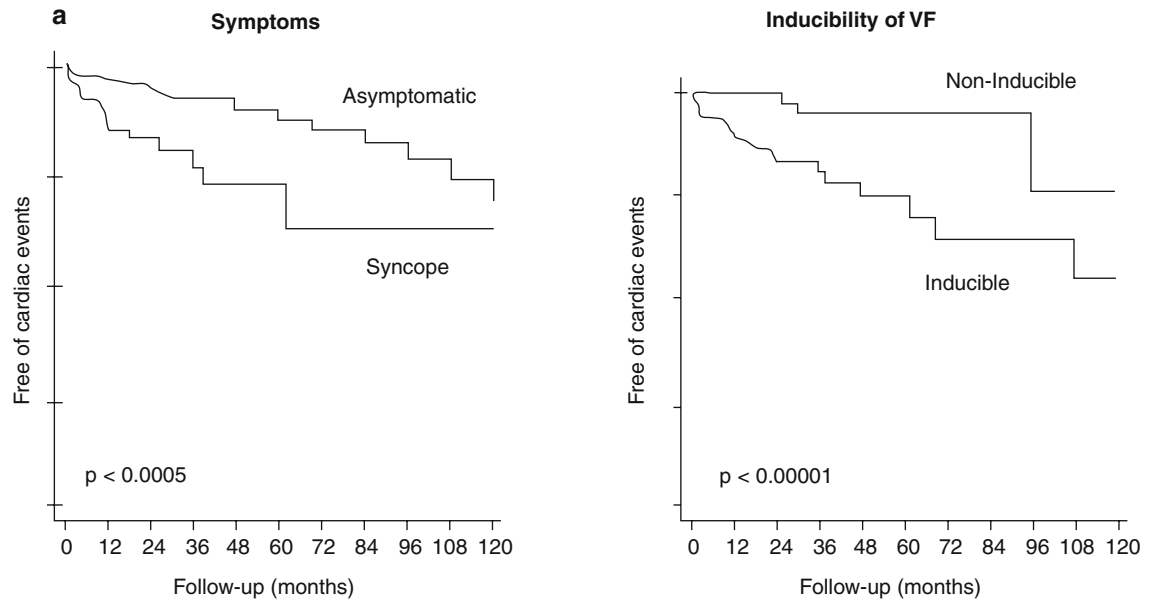
10.7 Prognosis and Risk Stratification

Prognosis and risk stratification are probably the most controversial issues in Brugada syndrome. The main clinical studies arising from the largest databases differ on the risk of SD or VF in the population with Brugada syndrome, and particularly on defining the specific risk markers with regard to prognosis.

In our most updated population with Brugada syndrome coming from the international registry, the percentage of patients who experienced *SD or VF* throughout lifetime was 25% (177 out of 724 patients).[73] The mean age at cardiac events was 42 ± 15 years. Of course, such a high rate might have been influenced by a baseline high-risk population referred for the international registry and included in this analysis. In fact, our reported annual rate of events has decreased from the first patients included in the registry[4] to the most recent published series,[39,41,73] the change probably reflecting the inherent bias during the first years following the description of a novel disease, in which particularly severe forms are most likely to be diagnosed. It is important to note that, in the global series, the probability of having a cardiac event during lifetime varied widely (from 3% to 45%) depending on the baseline characteristics of the individuals. Thus, a careful risk stratification of every individual seems mandatory.

Several clinical variables have been demonstrated to predict a worse outcome in patients with Brugada syndrome. In all the analysis of our series over time, the presence of symptoms before diagnosis, a spontaneous type 1 ECG at baseline, the inducibility of ventricular arrhythmias at the electrophysiological study (EPS) and male gender have consistently shown to be related to the occurrence of cardiac events in follow-up.[4,36,39,41,73]

Little controversy exists on the value of a *previous cardiac arrest* as a risk marker for future events. Our data state that up to 62% of patients recovered from an aborted SD are at risk of a new arrhythmic event within the following 54 months.[39] Thus, these patients should be protected with an ICD irrespective of the presence of other risk factors (indication class I).[12] Because there is not such a general agreement on the best approach toward patients who have never developed VF, we conducted a prospective study including 547 individuals with Brugada syndrome and no previous cardiac arrest.[41] Of them (mean age 41 ± 45 years, 408 males), 124 had presented previous syncope (22.7%) and 423 (77.3%) were asymptomatic and had been diagnosed during routine ECG or family screening. The baseline ECG showed a type 1 ECG pattern spontaneously in 391 patients (71.5%). During a mean follow-up of 24 ± 32 months, 45 individuals (8.2%) developed a first major cardiac event (documented VF or SD).[41] By univariable analysis, a history of *previous syncope* (HR 2.79 [1.5–5.1] 95% CI, $p = 0.002$), a *spontaneous type 1 ECG* (HR 7.69 [1.9–33.3] 95% CI, $p = 0.0001$), *male*



Multivariable	HR	95% CI	p
Syncope	2.51	1.2-5.3	0.017

Multivariable	HR	95% CI	p
Inducibility of VF	5.88	2.0-16.7	0.0001

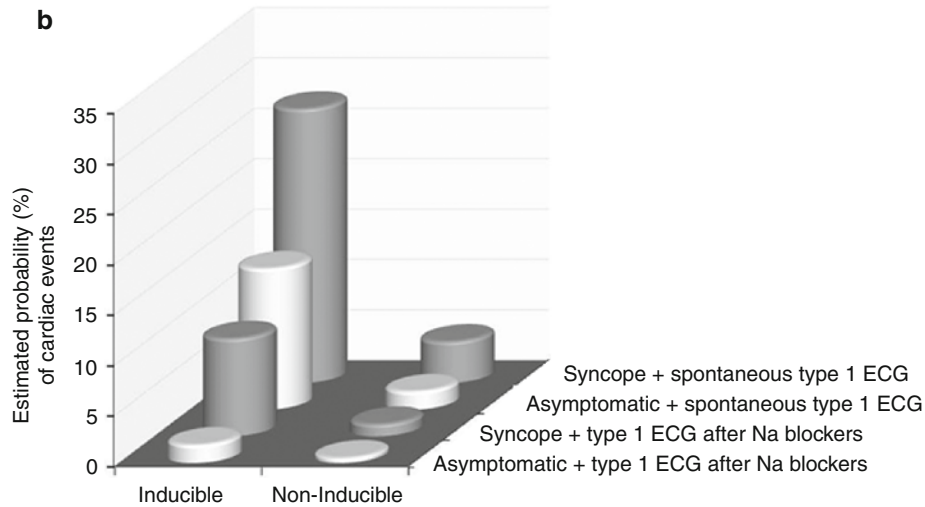


Fig. 10.10 Cardiac events (sudden death or documented ventricular fibrillation) during follow-up. (**a**) Kaplan Meier analysis according to previous symptoms and inducibility of ventricular fibrillation in the electrophysiological study, both independent predictors in the series by Brugada et al.[41] (**b**) Estimated probability of events in follow-up by logistic regression according to symptoms, inducibility of ventricular arrhythmias at the electrophysiological study and baseline ECG (Data from Brugada et al.[41]) *SD* sudden death, *VF* ventricular fibrillation, *EPS* electrophysiological study. *Induced type 1 ECG after administration of sodium channel blockers

gender (HR 5.26 [1.6–16.6] 95% CI, $p = 0.001$) and inducibility of ventricular arrhythmias at the *EPS* (HR 8.33 [2.8–25] 95% CI, $p = 0.0001$) were significantly related to VF or SD in follow-up. Multivariable analysis identified previous syncope and inducibility of VF as the only independent risk factors for the occurrence of events in follow-up (Fig. 10.10a).[41] Logistic regression analysis allowed the definition of eight categories of risk, of which asymptomatic patients with normal ECG at baseline and noninducible VF at the EPS would

represent the lowest-risk population, and patients with syncope, spontaneous type 1 ECG, and inducibility at EPS would have the worst outcome (Fig. 10.10b). Further analysis indicated that EPS was particularly useful in predicting cardiac events among asymptomatic patients with no family history of SD (named fortuitous cases, $n=167$).[73] Indeed, 11 out of 167 patients (6%) presented documented VF during follow-up, and the only independent predictor in this subgroup was the inducibility at EPS. In contrast, not performing an EPS in this subgroup of patients with the aim of identifying those at risk was shown to be predictive of effective SD ($p=0.002$).[73]

Other groups agree that previous symptoms and a spontaneous type 1 ECG are risk factors, although they have found a much lower incidence of arrhythmic events for the whole population (6.5% in 34 ± 44 months of follow-up in the work of Priori et al.[40] and 4.2% in 40 ± 50 months of follow-up in that of Eckardt et al.[42]). The worse outcome in our series may probably reflect a more severely ill baseline population.[42] The other large registries also agree that EPS inducibility is greatest among patients with previous SD or syncope,[40,42] but failed to demonstrate a value of the EPS in predicting outcome. Several reasons could explain this discrepancy[73]: (1) the use of multiple testing centers with nonstandardized stimulation protocols; (2) the inclusion of patients with type 2 and type 3 ST-segment elevation (and not type 1) in some series, suggesting that they may contain individuals who do not have the syndrome; (3) the lack of events during follow-up in the other registries. The latter might change when longer follow-ups are available because events can only increase in follow-up and so does the positive predictive value.[73]

Male gender has consistently shown a trend to present more arrhythmic events in all the studies.[39–42] In a series of 384 patients, we recently observed that men and women differed in baseline characteristics at time of first evaluation (Fig. 10.7a) and also in follow-up (Fig. 10.7b).[36] Importantly, our data also confirmed that the classical risk markers defined for mixed populations (symptoms, spontaneous type 1 ECG, and inducibility of VF) were all useful for identifying male patients at risk. However, in the presence of a very low rate of events, none of these markers showed power enough to predict outcome in the female population. In contrast, conduction disturbances were found to correlate with prognosis in women, and specifically the PR interval was the only independent predictor of outcome in the female population.[36]

Spontaneous *AF*, which can appear in 10–53% of cases,[44,62] has been recently shown to have prognostic significance. Kusano et al., in a series of 73 patients with Brugada syndrome, observed that spontaneous AF was associated with higher incidence of syncopal episodes (60.0% vs 22.2%, $p<0.03$) and documented VF (40.0% vs 14.3%, $p < 0.05$).[62] Multiple ECG parameters have been assessed in the search for new risk markers, of which a prolonged QTc in V2, the aVR sign, the presence of T wave alternans, the early repolarization pattern in inferior or lateral leads, and probably a wide QRS complex seem to be the most important (see Diagnosis: ECG findings).[54–57,61]

Interestingly, a positive family history of SD or the presence of a *SCN5A* mutation have not been proven to be risk markers in any of the large studies conducted thus far.[40,42,74] However, recent data suggest that other genetic findings might correlate with phenotype and even have prognostic implications (see Cardiogenetics aspects).

10.8 Treatment

10.8.1 Implantable Cardioverter Defibrillator

The ICD is the only proven effective treatment of the Brugada syndrome thus far. On the basis of available clinical and basic science data, a II consensus conference was held in September 2003, focused on risk stratification schemes and approaches to therapy.[12] The *recommendations* for ICD implantation stated by this consensus are summarized in Fig. 10.11. Briefly, symptomatic patients should always receive an ICD. Asymptomatic patients may benefit from EPS for risk stratification: ICD should be implanted in those with inducible VF having a spontaneous type 1 ECG at baseline or a sodium channel blocker–induced ECG with a positive family history of SD. Finally, asymptomatic patients who have no family history of SD and who develop a type 1 ECG only after sodium channel blockade should be closely followed up, without enough evidence existing for the usefulness of EPS or a direct indication for ICD.[12] It is important to note that a type 1 ECG can also be induced by certain circumstances other than the deliberate administration of sodium blockers during a pharmacological test. This is the case of patients who "spontaneously"

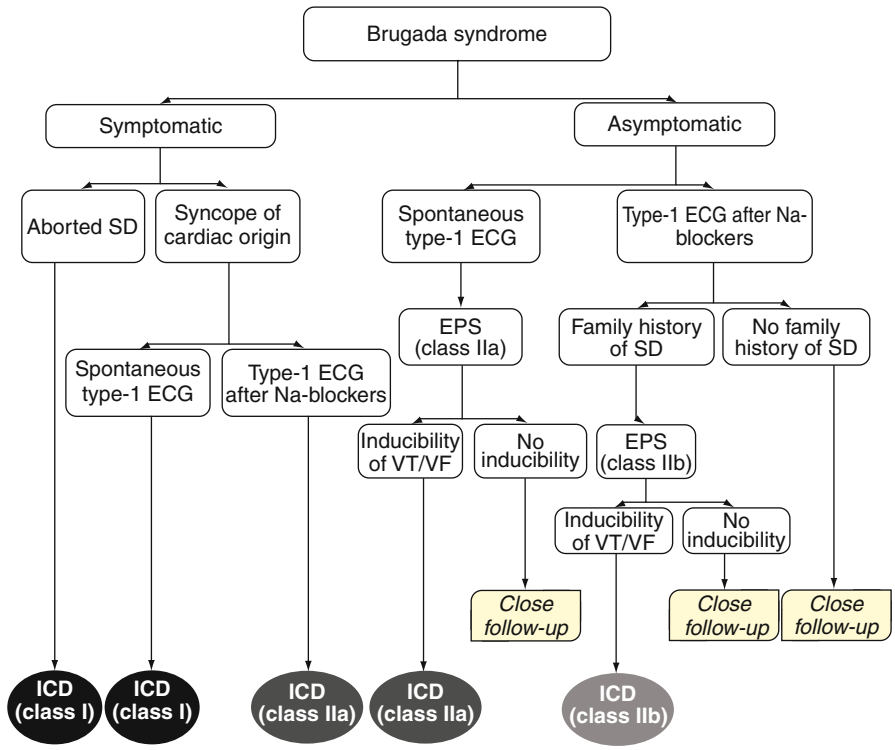


Fig. 10.11 Indications for implantable cardioverter defibrillator (*ICD*) implantation in patients with Brugada syndrome. Class I designation indicates clear evidence that the procedure or treatment is useful or effective; Class II, conflicting evidence about usefulness or efficacy; Class IIa, weight of evidence in favor of usefulness or efficacy; Class IIb, usefulness or efficacy less well established (Modified from Antzelevitch et al.[12] With permission)

develop a type 1 ECG during electrolyte imbalances, administration of certain drugs (particularly anesthetics) and, more importantly, febrile episodes.[75] Although these should probably be considered cases of induced rather than spontaneous type 1 ECG with regard to therapy (Fig. 10.11), to date there is no definite information concerning the long-term prognosis (and thus, indications of ICD implantation) in this particular subgroup of patients. Our data, however, do show that up to 50% of these patients are at risk of developing arrhythmic complications, possibly fatal, during the acute event that unmasks the characteristic type 1 ECG.[75] Consequently, close monitoring and therapeutic intervention with antipyretics or by termination of the culprit medication is mandatory in these circumstances.[75]

From the 2 main retrospective studies conducted on patients with Brugada syndrome who have received primary prophylactic ICD, it can be concluded that ICD is an effective therapy for patients at risk,[76,77] which can have an annual rate of *appropriate shocks* of up to 3.7%.[77] It is important to note that this rate is not only comparable to those reported in other ICD trials dealing with other cardiac diseases,[78,79] but also is affecting young and otherwise healthy people, whose life expectancy could be more than 30 years. Therefore, should this rate remain constant in time, it seems that most patients would likely experience an appropriate shock in a lifetime. However, perhaps just because of being young, a noteworthy rate of *inappropriate shocks* by the device has also been reported. In the study by Sacher et al.,[76] 45 (20%) out of 220 patients had inappropriate shocks in follow-up. In our series, the rate was even higher (36%).[77] The reasons for inappropriate therapies were mainly sinus tachycardia, supraventricular arrhythmias, T-wave oversensing, and lead failure in both studies.[76,77] On the basis of these results and because ICD is not affordable worldwide, there is growing effort to find pharmacological approaches to help treat the disease.

10.8.2 Pharmacological Options

With the aim of rebalancing the ion channel currents active during phase 1 of the action potential, so as to reduce the magnitude of the notch (Fig. 10.3), two main pharmacologic approaches have been assessed

Table 10.3 Pharmacological approach to therapy in the Brugada syndrome

Action	Proved on
• **Ito blockers:**	
4-aminopyridine	Effective in experimental models (suppression of phase-2 reentry)[10] Probable neurotoxicity in humans
Quinidine	Effective in experimental models (suppression of phase-2 reentry)[10] Initial results showing effectiveness in clinical practice: ↓ inducibility of VF[63] ↓ spontaneous VF in follow-up[63, 80] Adjunctive therapy in patients with ICD and multiple shocks[80] Effective in electrical storm[81] A possible option in children[49]
Tedisamil	Effective in experimental models (suppression of phase-2 reentry)
AVE0118	Effective in experimental models (suppression of phase-2 reentry)
• **ICa activators:**	
Isoproterenol	Effective in experimental models (suppression of phase-2 reentry)[10] Effective in electrical storm[82]
Cilostazol	Controversial preliminary results in preventing VF[83,84]
• **INa openers:**	
Dimethyl Lithospermate B (dmLSB)	Effective in experimental models (suppression of phase-2 reentry)

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(Table 10.3): (1) drugs that decrease outward positive currents, like Ito inhibitors; and (2) drugs that increase inward positive currents (ICa, INa).

Quinidine, a drug with Ito- and IKr-blocking properties, has been the most assayed drug in clinical studies. In a work by Belhassen et al.,[63] 25 patients with inducible VF were treated with quinidine (1,483 ± 240 mg orally). After treatment, 22 (88%) of 25 patients were no longer inducible at the EPS, and none of the 19 patients with ongoing medical therapy with oral quinidine developed arrhythmias during follow-up (56 ± 67 months).[63] However, 36% of the patients had transient side effects that led to drug discontinuation. Preliminary data have also proven quinidine as a good adjunctive therapy in patients with ICD and multiple shocks[80] and as an effective treatment of electrical storms associated to Brugada syndrome.[81] More recently, quinidine has been proposed as a good alternative to ICD implantation in children with the syndrome and at high risk for malignant arrhythmias.[49]

β-Adrenergic agents, through an increase in ICa currents, decrease transmural dispersion of repolarization and epicardial dispersion of repolarization in experimental models.[10] Clinically, they have proved to be effective in the treatment of electrical storms associated to Brugada syndrome.[82] Recently, phosphodiesterase III inhibitors have appeared as a new appealing option because they would increase ICa and decrease Ito. Indeed, *cilostazol* was effective in preventing ICD shocks in a patient with recurrent episodes of VF.[83] However, a recent publication reports the failure of such drug in another patient with multiple ICD discharges despite sustained therapy.[84]

10.9 Cardiogenetics Aspects

10.9.1 Genetic Diagnosis and Genotype–Phenotype Correlation

Since the first description in 1998,[8] *SCN5A* encoding the cardiac sodium channel has been the gene most frequently linked to the Brugada syndrome. Although mutations in new genes have been described in the last 2 years (*GPD1-L*, *CACNA1c*, *CACNB2b*, *KCNE3*),[24,26,27] their contribution to the overall population with the disease in still unknown. However, initial studies performed in negative-*SCN5A* carriers suggest that these and other candidate genes (*Caveolin-3*, *Irx-3*, *Irx-4*, *Irx-5*, *Irx-6*, *Plakoglobin*, *Plakophilin-2*, *SCN1B*, *SCN2B*, *SCN3B*, and *SCN4B*) are unlikely to be major causal genes of the Brugada syndrome.[85,86] Therefore, *SCN5A* remains the first candidate gene to analyze during genetic testing, although screening of other genes involved in the action potential could be useful when SCN5A analysis is found to be negative. It is important to note that *SCN5A* mutations are only found in around 18–30% of cases of Brugada syndrome,[12] leaving a great majority of patients with a negative genetic test. This implies that, whereas the finding of a *SCN5A* mutation provides the diagnosis in patients with phenotype of Brugada syndrome, a negative result does not rule out the disease. In these cases, especially if the test is also negative for mutations in other genes,

the diagnosis must be based on the clinical phenotype, mainly through the basal or induced ECG findings.

Because so far mutations in the *SCN5A* gene are responsible for the greatest proportion of cases with Brugada syndrome, the first studies on genotype–phenotype correlation have been focused only in *SCN5A* mutation carriers. Very recently, Meregalli et al. presented their results on 147 patients with Brugada syndrome or progressive cardiac conduction disease carrying 32 different mutations in the *SCN5A* gene. The authors found that those patients carrying a mutation leading to a truncated protein (nonsense or frameshift with premature stop codon) were more likely to present syncope (25% of cases) than patients with a missense mutation functionally known to be inactive (and thus generating a >90% of peak INa reduction, syncope rate of 11%) or missense mutations known to be functionally active (≤ 90% of peak INa reduction, syncope rate of 5%, $p = 0.03$).[87] However, no differences in the rate of major arrhythmic complications (SD or VF) were found according to the type of mutation.[87] Our data on 188 patients (all with Brugada syndrome) carrying 69 different mutations in *SCN5A* demonstrate that the presence of a mutation leading to a premature stop codon is related to a greater rate of SD and/or documented VF.[88] Indeed, the incidence of major cardiac events during a lifetime was 23.9% in patients with truncated protein, and 7.7% in patients with other types of mutation ($p = 0.01$).[88] Moreover, in our series, the presence of a mutation leading to a truncated protein was confirmed as an independent predictor of cardiac events (HR 2.9, 95% CI 1.2–7.2, $p = 0.02$), together with the classical clinical risk factors reported in previous series.[88]

In recent years, *polymorphisms* have been acquiring greater importance to explain certain phenotypes of genetic diseases. In the *SCN5A* locus, the common H558R polymorphism has been shown to restore (at least partially) the sodium current impaired by other simultaneous mutations causing either cardiac conduction disturbances (T512I)[89] or Brugada syndrome (R282H).[90] Thus, this polymorphism seems to give rise to less severe phenotypes by mitigating the effect of nearby mutations. According to this, our data on 75 genotyped Brugada patients with SCN5A mutation demonstrate that those carrying the common AA genotype (H558H) have longer QRS duration in lead II ($p = 0.017$), higher J-point elevation in lead V2 ($p = 0.013$), higher rate of "aVR sign" ($p = 0.005$) and a trend toward more symptoms ($p = 0.06$) than carriers of the polymorphisms AG (H558R) or GG (R558R).[91]

From these data, one can conclude that genetic testing may be useful in the risk stratification of patients with Brugada syndrome who are carriers of a *SCN5A* mutation. This concept is particularly important because, in contrast to previously defined clinical variables, genetic information is constitutional and thus invariable over time within the same individual.

10.9.2 Family Screening

The first step after identification of a proband with Brugada syndrome is to evaluate his or her individual risk of SD and indicate ICD if necessary (see Prognosis and risk stratification). Genetic testing is recommended because a positive result helps confirm the disease in patients with borderline phenotype, may provide information on arrhythmic risk during lifetime (see above), and allows the identification of family members who are also carriers of the disease.

Given that the Brugada syndrome is commonly an inherited disorder, family screening should always be performed to identify possible relatives who are unknowingly at risk of SD. The first step would be to construct a family pedigree as the one shown in Fig. 10.12. It is important to remind that hereditary forms of Brugada syndrome are autosomal dominant not linked to sex, and thus each affected patient has a 50% probability of transmitting the disease to his/her offspring.

If genetic testing is available and the responsible mutation has been identified in the proband, genetic testing of all other family members (starting by first degree-related) is the best approach for family screening because it allows both to establish and rule out the disease with the maximum sensitivity and specificity. If genetic testing is not available or the responsible mutation has not been identified, all direct relatives should be studied first with basic anamnesis and a basal ECG. For those with diagnostic type 1 ECG, and thus, carriers of the disease, conventional risk stratification should be performed in order to estimate their probability of cardiac events in follow-up. In those family members with normal ECG at baseline, as long as they are asymptomatic, our data indicate that the probability of cardiac events in

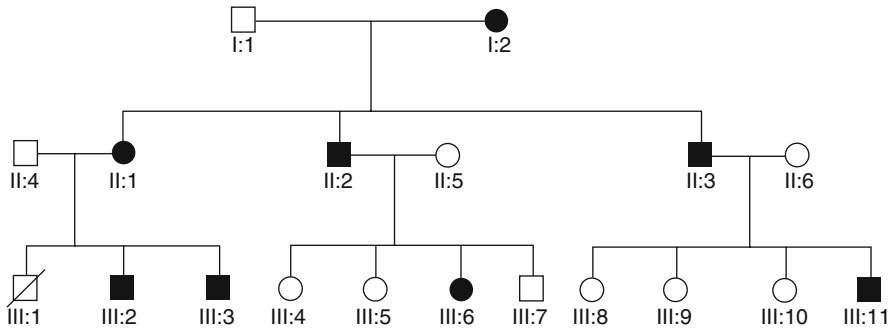

Fig. 10.12 Example of a family pedigree. Squares indicate males, circles indicate females. Affected patients are represented in black solid figures, while open figures indicate non-affected individuals. Sloping lines indicate deceased individuals

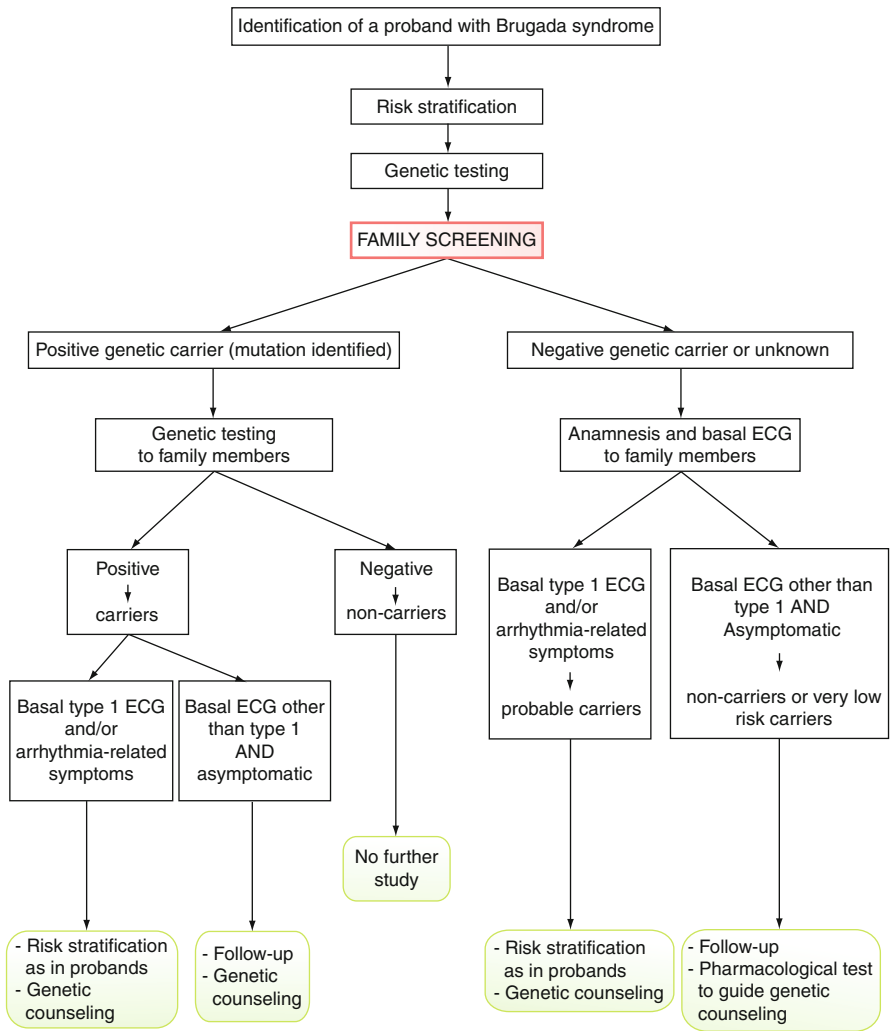

Fig. 10.13 Proposed algorithm for family screening after identification of a proband with confirmed Brugada syndrome

follow-up is extremely low (1/131 at 100 months, unpublished data), meaning that either they are not carriers of the disease, or, if they are, have little expressivity and thus are at a very low risk of arrhythmias. Pharmacological provocative test could be performed in these patients to increase the penetrance and better identify possible disease carriers, which would be useful for family planning and genetic counseling. The proposed algorithm for family screening is presented in Fig. 10.13.

10.10 Summary

The Brugada syndrome is characterized by a typical ECG morphology and an increased susceptibility to present ventricular arrhythmias and sudden death in the absence of structural heart disease. The characteristic ECG pattern, known as coved-type or type 1, consists of a persistent ST-segment elevation in right precordial leads followed by negative T-waves, and must be distinguished from other conditions that also present with right ST-segment elevation. A number of mutations in several genes encoding cardiac transmembrane channels have been linked to the syndrome, but loss-of-function mutations in *SCN5A* encoding the sodium channel remain the most common genetic finding in patients with the syndrome. In recent years, experimental studies have confirmed that it is an imbalance between inward and outward positive currents during the phase 1 of the action potential the main mechanism that underlies both the ST-segment elevation and the susceptibility to develop ventricular arrhythmias. This hypothesis also explains the effect of certain modulators and certain drugs with clinical applications, for example, sodium-channel blockers for unmasking concealed forms of the disease or Ito blockers such as quinidine for pharmacological therapy, usually coadjunctive to ICD. Because the clinical phenotype can be widely variable, risk stratification is mandatory in all diagnosed patients, and should be based on the presence of previous symptoms, basal ECG findings, results of the EPS, gender, and probably also on genetic findings. ICD is the only proven effective therapy for patients at high risk. Genetic testing, although only positive in a minority of patients, can help confirm the disease in patients with borderline phenotype, may provide prognostic information, and can be extremely valuable for family screening.

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