

BRUGADA SYNDROME

Definition

Brugada syndrome is an inherited disease characterized by a coved type ST-segment elevation followed by a negative T wave in the right precordial leads, and an increased risk of sudden cardiac death, in the absence of ischemia, electrolyte disturbances, or structural heart disease.^{1,2} Three different ECG patterns have been described (Figure 1), but only type 1, observed either spontaneously or during a sodium channel blocker test, establishes the diagnosis. Type 1 pattern is defined by a coved-type ST-segment elevation ≥ 2 mm (0.2 mV) in ≥ 1 right precordial leads (V_1 to V_2) positioned in the 4th, 3rd, or 2nd intercostal space. In patients with type 2 or type 3 ST-segment elevation, Brugada syndrome is diagnosed only when a type 1 ST-segment elevation is unmasked using a sodium channel blocker, according to current guidelines.³ To avoid overdiagnosis, a recent consensus report recommends that diagnosis of Brugada syndrome should require that the patient also present with 1 of the following: documented VF or polymorphic VT, syncope of probable arrhythmic cause, a family history of SCD at <45 years old with negative autopsy, coved-type ECGs in family members, or nocturnal agonal respiration.⁴

Epidemiology

The prevalence of the disease in the general population cannot be accurately assessed due to the dynamic nature of the ECG pattern that can fluctuate over time, but it is estimated to be 1/2,000-10,000 inhabitants in the western world, being 8-10 times more prevalent in males than in females.^{2,5-7} It is probably more frequent in the Far Eastern countries (initially described as sudden unexplained death syndrome). An increased prevalence of Brugada-type ECG has been observed among patients with schizophrenia.⁸ Inheritance in Brugada syndrome occurs as an autosomal dominant trait. In up to 60% of patients the disease can be sporadic, that is, absent in parents and other relatives. Patients with Brugada syndrome have an annual incidence of cardiac arrest between 0.5 to 2%.^{9,10}

Genetics and Pathophysiology

The pathophysiological mechanism of the Brugada syndrome is rather elusive, and it has been proposed that the ECG manifestations are the phenotype of a multitude of possible etiologies, with the final common pathway viewed as a disease of 'reduced RVOT conduction reserve'.¹¹ Two main theories have been proposed to explain the pathophysiology of Brugada syndrome. Slow discontinuous conduction and steep dispersion of **repolarization**, that are mainly present

in the right ventricular outflow tract and can promote sustained reentry, may be the underlying electrophysiologic mechanisms of Brugada syndrome.¹² Genetic mutations in 21 genes that alter ion channel functions have been identified that may also affect the QT interval, but the only gene convincingly implicated is SCN5A (Table 1). SCN5A is the gene encoding the α -subunit of the cardiac sodium channel ($\text{Na}_v1.5$), leading to reduced cardiac sodium current (I_{Na}). Sodium loss-of-function conditions create an imbalance between outward and inward positive currents during phase 1, enhancing repolarization and resulting in the appearance of a particular notch in the action potential mediated by the transient outward potassium current (I_{to}). This gives rise to a transmural voltage gradient between epicardium and endocardium, resulting in the characteristic ST segment elevation and propensity to ventricular arrhythmias probably through phase-2 reentry mechanisms. The **depolarization** hypothesis underlines the role of conduction delay induced by SCN5A mutations, particularly in the RVOT.⁵

More than 300 mutations in the SCN5A gene have been so far identified, and a pathogenic/likely pathogenic gene variant is found in approximately 20% to 25% of European patients with Brugada syndrome and has been associated with higher risk of ventricular arrhythmias and sudden death.^{13,14} In Asian patients the prevalence is lower (11-16%).¹⁵ These patients have more prominent electrical abnormalities,¹⁶⁻¹⁸ and a risk of a lethal arrhythmia when the mutations are of the loss of function type.¹⁹ SCN10A has also been identified as a susceptibility gene,²⁰ but the functional significance of SCN10A variants remains unclear.²¹ Mutations in the plakophilin-2 (PKP2) gene that reduce I_{Na} may also yield a Brugada syndrome phenotype.²² Other mutations, in 21 genes overall, that affect calcium and potassium channel or act through other mechanisms have also been described but are rare. A cross-ancestry genome-wide meta-analysis of BrS in individuals of Japanese and European ancestries has also identified six novel susceptibility loci, including the *CAMK2D* locus.¹⁵ Thus, although only 1 gene (*SCN5A*) is having definitive evidence as a cause of sudden death, Brugada syndrome may be a polygenic disease. Epicardial interstitial fibrosis and reduced gap junction expression have also been identified at cardiac autopsy, and support the depolarization hypothesis.²³ Delayed onset of right ventricular contraction that can be seen on echocardiography also suggest that structural abnormalities are intrinsic to the syndrome.²⁴ Brugada syndrome is associated with increased collagen content throughout both ventricles, with maximal collagen proportions observed within BrS RVOT epicardium.²⁵ It has been proposed that Brugada syndrome, ERS, and idiopathic VF may form part of a spectrum of subtle subepicardial cardiomyopathy.²⁶

Drug-induced Brugada syndrome occurs predominantly in adult males, is frequently due to drug toxicity, and occurs late after the onset of therapy. It may occur following treatment with cardiac or noncardiac drugs (www.brugadadrugs.org).²⁷

Presentation

The syndrome typically manifests during adulthood with either detection of the typical ECG pattern (type 1) or development of polymorphic VT or VF in 10-25% of patients during their life time. The first arrhythmic event typically occurs in men aged 40 to 50 years (SABRUS Registry).²⁸ In patients with typical type Brugada pattern (either spontaneously or after administration of sodium channel blockers) the event rate is 2.5% per year.¹⁶ Sudden cardiac death may occur typically at rest or during sleeping, and is precipitated by fever or the consumption of large meals, presumably due to glucose-induced insulin secretion that may enhance ST-segment elevation.²⁹ Syncope, nocturnal agonal respiration, palpitations and chest discomfort may also occur. Ventricular arrhythmias are usually polymorphic VT or VF, but monomorphic VT may also occur in 4% of patients.³⁰ Patients may also be entirely asymptomatic, and approximately 20% of them develop supraventricular arrhythmias such as AF or atrial flutter, or sick sinus syndrome. New-onset AF or AVNRT may be the first clinical manifestation of Brugada syndrome.³¹ Arrhythmic events in asymptomatic patients with Brugada syndrome have an annual incidence of 0.5%.¹⁰ Usual age range for the first arrhythmic event is 38-48 years.²⁸

Diagnosis

Diagnostic criteria are presented in Table 2. Placement of the right precordial leads in a superior position can increase the sensitivity of the ECG for detecting the Brugada phenotype, both in the presence or absence of a drug challenge (Figure 2). Conditions that are associated with ST-segment elevation (Table 3) should be ruled out. A variety of drugs have also been reported to produce a Brugada-like ST-segment elevation (Table 3), although it is not yet clear whether or to what extent a genetic predisposition may be involved. Lead V₃ may not yield diagnostic information; typical ECG changes in one only of V₁ or V₂ leads should be enough for diagnosis.³²

Three repolarization patterns are described (Figure 1):

- **Type-1 ECG pattern** Coved ST-segment elevation ≥ 2 mm followed by a negative T-wave, with little or no isoelectric separation, in >1 right precordial lead (from V₁ to V₃), imitating incomplete right bundle branch block but without the typical widened S wave in the left lateral lead.
- **Type-2 ECG pattern** ST-segment elevation followed by a positive or biphasic T-wave with a saddleback configuration.
- **Type-3 ECG pattern** Right precordial ST-segment elevation ≤ 1 mm with either a coved-type or a saddleback morphology.

Only type 1 is diagnostic of Brugada syndrome, but the ECG may fluctuate over time in

Brugada patients, and thus can change from type-1 to type-2 or type-3, or even be transiently normal. Vagal maneuvers, heavy meals, and β blockers accentuate the ECG patterns. Only the coved-type ST-segment elevation (type-1 ECG pattern) is diagnostic of the syndrome in the presence of clinical criteria described in Table 2. Mild prolongation of the PR interval may also be seen. Patients displaying the characteristic type-2 ECG without further clinical criteria should be described as having Brugada ECG pattern and not Brugada syndrome, unless if administration of sodium channel blockers reveals a typical type-1 pattern.

Brugada-like ECG can occasionally appear after direct current cardioversion or with the administration of certain drugs that should be probably avoided in diagnosed cases of the syndrome (Table 4), but it is not known whether a genetic predisposition is involved. Another confounding factor is the type of ST-segment elevation encountered in well-trained athletes (Figure 3), which is distinguished by an upslope rather than a downslope pattern, and by remaining largely unaffected by challenge with a sodium channel blocker. Brugada syndrome can be masked by complete RBBB. Spontaneous ST-segment elevation or relief of RBBB and demonstration of coved ST-segment elevation by right ventricular pacing can be useful for diagnosis (Figure 4).³³ Type-2 Brugada pattern presents characteristically an r'-wave in leads V1 – V2 that may be confused with incomplete RBBB, pectus excavatum, ARVC and athlete's ECG. The characteristics of the triangle formed by the ascendant and descendant arms of the r'-wave in leads V1–V2 are useful. A β angle $\geq 58^\circ$, and a duration of the base of the triangle ≥ 4 mm in leads V1–V2 indicate Brugada pattern (Figure 5).^{34,35}

ST-elevation ≥ 0.1 mV in lead aVR may also be seen in the ***familial ST-depression syndrome***, an autosomal inherited cause of polymorphic ventricular tachycardia. However, there is concave-upward ST-depression ≥ 0.1 mV in at least 4 leads (V3–V6 and I–III) 80 ms after J point, and with or without a notch in the ascending part of the ST segment.³⁶

Pharmacological challenge.

Drugs used are:

Ajmaline 1 mg/kg over 5 min IV (the best for this purpose)

Flecainide 2 mg/kg over 10 min IV, or 200-300 mg PO

Procainamide 10-15 mg/kg over 10 min IV

Psilicainide 1 mg/kg over 10 min IV

An unequivocal type 1 Brugada pattern is required for a positive result. This is characterized by J point elevation of at least 0.2 mV with coved ST elevation and T wave inversion. At least one ECG lead is required to demonstrate the type 1 Brugada pattern in standard or high positions: V1 and V2 in the second, third, and fourth intercostal spaces. The J point is defined as the end of the QRS complex, which can be identified most clearly in the limb lead, or if not feasible, in the lateral leads (i.e. lead II or V6) (Figure 6).³⁷

In young patients it can be performed as a bedside test. A pacing electrode may be necessary in patients at high risk for AV block. The pharmacological test should be monitored with a continuous ECG recording and should be terminated when: 1) the diagnostic test is positive; 2) premature ventricular beats or other arrhythmias develop; 3) QRS widens to $\geq 130\%$ of baseline. Isoproterenol is the antidote when required. Sodium channel blockade may provoke the Brugada ECG pattern in conditions such as ARVD (see ARVC chapter) and Chagas disease.⁹

The type 1 Brugada ECG pattern may be provoked by ajmaline in some healthy subjects.³⁸ Thus, due to the debated specificity and the overall very low risk for future events in asymptomatic individuals, a sodium blocking challenge test should not be performed in asymptomatic patients with a Type 2 Brugada pattern and no family history of BrS or sudden death.^{39,40} However, procainamide-induced type 1 Brugada patterns are very likely to represent a true positive (compared with a significant rate of false positives with ajmaline).⁴¹ Asymptomatic patients with a procainamide-induced type 1 Brugada pattern are at very low risk of malignant ventricular arrhythmias.⁴¹

Electrophysiology study The value of programmed ventricular stimulation (2-3 extrastimuli from the apex and RVOT) is still controversial (see risk stratification).

Noninvasive mapping with electrocardiographic imaging may also assist differentiation between Brugada syndrome and RBBB.¹²

Echocardiography may reveal the delayed onset of right ventricular contraction that reflects delayed depolarization over the anterior aspect of the RVOT epicardium.

Exercise testing is useful for risk stratification. Augmented ST-segment elevation during recovery from exercise predicts cardiac events.⁴²

A biomarker profile of autoantibodies against four cardiac proteins, namely α -cardiac actin, α -skeletal actin, keratin, and connexin-43, has been identified from sera of BrS patients and was highly sensitive and specific, irrespective of genetic cause for BrS, but experience is limited.⁴³

Genetic testing

Genetic testing indications are presented in Table 5 and Figure 6.⁴⁴ Genetic analysis and classification of variants following ACMG guidelines, has revealed that the diagnostic yield for pathogenic/likely pathogenic variants in European patients SCN5A is approximately 20% in European patients, compared to 6-11% in Asian patients.^{14 15} Genetic test results should be interpreted in the context of the fact that 2% of healthy Caucasians and 5% of healthy non-white subjects also host rare missense SCN5A variants,^{45,46} as well as the fact that evidence suggests that BrS is likely a polygenic disorder rather than a simple Mendelian monogenic disease.¹⁵ However, loss of function SCN5A mutations, as opposed to

other SCN5A variants, are associated with the risk of a lethal arrhythmia.^{14,19} Routine genetic evaluation of genes other than SCN5A (such as SCN10A) is not currently warranted in the clinical care of patients with BrS.¹³ Genetic screening is also recommended for family members of Brugada syndrome probands who have been successfully genotyped.¹

Risk stratification

1. Previous history of cardiac arrest or syncope, a spontaneous type-1 ECG at baseline especially fever-induced, and male gender have been shown to be related to the occurrence of cardiac events during follow-up.⁴⁷ Patients with aborted sudden death have a cardiac event rate of 7.7%/year.^{47,48}
2. The presentation of Brugada syndrome has changed, and there is a decrease in aborted sudden cardiac death.⁴⁹ Asymptomatic patients with Brugada ECG pattern have a low incidence of arrhythmic events (0.2% per year), and the arrhythmic risk is extremely low in the patients with the true drug-induced-only Brugada ECG (0.03% per year).⁵⁰
3. SCN5A mutation carriers exhibit more pronounced epicardial electrical abnormalities and a more aggressive clinical presentation,¹⁷ especially in females,⁶ and when the mutation is of the loss of function type.¹⁹
3. A family history of SCD in general does not appear to carry prognostic ability,^{28,48,51,52} but it is significant if SCD occurs in first degree relatives.⁵³
4. The inducibility of ventricular arrhythmias during the EPS may also bear ominous prognosis,^{54 10,55,56} but this is disputed.^{48,52,57} VF may be induced in up to 9% of apparently healthy individuals when aggressive stimulation protocols are used.⁵⁸ In the FINGER registry, inducibility of sustained ventricular arrhythmias was significantly associated with a shorter time to first arrhythmic event in the univariate analysis, but in the multivariate analysis, it did not predict arrhythmic events.⁴⁸ The PRELUDE registry reported their results on 208 patients followed for approximately 3 years. VT/VF inducibility was unable to identify high-risk patients, whereas the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation were indicators of high risk.⁵² However, in a subsequent study on a large patient cohort, induced ventricular arrhythmias (stimulation at the apex only) were associated with an increased risk of arrhythmic events during long-term follow-up.⁵⁵ In a meta-analysis of individual patient data without cardiac arrest from 8 studies, arrhythmias induced with programmed ventricular stimulation, especially with 1 or 2 extrastimuli, were associated with future ventricular arrhythmia risk, although a lack of induction did not necessarily portend low ventricular arrhythmia risk in patients with high-risk clinical features.⁵⁶ In another meta-analysis of 6 studies in asymptomatic patients, inducibility of VA in asymptomatic patients did not predict higher VA

or ICD shocks, and the low event rate in the asymptomatic population in almost all studies suggests that this population is at low risk for future cardiac events.⁵⁷ EPS is given a IIb-B-NR recommendation by the ACC/AHA/HRS 2017 GL on syncope.⁵⁹ In a subsequent report on a series with prolonged follow-up (up to 22 years), patients with spontaneous type-1 Brugada ECG pattern and positive EPS had significantly higher event rates than patients with negative EPS (0.7% vs 0.2% per year).⁵⁰

5. Type 1 ST elevation in the limb ECG leads can be seen in 10% of the patients with Brugada syndrome and is an independent predictor for a malignant arrhythmic event.⁶⁰ A wide and/or deep S-wave in lead I of the surface ECG study, reflecting delayed activation of the RVOT, is also a predictor of life-threatening ventricular arrhythmias.⁶¹ The combination of a fragmented QRS with an inferolateral early repolarization pattern (Figure 7), may also confer an adverse prognostic significance.⁶²

6. Augmentation of ST-segment elevation ≥ 0.05 mV in V_1 to V_3 leads observed at early recovery (1 to 4 min) after treadmill exercise has been reported to predict future arrhythmic events.⁴²

7. Asymptomatic patients with a Type 2 Brugada pattern and no family history of BrS or sudden death have a very low risk of future events.³⁹

8. The prognostic significance of NSVT is not known, but syncope indicates high risk, and could be due to sustained or long runs of non-sustained VT.

9. Women do not constitute a risk-free group. Neither clinical risk factors nor EPS predicts future arrhythmic events, and only AF and positive genetic test are risk factors for future arrhythmic events.⁶³

10. The value of risk stratification in Brugada syndrome in asymptomatic patients, in general, is low,^{2,64} and in a large cohort of patients, the two main risk scores the Shanghai and Sieira (Table 6) identified very high- and low-risk patients but did not allow stratifying the risk of arrhythmic events in intermediate-risk patients.⁶⁵ In this large cohort, the event rate at 10 years was significantly higher only with a score of 5 of the Sieira score, whereas the Shanghai score did not allow to better stratify the risk of SCA.⁶⁵

Therapy

Cardiac arrest or syncope in the presence of a diagnostic ECG are indications for **ICD** (Table 7 and Figures 8 and 9). These patients have a 48% and 19% chance of appropriate shock within the next 10 years, respectively).⁴⁷ The decision to implant an ICD should be weighted against a reported 36% risk of complications such as lead failure and inappropriate shocks.⁴⁷ Special care during implantation, adequate device programming, and regular follow-up are necessary to reduce adverse events.⁶⁶ T-wave oversensing is a potential reason of

inappropriate shocks, and its incidence is significantly lower using an integrated bipolar lead system when compared with a dedicated bipolar lead system.⁶⁷ Avoidance of ICD implantation or replacement, may be considered in elderly BrS patients who remain free from VF until 70 years of age.⁶⁸ The subcutaneous ICD is also an option for primary prevention in young patients without need of pacing.⁶⁹ **Quinidine**, a drug that blocks I_{to} that is particularly expressed in the distal Purkinje cells, has been successfully tried.⁷⁰ Quinidine-induced diarrhea is treated with cholestyramine.⁵ Quinidine therapy should be considered in pregnant women with BrS who have arrhythmic events during **pregnancy** (ESC 2025 GL on pregnancy, IIa C).⁷¹ **Denopramine, colistazol and bepridil** have also been proposed for VF suppression.⁵ Controversy exists about asymptomatic patients with a spontaneous type-1 ECG at baseline or after pharmacological challenge.^{9,54}

Catheter ablation over the epicardial RVOT has been reported to result in normalization of the Brugada ECG pattern and prevent clinical VF, but experience is limited.⁷² Drugs that should be avoided in Brugada syndrome are listed on www.brugada.drugs.org.

A clear association between exercise and sudden death has not been established in Brugada syndrome, and recommendations to these patients should be better individualized.⁷³

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