REVIEW ARTICLE

The Diagnosis, Risk Stratification, and Treatment of Brugada Syndrome

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SUMMARY

Background: Brugada syndrome (BrS) is among the more common familial arrhythmia syndromes, with an estimated prevalence of 1 to 5 per 10 000 persons. It is characterized by a right ventricular conduction delay, dynamic or persistent ST-segment elevations in the precordial leads $V_{1–3}$, and an elevated risk of syncope and sudden cardiac death in young adults without structural heart disease.

Methods: This article is based on original and review articles on BrS that appeared in English from 2010 onward and were retrieved by a selective search in PubMed, with special attention to international consensus publications on inherited arrhythmogenic diseases.

Results: According to the new diagnostic criteria, the diagnosis of BrS requires typical ECG changes in only one precordial lead. This will likely increase sensitivity, but may also lead to an increase in asymptomatic patients. Established risk markers include sudden cardiac arrest and a spontaneous type 1 ECG with arrhythmic syncope. Patients with these findings benefit from the implantation of a cardioverter-defibrillator. There is no validated algorithm for risk stratification of asymptomatic patients. Because of the low prevalence of BrS, there have been no randomized controlled trials (RCTs) in this disease, and all recommendations are based on expert opinion. BrS is usually inherited in an autosomal dominant manner. Recently discovered gene polymorphisms modify the risk of BrS, challenging the conception of BrS as a monogenetic disease. Electro-anatomic mapping studies have revealed, for the first time, an arrhythmogenic substrate over the right ventricular outflow tract in BrS patients.

Conclusion: BrS is one important differential diagnosis to consider in patients presenting with syncope or sudden cardiac arrest. The goal of current research is to achieve a deeper understanding of the genetic and electrophysiological changes underlying BrS. Further insights in these areas will probably enable better risk stratification of asymptomatic BrS patients in the future.

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In 1992, the Spanish brothers Pedro and Josep Brugada described a new disease entity seen in eight patients. Its characteristics were right bundle branch block, persistent ST-segment elevation, and sudden cardiac death (1). In the following years, it was to become known as "Brugada syndrome" (2). With an estimated prevalence of 1 to 5 in 10 000, Brugada syndrome (BrS) is one of the commoner forms of inherited arrhythmogenic disease (3, 4). Characteristic features are:

- Right ventricular conduction delay
- Dynamic or persistent ST-segment elevations in precordial leads $V_{1–3}$, and
- Considerably increased risk of syncope and sudden cardiac death due to polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) in young adults without structural heart disease (1–6, e1).

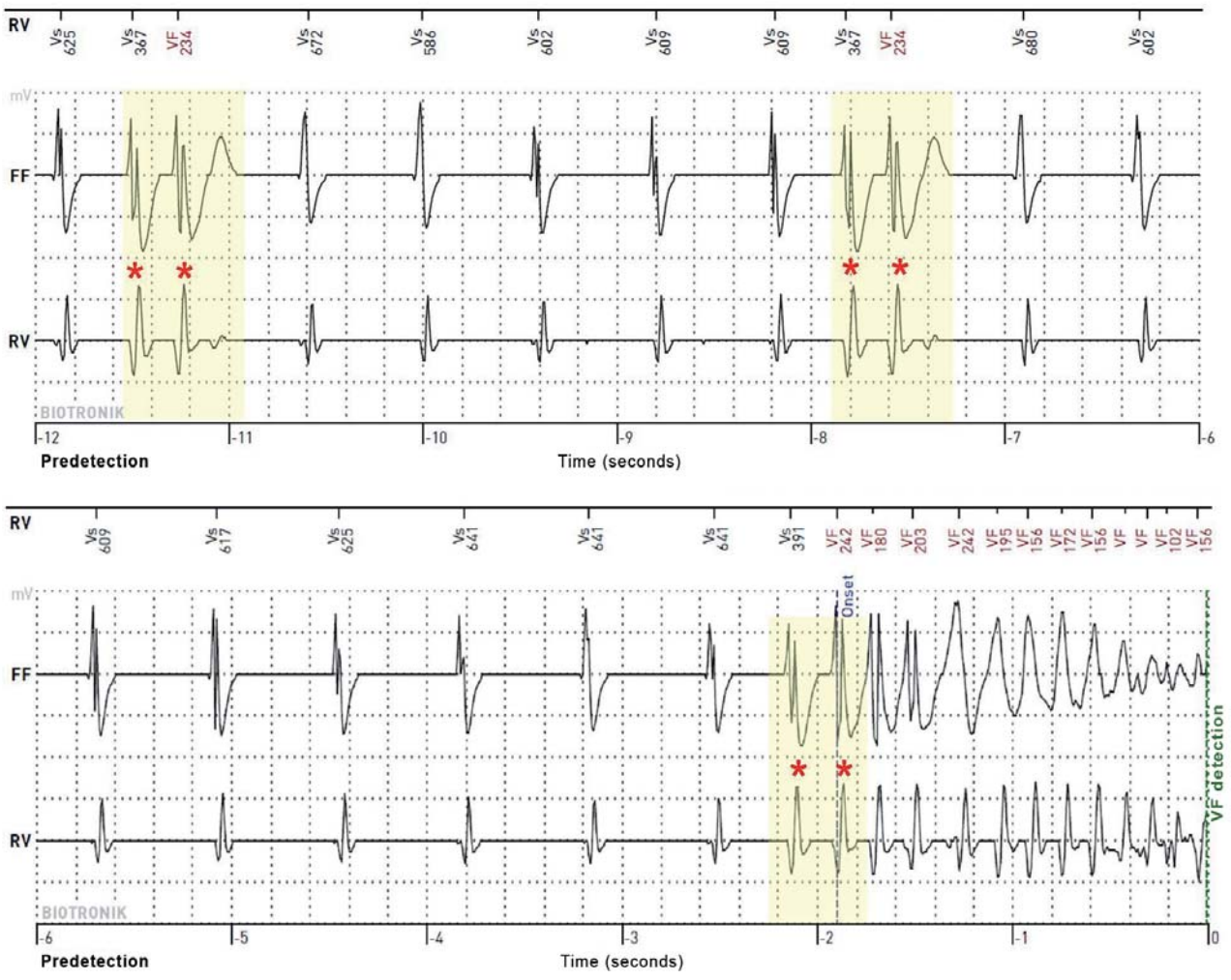
After sudden cardiac arrest the risk of VT/VF recurrence is approximately 50% in the next 5 years (7). Men are considerably more often affected than women (8) and usually show a more severe phenotype (9), although many patients are asymptomatic at first diagnosis and in the course of the disease (10). BrS typically manifests during the third to fifth decades of life, but the disease can occur at any age (1, 8, e2). Symptoms range from palpitations and dizziness to recurrent syncope, nocturnal agonal respiration, and (aborted) sudden cardiac death.

Ventricular fibrillation in BrS typically occurs at night (11) or in resting phases during periods of increased vagal tone, and can be initiated by monomorphic ventricular extrasystoles (*Figure 1*) from the right ventricular outflow tract (RVOT) (e3–e5). Supraventricular arrhythmias (especially atrial fibrillation) are found in 15% to 30% of patients (e6–e9). Among the known triggers for the occurrence of cardiac arrhythmias in BrS are fever, which must be reduced immediately, and certain drugs (www.brugadadrugs.org) (1, 5–6).

Since there are no randomized, controlled and/or blinded studies for inherited arrhythmogenic diseases such as BrS, all the recommendations given in this text are based on expert opinion (evidence level C) and should be understood as follows (3–6):

- Class I recommendation: the therapeutic intervention is recommended.
- Class IIa recommendation: the therapeutic intervention may be useful/effective.

FIGURE 1



Spontaneous ventricular fibrillation in a 50-year-old man with sudden cardiac arrest as the first manifestation of Brugada syndrome. The recording of the implantable cardioverter–defibrillator (ICD) consists of three channels. The marker channel (RV) shows the interpretation of sensed events (Vs = ventricular sensing) by the ICD. The far field (FF) and the right ventricular (RV) electrograms (EGM) are derived between the tip of the electrode and the ICD can (FF) and between the distal tip and proximal ring of the ICD electrode (bipolar, RV), respectively. The predetection time is given in seconds. The defibrillator EGM shows monomorphic ventricular extrasystoles (as couplets, asterisks) with identical coupling intervals (in milliseconds), which eventually trigger ventricular fibrillation (VF).

- Class IIb recommendation: the therapeutic intervention may be considered.
- Class III recommendation: the therapeutic intervention is not recommended.

Pathophysiology

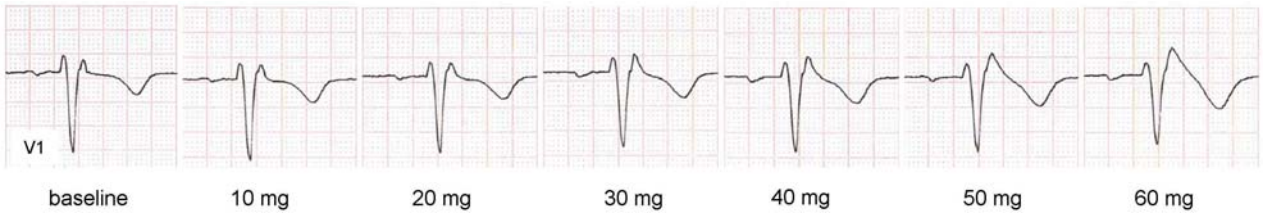
As the site of origin of malignant arrhythmias, the right ventricle has been described as the weak point and the RVOT as the Achilles heel of BrS (e10, e11). Whether BrS is caused by a disturbance of depolarization, repolarization, or cardiac development in this region of the heart is a question under debate (12, 13). Some studies show reduced conduction velocity in the RVOT (14, 15), reduced gap junction expression (e12), and increased fibrosis (14, e12), suggesting disturbed depolarization.

The repolarization hypothesis postulates an unbalance between depolarizing inward currents (sodium and L-type calcium currents, I_{Na} and $I_{Ca,L}$) and the prominent transient outward potassium current (I_{to}) during early repolarization in the epicardial RVOT (13). Animal studies have recently demonstrated reduced conduction reserve in the fetal and the adult RVOT (e13).

Diagnosis

To date, the diagnosis of BrS has required a typical type 1 ECG ("coved type") *(Figure 2)* in at least two

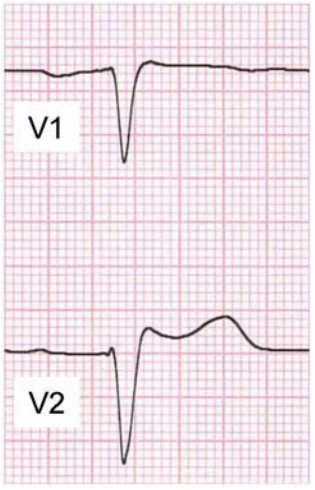
FIGURE 2



Dynamic ST-segment elevation during fractionated administration of ajmaline. After 12 minutes and a total of 60 mg ajmaline, V_1 (2^{nd} intercostal space) shows a type 1 ECG with coved ST-segment elevation (ST-segment elevation ≥ 2 mm with descending ST segment, and inverted T wave, "coved" pattern [e23]).
V1 = precordial lead; ECG = electrocardiogram

Type 2 ECG with saddle-back type ST-segment elevation in V_2, suspicious for Brugada syndrome: high take-off of r' ≥ 2 mm with ST segment elevation ≥ 0.5 mm and positive T wave, where $T_{max} > ST_{min} > 0$, saddle-back pattern (e23)

FIGURE 3



precordial leads ($V_{1–3}$) and the presence of one clinical criterion:

- Documented ventricular arrhythmia: Polymorphic VT or VF
- Arrhythmia-related symptom: Syncope, seizure, or nocturnal agonal respiration
- Positive family history: Sudden cardiac death before age 45 or type 1 ECG in relatives (8, 11).

New diagnostic criteria

To increase diagnostic sensitivity, the expert consensus statement of 2013 on inherited arrhythmogenic diseases (5, 6) omits any clinical criterion (e14) and demands diagnostic ECG changes in only one right precordial lead (e15). Once any possible differential diagnoses with similar ECG changes ("phenocopies") (e16)—for example, electrolyte disturbances, pericarditis, acute myocardial infarction, or pulmonary embolism (8)—and arrhythmogenic right ventricular cardiomyopathy (e17) have all been excluded, BrS is definitively diagnosed if a type 1 ECG is observed in V_1 or V_2, either spontaneously or induced by Na^+-channel blockade (e.g., using ajmaline) (e18–e20). The precordial leads V_1 and V_2 may be placed in the standard position or higher, up to the second intercostal space (ICS) (*Figure 2*) (5, 6). Both echocardiographically (e21) and by magnetic resonance imaging (MRI) (e22), a correlation has been demonstrated between the anatomical location of the RVOT and the intercostal space in which diagnostic ECG changes occur. The new diagnostic criteria have already been validated in a first case series of patients with known BrS (e21).

The saddle-back type 2 and type 3 ECG patterns are suspicious for, but not diagnostic of BrS (8) and the two patterns have now been grouped together into one type 2 ECG (saddle-back pattern) (*Figure 3*) (e23). When encountering a type 2 ECG the diagnosis of BrS may only be made after drug-induced conversion to a type 1 ECG (5, 6). Because of frequent fluctuations between diagnostic, non-diagnostic, and normal ECGs without ST-segment changes, repeated ECG recordings should be performed for accurate risk stratification (16, e24). In asymptomatic patients, other ECG changes may support the diagnosis (5), such as:

- First-degree atrioventricular block (e25)
- Right bundle branch block (e25)
- Fragmented QRS complex (17)
- Increased ST-segment elevation during exercise (e26) or during the recovery phase after exercise (e27–e29)
- Ventricular extrasystoles with left bundle branch block pattern (*Figure 4*) (e3, e4)
- Atrial fibrillation (e14).

Genetics

BrS is a genetic disease with an autosomal dominant pattern of inheritance and incomplete penetrance (3–4). To date, changes in 22 genes have been linked with BrS (18, e30–e32). Of practical relevance is the most frequent mutation in the Na^+ channel gene *SCN5A*, which has been shown to be present in 20% to 30% of patients (e33, e34). The other involved genes represent rare sporadic cases or individual BrS families (18, 19, e35). In functional terms, the mutations show either a loss-of-function effect on depolarizing currents (I_{Na} or $I_{Ca,L}$) or a gain-of-function effect on repolarizing

currents (I_{to} and ATP-sensitive potassium current, $I_{K\text{-}ATP}$) (19). Whether these aforementioned gene mutations are actually causative of BrS or only have a modifying role is a matter of ongoing debate (19, 20). More recent data show frequent genetic variants (single nucleotide polymorphisms, SNPs) in *SCN5A*, *SCN10A*, and *HEY2* (*SCN5A* codes for the alpha subunit of the voltage-gated Na^+ channel Na_v 1.5; *SCN10A* codes for the voltage-gated Na_v 1.8; *HEY2* codes for the transcription factor HEY2). These gene polymorphisms influence individual disease risk and may in the future allow the development of a genetic risk score that could be of practical clinical use (21).

At present, molecular genetic testing is indicated for all patients with a type 1 ECG (class IIa recommendation) (3–4, 18). Because the interpretation of the genetic results may be challenging—especially in *SCN5A*-related "overlap" syndromes (long QT syndrome type 3, progressive cardiac conduction defect, J-wave syndrome, and others) (e36)—genetic counseling should take place in collaboration with a center with proven expertise (3, 4).

Risk stratification

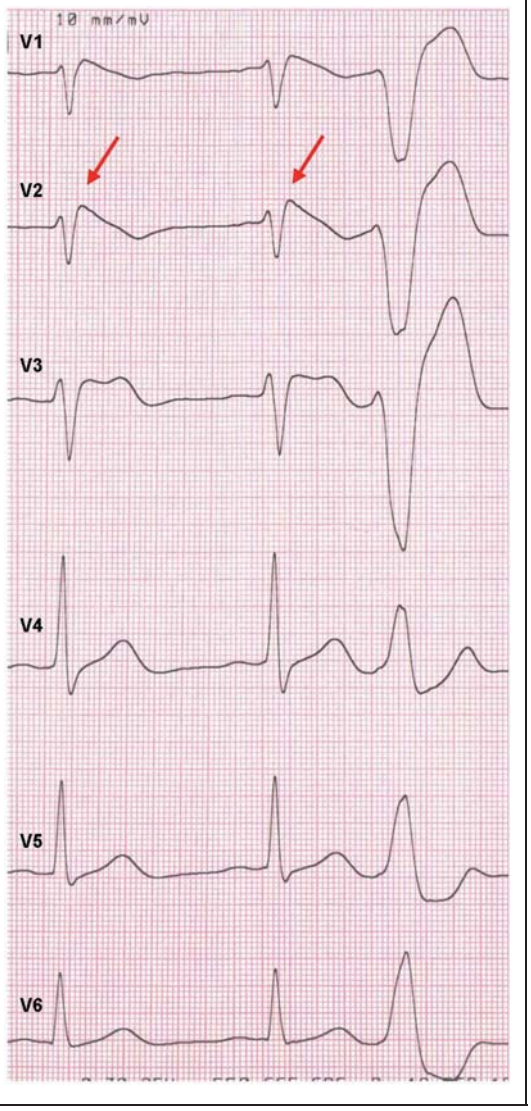
With the clinical diagnostic criterion no longer being used, risk stratification (*Figure 5*) plays a critical role, both to identify patients at high risk of sudden cardiac death, who actually would benefit from placement of an implantable cardioverter–defibrillator (ICD), and to identify asymptomatic patients with a very low risk, in order to spare these patients from undergoing a probably unnecessary ICD placement (5–6, 19) and potential ICD-related complications (7, e37–e41).

Classical risk markers

Since BrS was first described (1), numerous markers for risk stratification have been identified, but only symptoms (sudden cardiac arrest and syncope), and a spontaneous type 1 ECG have consistently been associated with a raised VT/VF risk in all studies and thus have prognostic impact (10, 19, 22, 23). Established risk markers are sudden cardiac arrest and a spontaneous type 1 ECG in association with the occurrence of arrhythmic syncope (5, 6). Nonarrhythmic syncope (e.g., vasovagal or orthostatic syncope), which is also often seen in BrS patients, has no prognostic impact, and it is therefore important to distinguish between these two entities during history-taking (24).

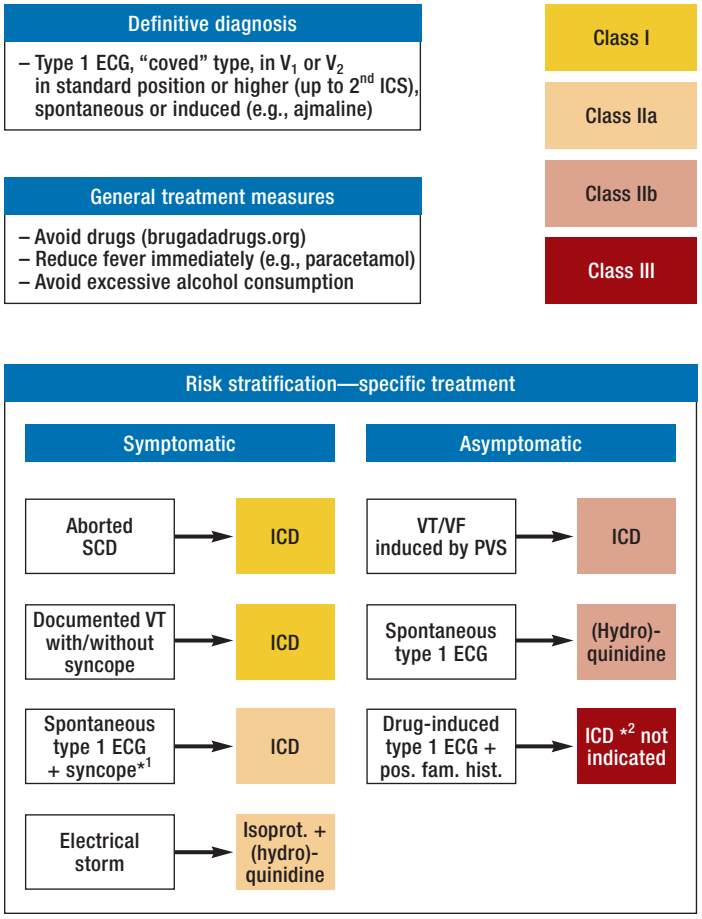
Asymptomatic patients with BrS show, over the follow-up periods reported to date, a very low incidence of malignant arrhythmias (e.g., 0.5% per year in the largest BrS registry [10], with 1029 patients and a follow-up of 14–54 months) (19). As a method of assessing individual risk of ventricular arrhythmias, the current expert consensus (5, 6) mentions programmed ventricular stimulation, which tests the inducibility of VF in the setting of an electrophysiological examination. However, there is still disagreement between the initiators of the Brugada registry and other groups regarding the prognostic impact of VF inducibility (25–28). In the Brugada registry, VT/VF induction in previously asymptomatic BrS patients was associated with a markedly higher risk of ventricular arrhythmias in the future (27), but two meta-analyses reported no prognostic impact of VT/VF inducibility (22, 26). The meta-analyses results were confirmed in the FINGER (France, Italy, Netherlands, Germany) study (10) and in the prospective Italian PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) study (23), and the former class IIa recommendation for ICD implantation in patients with inducible VF (11) has been downgraded to IIb in the recent expert consensus statement (5, 6) (*Figure 5*). In one study, a combination of programmed ventricular stimulation and clinical

FIGURE 4



Ventricular extrasystole with left bundle branch block pattern from the right ventricular outflow tract in a patient with Brugada syndrome with spontaneous type 1 ECG in V_2 (arrows) and type 2 ECG in V_3

FIGURE 5



Algorithm for diagnosis, risk stratification, and treatment of Brugada syndrome
(adapted from Priori et al. [5, 6])
*1 Arrhythmic;
*2 For explanation see text, *Risk stratification* and *Treatment*
ICS, intercostal space; SCD, sudden cardiac death; ICD, implantable cardioverter–defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; PVS, programmed ventricular stimulation; ECG, electrocardiogram; pos. fam. hist., positive family history; isoprot., isoproterenol

parameters was used for risk stratification of asymptomatic patients (29), and Giustetto (e42) and Brugada et al. (27) emphasize the high negative predictive value of programmed ventricular stimulation. Asymptomatic patients should be reassessed at regular intervals; in particular, a spontaneous type 1 ECG indicates an elevated risk for ventricular arrhythmias (16).

Novel risk markers

A relatively new risk marker and sign of disturbed depolarization has been described in patients with BrS: a fragmented QRS complex (fQRS) (*Figure 6*) (17). fQRS is defined by two or more spikes within the QRS complex in leads V_1–V_3 (23). QRS fragmentation, initially identified as a risk marker after myocardial infarction (e43), appears, according to early study results, to be associated with a markedly higher risk of VF in BrS patients (17, 23, 30). The question of whether fQRS in V_1–V_3 reflects the arrhythmogenic substrate (see *Catheter ablation*) has not yet been investigated. The ECG filters need to be adjusted to detect the high-frequency QRS fragmentation (17).

About 10% of BrS patients (a higher percentage than in the normal population) show signs of early repolarization (ER) in the inferolateral leads (e44) (*Figure 7*). These ECG changes, long regarded as benign (e45), can be associated with an increased risk of sudden cardiac death and the occurrence of VF, now known as ER syndrome (e46–e48). In early studies, BrS patients with signs of early repolarization show a more severe phenotype and a considerably increased risk of VF, respectively (30–33). In addition, there is an increased risk of an "electrical storm" (≥3 VT/VF episodes within 24 hours) if additional signs of ER are present (33, 34). Patients with right precordial fQRS and inferolateral ER appear to have a particularly high risk of VF (30).

In two studies, paroxysmal atrial fibrillation was associated with more frequent syncope and/or ventricular fibrillation (e7, e8).

Not relevant to risk stratification

According to the study results (10, 22, e49), a family history of sudden cardiac death or the presence of a *SCN5A* mutation has no prognostic impact and is therefore currently not included in risk stratification (5, 6).

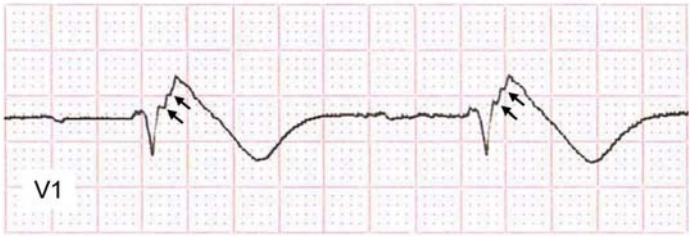
Treatment

Implantable cardioverter–defibrillator

In symptomatic BrS patients (aborted sudden cardiac death, documented VT with or without syncope), implantation of an ICD is clearly indicated (class I recommendation) (5, 6) (*Figure 5*). Because of the high risk of ventricular arrhythmias, ICD implantation is also indicated in symptomatic BrS patients with arrhythmic syncope and a spontaneous type 1 ECG (class IIa recommendation) (5–6, 35) (*Figure 5*). ICD implantation is the only treatment shown in studies to be effective in preventing sudden cardiac death in BrS patients (7). To avoid inappropriate ICD shocks, a single VF detection zone with a long detection time can be programmed (7, e50). The role of the subcutaneous ICD (S-ICD) is about to be evaluated in a multicenter study (S-ICD Brugada; NCT02344277).

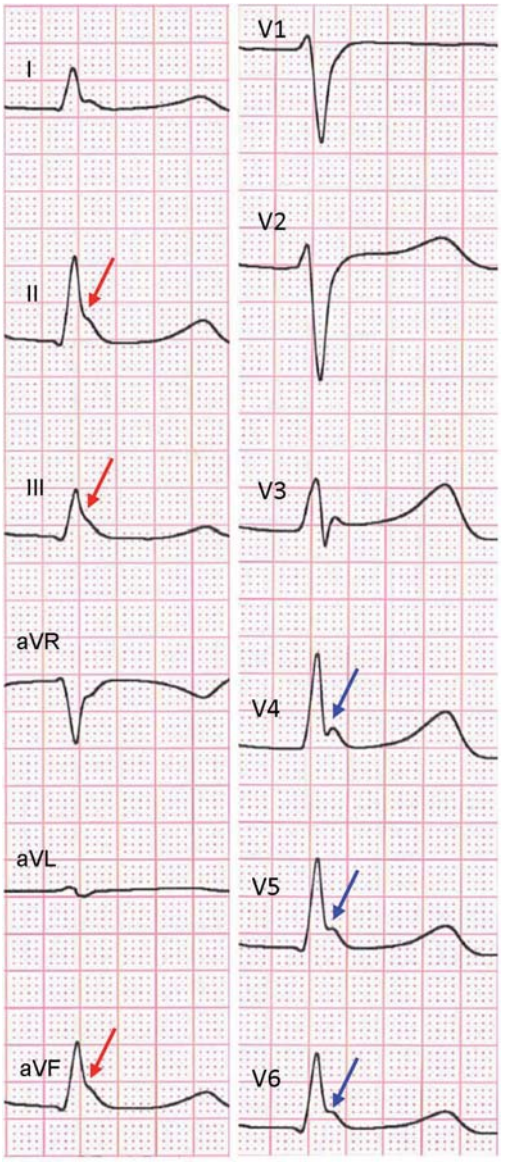
For asymptomatic BrS patients, individual risk assessment including consideration of other risk factors (age, sex, baseline ECG, and inducibility) is recommended (5, 6). Because of the very low risk of ventricular arrhythmias in asymptomatic BrS patients (10) without spontaneous type I ECG (19), primary prophylactic ICD implantation on the basis of only a drug-induced type I ECG and a positive family history of sudden cardiac death is currently not recommended (class III recommendation) (5, 6) (*Figure 5*). It is important to realize that these recommendations represent a snapshot and that the current follow-up times do

FIGURE 6



Fragmented QRS complex (fQRS) with two spikes (arrows) within the QRS complex in V_1 in a patient with Brugada syndrome with type 1 ECG

FIGURE 7



Early repolarization pattern in the form of QRS "slurring" (red arrows) and "notching" (blue arrows) in the inferior (II, III, aVF) and lateral ($V_{4–6}$) leads in a 49-year-old man with sudden cardiac arrest as the first manifestation of Brugada syndrome

not allow any definite conclusions about the long-term risk in this patient group (e51). The most recent data from the Brugada registry show for example VT/VF-related ICD shocks in 13% of initially asymptomatic patients with BrS (mean follow-up: 7 years) (e41).

General therapeutic measures

In patients with BrS, many substances in addition to class IC antiarrhythmics can have a proarrhythmic effect and need to be avoided. These include certain beta-blockers, various psychoactive and anesthetic drugs, antihistamines, cocaine, and alcohol consumed in excessive quantities. Fever, another important trigger of ECG changes and VT/VF in BrS patients, must be treated immediately with an antipyretic, e.g., paracetamol (class I recommendation) (5, 6) (*Figure 5*).

A current list of contraindicated drugs and further information about how to act in cases of fever, anesthesia, and recurrent ventricular arrhythmias, is available at www.brugadadrugs.org.

Drug therapy

In case of electrical storm (≥ 3 VT/VF episodes within 24 hours), beta-sympathomimetics such as isoproterenol and I_{to}-blockers such as (hydro)quinidine are used (class IIa recommendation) (5, 6, e3, e52) (*Figure 5*). Any precipitating factors such as fever or hypokalemia must be treated at the same time (e3, e52). Isoproterenol can result in immediate reduction of the typical ST elevation (e53) and reduction of (VF-initiating) ventricular extrasystoles with VF suppression (e54). After treatment with (hydro)quinidine, ST elevation may also decrease, in some cases to the point of normalization of the ECG (e55), and VF suppression has been reported in about 85% of patients (36). In addition to its known gastrointestinal side effects, especially a significantly prolonged QTc time may limit (hydro)quinidine treatment (19).

Treatment with (hydro)quinidine can also be considered in hitherto asymptomatic BrS patients with a spontaneous type 1 ECG (class IIb recommendation) (5, 6) (*Figure 5*). One study that was terminated early (NCT00927732) (e56) and one study that is still recruiting (NCT00789165) (e57, e58), using (hydro)quinidine in asymptomatic patients with BrS,

show good long-term drug tolerability and a low incidence of arrhythmias, although patient numbers are still small (about 200 patients in total).

Catheter ablation

For the first time, the current expert consensus includes catheter ablation in its therapeutic recommendations for BrS. Catheter ablation may now be considered in BrS patients with a history of electrical storms or repeated appropriate ICD shocks in whom other treatments have failed (class IIb recommendation) (5, 6). Haïssaguerre et al. and other groups have already demonstrated successful endocardial catheter ablation of the VF triggers (RVOT extrasystoles) in a few BrS patients (37, e59). However, these triggers occur extremely rarely and thus a substrate-based approach has been developed. For the first time, Nademanee et al. have identified fractionated electrograms (a typical feature of disturbed depolarization) over the anterior RVOT as an arrhythmogenic substrate in nine highly symptomatic BrS patients. After epicardial catheter ablation of these potentials, the ECG normalized and there was no further VF episode in eight of nine patients off any antiarrhythmic drugs during a mean follow-up of 20 months (38). Similar results were obtained by Cortez-Dias et al. who performed epicardial catheter ablation in a highly symptomatic woman with BrS (39). As a further indication of disturbed depolarization in BrS, Sacher et al. showed that a drug-induced ECG conversion (type 2 to type 1 ECG) correlated with a further increase of the duration of the epicardial fractionated potentials (40).

KEY MESSAGES

- Brugada syndrome is an important differential diagnosis for syncope and (aborted) sudden cardiac death in young adults without structural heart disease.
- Based on the new diagnostic criteria of 2013, Brugada syndrome is diagnosed in patients with spontaneous or drug-induced type 1 ECG in V_1 or V_2 (positioned in the 4th, 3rd, or up to the 2nd intercostal space).
- Symptomatic patients with sudden cardiac arrest or a spontaneous type 1 ECG plus arrhythmic syncope are at high risk of sudden cardiac death and should be provided with an implantable cardioverter–defibrillator (ICD).
- Novel noninvasive risk markers may be a fragmented QRS complex in the right precordial leads and signs of early repolarization in the inferolateral leads.
- Using electro-anatomic mapping techniques, an arrhythmogenic substrate of the right ventricular outflow tract (RVOT) has for the first time been demonstrated in patients with Brugada syndrome. Catheter ablation of these fractionated potentials can prevent recurrence of ventricular fibrillation in highly symptomatic patients in whom other treatments have failed.

Conflict of interest statement
The authors declare that no conflict of interest exists.

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REVIEW ARTICLE

The Diagnosis, Risk Stratification, and Treatment of Brugada Syndrome

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