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BRUGADA SYNDROME: FROM DIAGNOSIS TO TREATMENT AND PREVENTION – CURRENT KNOWLEDGE

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ABSTRACT

Brugada syndrome is a rare inherited cardiac arrhythmia disorder characterized by a high risk of sudden cardiac death in structurally normal hearts. This channelopathy is associated with syncope caused by ventricular tachyarrhythmias, especially among the male population. Current studies results show that this illness is not solely inherited in an autosomal dominant manner, which occurs in only 3 out of 10 patients. Intensive research has deepened the understanding of its genetic, electrophysiological and clinical aspects. However, Brugada syndrome remains a major diagnostic and therapeutic challenge, especially in asymptomatic patients and in risk stratification. The main type of treatment remains implantable cardioverter-defibrillator, but results of clinical studies show that epicardial ablation can also represent satisfactory results. This review provides a summarized synthesis of current knowledge on Brugada syndrome, including epidemiology, pathophysiology, genetic basis, clinical presentation, electrocardiographic characteristics and diagnostic criteria, risk stratification, treatment approaches and preventive measures in a comprehensive and detailed way.

KEYWORDS

Brugada Syndrome, SCN5A, ECG, ICD, Ablation

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Introduction

Brugada syndrome stands as one of the most significant inherited channelopathies, causing sudden cardiac deaths (SCD) in the young population. It was first described in the early 1990s by the Brugada brothers as a distinct clinical entity. Early observations emphasized the male predominance, familliar occurrence and higher risk of fatal ventricular arrhythmias during sleep or in patients undergoing fever. This cardiac syndrome is associated with a characteristic electrocardiographic (ECG) pattern and specific magnetic resonance imaging (MRI) changes, especially in the right ventricular outflow tract (RVOT). This illness is highly heterogeneous both clinically and genetically, making its diagnosis and management difficult. The identification of patients at high risk of life-threatening arrhythmias remains a major clinical challenge. [1,2]

Methodology: A narrative literature review was conducted in accordance with current standards for evaluating the quality of review articles. Research was designed on the newest studies and clinical publications. PubMed was used to create the database. This manuscript is focused on recent aspects of pathophysiology, diagnostic methods and therapeutic strategies.

Discussion

1. Epidemiology

Brugada syndrome is considered a relatively rare disease, with an overall prevalence of 2–5 per 10,000 people worldwide. However, its distribution is uneven, with a much higher prevalence in Southeast Asia, where it is a major cause of sudden unexplained nocturnal death. Importantly, BrS accounts for a significant proportion of unexplained sudden deaths, especially in early-to-middle adulthood populations and in geographical regions with a high prevalence of sudden unexplained death syndrome (SUNDS). One of the most important epidemiological features of BrS is the strong male predominance. Men are affected far more frequently than women, with reported ratios as high as 5:1 for the male population. [3,4] This difference is thought to be hormonally modulated, with the main role played by testosterone in modulating the cardiac ionic currents, in particular the transient outward potassium current (Ito). The syndrome is diagnosed mostly in adulthood but can occur at any age, including pediatric populations, where it can present more aggressively, especially in the presence of fever. [5,6]

2. Genetics and molecular pathophysiology

2.1 Genetic basis

BrS is predominantly inherited in an autosomal dominant way with incomplete penetrance. The most common genetic culprit is a pathogenic missense variant of the SCN5A gene, encoding the α unit of the cardiac voltage-dependent sodium channel NaV1.5. This protein is situated in the membrane of a cardiomyocyte and plays a significant role in the regulation of electrical transmission between cardiac cells. Mutation of that gene typically results in loss-of-function effects with diminished sodium current and reduced inward sodium current. This process leads to impairment of depolarization and, as a result, conduction delay, fragmented electrograms or arrhythmias. [7,8] What is more, SCN5A mutations can be identified in only about 20–30% of patients. Among the other patients, scientists identified alterations in the genes encoding calcium channels (CACNA1C, CACNB2B), potassium channels (KCND3, KCNE3) and regulatory proteins involved in ion channel trafficking (PKP2, RYR2). [3,9] Recent advances underscore a complex, often oligogenic basis for BrS, with common variants at SCN5A, SCN10A, and HEY2 loci modulating risk and phenotype. Genome-wide association studies (GWAS) have identified >20 risk loci, highlighting the interplay between rare and common genetic variation. The significance of the remaining gene quantities must be studied. [10,11]

2.2 Molecular and cellular mechanisms

Brugada syndrome is a disease process that is fundamentally related to an imbalance of inward and outward ionic currents during the early phases of cardiac action potential. Reduced inward sodium current (INa) is essential and results in impaired depolarization and a decrease in conduction speed. However, increased outward potassium current, particularly Ito, results in enhanced repolarization gradients across the ventricular wall. This difference is especially pronounced in the RVOT, which is considered the main arrhythmogenic substrate. [9,12,13] One scientific analysis presents the fact that exosomal C-type natriuretic peptide (CNP) messenger RNA (mRNA) levels were significantly increased in patients with Brugada syndrome, while microRNA-138-5p (miRNA) was selectively downregulated, with other analyzed miRNAs showing no significant differences. Additionally, positive correlations between CNP expression and selected miRNAs suggest coordinated regulatory pathways. These findings indicate the potential presence of early molecular remodeling underlying the pathogenesis of BrS. [14]

2.3 Structural abnormalities

Although BrS has been traditionally considered a pure channelopathy, growing evidence indicates the presence of subtle structural abnormalities, including histologically confirmed interstitial fibrosis and altered gap junction expression, especially in the area of the RVOT but also at the His bundle or even Purkinje fibers. These lesions may be the origin of arrhythmias generation and support the notion of BrS as a disease with both electrical and structural components. [15-17]

3. Clinical features

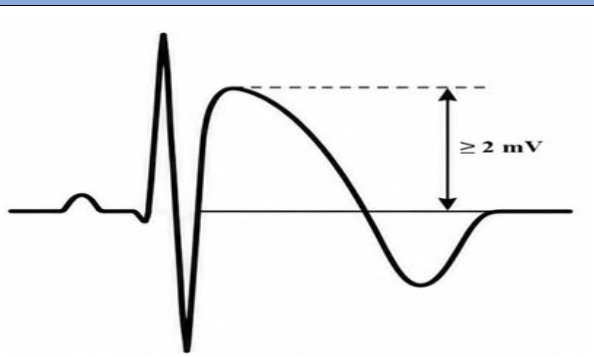
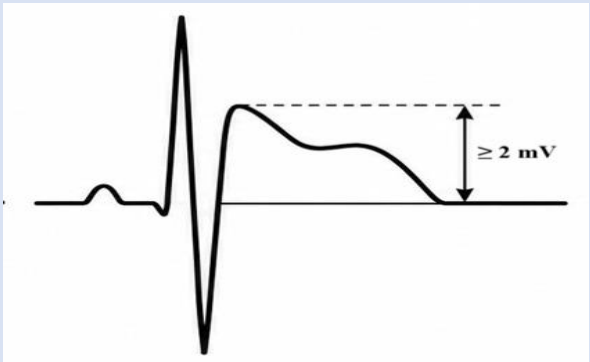
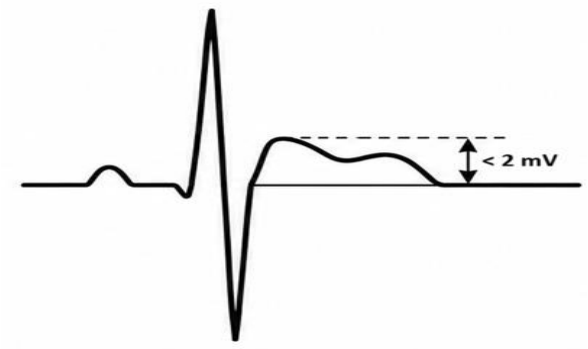
The clinical spectrum of Brugada syndrome is extremely heterogeneous. The multitude of symptoms ranges from palpitations, chest discomfort or unexplained syncope to nocturnal agonal respiration or even SCD as the first manifestation. Moreover, this condition may occur alongside various arrhythmias, such as atrial fibrillation. The most important fact is that the majority of patients do not present any kind of clinical symptoms and the illness is diagnosed by accident. Faintness and episodes of fatal tachyarrhythmias often occur during sleep or at rest, which reflects the effect of increased vagal tone. [18,19] Additionally**,** a certain multicenter retrospective study investigates how often bradyarrhythmias occur in patients with Brugada syndrome. The results show that they are relatively rare (1.9%) but are associated with a higher incidence of ventricular arrhythmias (4 events per 100 person-years). The outcomes suggest that bradyarrhythmias may be part of the broader disease process in Brugada syndrome but are not clearly independent predictors of worse outcomes. [20] Studies have shown a few well-established factors that can reveal or trigger arrhythmias in BrS, such as episodes of enhanced vagal tone, such as sleeping or binge eating. Additionally, electrolyte imbalance, fever, emotional stress, consumption of alcohol or cocaine may also lead to arrhythmic events. Treatment of fever with antipyretic drugs should be recommended to all patients with Brugada syndrome. Moreover, administration of certain groups of medicaments should be contraindicated in patients with this syndrome because of their potential to induce arrhythmias. These groups include antiarrhythmic class I agents represented by ajmaline, procainamide or flecainide, anesthetics like bupivacaine or propofol, antidepressants and neuroleptics, such as lithium, lurasidone or clozapine. What is intriguing, quinidine, a member of the class I group, is not contraindicated. Instead, it serves as a diagnostic tool. [21-24]

4. Current approach to diagnosis

4.1 Electrocardiogram patterns

The diagnosis of Brugada syndrome depends mainly on characteristic 12-lead ECG findings located in the right precordial leads V1-V3. According to the scientific literature, there are three types of ECG patterns of this disorder. However, referring to guidelines, only type 1 can be recognized as a diagnostic one. Type 2 and type 3 are considered as not specific enough to confirm diagnosis and, as a result, non-diagnostic features in ECG. Due to that fact, provocative testing should be performed to confirm the diagnosis. Type 1 is defined as at least one right precordial V1-V3 ECG lead, placed in the second, third, or fourth intercostal spaces, having a J point elevation of ≥ 2 millivolts (mV), a coved ST-segment elevation ≥ 2 millimeters (mm), and T wave inversion. It may occur spontaneously or be brought on by fever or exposure to sodium channel blockers (SCB) . Type 2 is characterized by a positive or biphasic T wave after a biphasic (saddleback) ST-segment elevation ≥ 2 mV. Type 3 is also referred to as biphasic ST-segment elevation. However, the cut-off point is less than 2 mV. [23,25,26] A potential challenge in the ECG-based diagnosis is the dynamic and often intermittent presentation of these patterns. ECG manifestations may be concealed under baseline conditions and become apparent only under specific triggers. Previously described factors, like fever or CSB may unmask or accentuate diagnostic features. For this reason, repeated ECG recordings and modified lead placement, including higher intercostal positioning of V1–V3 leads are recommended to improve sensitivity, especially in ambiguous cases. [27]

Table 1. Electrocardiogram patterns of Brugada Syndrome

Type	ECG pattern	Description	Reference
1		Coved ST-segment elevation ≥ 2 mm with a negative T wave	23
2		Biphasic ST-segment elevation ≥ 2 mm with a positive T wave	23
3		Biphasic ST-segment elevation < 2 mm	23

4.2 Pharmacological provocation testing

For patients with suspected BrS but nondiagnostic baseline ECGs, SCBs are used to unmask a diagnostic type 1 pattern. Three medications are used in clinical practice: ajmaline, flecainide and procainamide. Some evidence papers show that ajmaline is considered to be the most sensitive agent for this purpose and represents a better safety profile. The test is performed with continuous ECG monitoring and immediate availability of resuscitation equipment due to the risk of inducing malignant arrhythmias. A positive result is defined by the conversion of a non-diagnostic ECG pattern into a type 1 pattern. It is important to note that in asymptomatic or low-risk individuals, the results must be interpreted with caution due to the potential for false positive outcomes. Therefore, patient history, diagnostic findings and clinical presentation must be considered in forming a proper diagnosis. According to guidelines, provocation testing is contraindicated in patients undergoing fever and patients affected with Mobitz type II block, complete heart block and severe sinus node anomalies. In general, provocative testing is not clinically useful and is not recommended as a standard procedure for asymptomatic patients with a type 2 or 3 Brugada ECG pattern and no family history supporting the illness. However, SCB provocation may still be taken into consideration if there are additional ECG characteristics that support the condition, such as leftward axis deviation or severe saddleback ST elevation in the upper precordial leads. [28,29]

4.3 Exercise stress test

Exercise stress testing (EST) plays a unique role in the diagnosis and risk stratification of Brugada syndrome. While peak exercise may rarely unmask conduction abnormalities, the early recovery phase, characterized by rapid parasympathetic rebound, more commonly reveals the diagnostic type 1 Brugada ECG pattern and is associated with an increased risk of arrhythmias. Observational studies indicate that EST is in general safe, but careful monitoring during early recovery is essential, as most arrhythmic events and unmasking of the Brugada pattern occur in this period. These findings suggest that EST, especially when combined with high precordial lead placement, can be a valuable tool in clinical evaluation and individualized risk assessment for Brugada syndrome. [30]

4.4 Small electronic device

A recent proof-of-concept study showed that smartwatch ECGs, when positioned at high precordial sites, can reliably detect the type 1 Brugada pattern. In a cohort of patients with confirmed Brugada syndrome, smartwatch recordings demonstrated high specificity (98–100%) and good sensitivity (79–85%) compared to standard 12-lead ECGs. These findings suggest smartwatches may aid in home-based screening, family monitoring, and documenting dynamic Brugada ECG changes, although further research is needed to confirm their utility in broader clinical practice. [31]

4.5 Genetic testing

According to guidelines, it is advised that individuals with Brugada syndrome should undergo genetic testing for pathogenic or likely pathogenic variants of the SCN5A gene. Previous findings correlated SCN5A variants with a high incidence of drug-induced type 1 Brugada ECG patterns, yet recent investigations reveal that only 75–80% of SCN5A-positive patients display this pattern when subjected to SBC testing, with merely 20% of BrS patients having a recognizable SCN5A variant. The heritability of BrS is currently understood to be multifaceted and polygenic. Therefore, the mere identification of an SCN5A variation is not a standard justification for SCB testing, as it may increase the risk of arrhythmias in some cases. [25,29,32]

4.6 Diagnostic Criteria

Currently, diagnosis requires a presentation of a spontaneous type 1 ECG pattern in patients without cardiac conditions regardless of the presence of clinical symptoms. Moreover, patients lacking other heart disorders who have survived a cardiac arrest caused by ventricular fibrillation (VF) or polymorphic ventricular tachycardia and display a provoked type 1 ECG can be recognized as affected with BrS. Recommendations indicate that patients with induced type 1 pattern and positive family history of this syndrome or family history of premature sudden cardiac deaths or cardiac-associated syncope or nocturnal agonal respiration should be considered as affected by the BrS. [25]

5. Risk stratification

Risk stratification is still one of the most challenging issues in the management of Brugada syndrome. The two most consistently validated predictors of arrhythmic events are symptoms suggestive of arrhythmic syncope or aborted SCD and the presence of a spontaneous type 1 Brugada ECG pattern. In contrast, asymptomatic individuals and those with drug-induced patterns present a much lower annual risk of SCD. However, distinguishing arrhythmic syncope from vasovagal or other benign causes remains a challenge, requiring detailed clinical evaluation [9,10,27] To address the limitations of a binary symptomatic/asymptomatic framework, several risk scores have been developed, each integrating clinical features, family history, ECG presentation, and, in some cases, genetic and EPS data. Up to date, the literature identifies the following models of risk stratification: Shanghai Score, Sieira Score, Brugada-Risk and Predicting Arrhythmic Event Score (PAT). A detailed description goes beyond the scope of this scholarly work. Despite these advances, no risk score has been universally adopted in international guidelines, and most models are limited by cohort heterogeneity and a lack of dynamic, longitudinal risk assessment. [33] The utility of EPS in risk stratification remains debated. While some pooled analyses suggest inducibility during test is associated with a two- or threefold increased risk of arrhythmic events, its incremental prognostic value, especially in asymptomatic or intermediate-risk patients, is modest at best. Other ECG markers, such as fragmented QRS, prolonged Tpeak-Tend interval, early repolarization, and type 1 pattern in peripheral leads have been proposed, but validation is inconsistent and their independent prognostic value remains uncertain. [1,9,10] While SCN5A variants are the only genetic markers with definitive evidence for causality, their presence alone does not reliably predict risk, due to incomplete penetrance and variability in phenotype expression. Integration of polygenic risk scores and advanced genetic testing may improve future risk prediction, but current guidelines recommend genetic testing mainly for cascade screening in affected families. [10]

6 Treatment management

6.1 Implantable cardioverter defibrillator

Management of Brugada syndrome focuses primarily on the prevention of SCD. The fundament of treatment is the implantation of an implantable cardioverter-defibrillator (ICD), which has been consistently shown to be effective in secondary prevention in patients with BrS who are survivors of cardiac arrest, experiencing arrhythmogenic syncope or life-threatening ventricular arrhythmia episodes. However, while ICD reduce mortality, it does not prevent arrhythmia recurrence and may be associated with complications, including inappropriate shocks, infections and reduced quality of life. The subcutaneous form of these device is a reasonable option to reduce lead-related complications. In asymptomatic patients with a drug-induced type 1 ECG pattern, ICD implantation is not routinely necessary, except for those with a spontaneous type 1 pattern and high-risk features. Regular follow-up with repeated ECGs or Holter monitoring and behavioral modifications is a sufficient form of prevention. [25,34-36]

6.2 Pharmacotherapy

Pharmacological therapy plays a complementary role, particularly in patients who are not candidates for ICD implantation or ablation or who experience recurrent arrhythmic events/electrical storms. Quinidine, a class Ia antiarrhythmic agent, has been emphasized as an effective option due to its ability to inhibit transient outward potassium current, thereby stabilizing cardiac electrophysiology and reducing VF episodes. Nevertheless, its use may be limited by side effects. Intravenous isoproterenol is the drug of choice in patients affected with episodes of electrical storms. Studies show that cilostazol might be an alternative option, especially when other drugs are unavailable or contraindicated. [37,38]

6.3 Epicardial ablation

Catheter ablation has emerged as a promising therapeutic strategy with relevant success rates and mild side effects like pericarditis. It is especially useful in high-risk or symptomatic patients with recurrent VF, ICD shocks or electrical storms not controlled by pharmacotherapy. It might be also beneficial for patients who are not candidates for ICD implantation or prefer to avoid complications associated with this procedure. Recent studies emphasize epicardial substrate ablation targeting abnormal electrograms in the RVOT, which has demonstrated efficacy in reducing arrhythmic burden, ECG normalization and improvement of life quality. Arrhythmogenic areas can be unmasked by sodium channel blockers or monophasic potential mapping that visualizes the Brugada substrate. Combined approaches, including pulmonary vein isolation and substrate modification, are being explored to address both ventricular and atrial arrhythmias associated with BrS. Additionally, novel approaches, such as cardioneuroablation have shown potential in selected cases by modulating autonomic influences on cardiac conduction. [37,39-42]

6.4 Modification of lifestyle

Preventive strategies in Brugada syndrome include both clinical monitoring and lifestyle modifications. Recommendations include immediate treatment of fever, avoidance of large meals and alcohol, cannabis or cocaine intake, and specific drugs mentioned in the previous part of this article. [25]

7. Conclusions

Brugada syndrome is a complicated and potentially lethal arrhythmogenic disease. Despite substantial progress in comprehending its pathophysiology and clinical management, important challenges remain, especially in relation to risk stratification and treatment of asymptomatic individuals. Pharmacological and interventional strategies continue to develop, but ICD therapy remains the mainstay of management for high-risk patients. Preventive measures, including avoidance of triggers and family screening, are important aspects of care. Further research is required to define diagnostic criteria and to develop more accurate, individualized therapeutic approaches.

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