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Advances in Diagnosis and Treatment of Brugada Syndrome: A Comprehensive Review

Authors:

1. **Bartosz Szepietowski,** Heliodor Swiecicki Clinical Hospital, ul. Przybyszewskiego 49, 60-355 Poznan, Poland

   https://orcid.org/0009-0001-6945-3871

   bartosz.szepietowski@gmail.com

2. **Wiktoria Mączyńska,** Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland

   https://orcid.org/0009-0008-9833-7598

   wika.maczynska@gmail.com

3. **Justyna Dutkiewicz,** Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland

   https://orcid.org/0009-0007-0352-7827

   justyna.dutkiewicz96@gmail.com

4. **Michał Wijata,** Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland

   https://orcid.org/0009-0004-0121-2854

   wijata.michal@gmail.com

5. **Anna Maria Wijata,** Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland

   https://orcid.org/0009-0005-7656-8318

   anna.wijata@icloud.com

6. **Zuzanna Adriana Przybyłek-Stępień,** Provincial Multidisciplinary Center of Oncology and Traumatology named after M. Copernicus University, ul. Pabianicka 62, 93-513 Lodz, Poland

   https://orcid.org/0009-0002-4857-1315

   przybylekstepienzuzanna@gmail.com

7. **Ryszard Bartosiński,** Provincial Hospital in Bielsko-Biała, Al. Armii Krajowej 101, 43-316 Bielsko-Biala, Poland

   https://orcid.org/0009-0005-3687-015X

   rabartosi@gmail.com

8. **Jan Szustak,** Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland

   https://orcid.org/0009-0006-0690-7211

   j.m.szustak@gmail.com

9. **Maria Kąpa,** Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Lodz, Poland

   https://orcid.org/0009-0008-5880-2416

   maria.kapa.332@gmail.com

10. **Jakub Marek Kaźmierczak,** Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Lodz, Poland

    https://orcid.org/0009-0002-0701-7983

    jakub.kazmierczak.md@gmail.com

11. **Ewelina Rycerz,** Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland

    https://orcid.org/0009-0006-5749-5720

    ewelina.rycerz1@gmail.com

12. **Piotr Pasek,** Copernicus Memorial Hospital, ul. Pabianicka 62, 93-513 Lodz, Poland

    https://orcid.org/0009-0001-6218-9887

    pasek.piotrus@gmail.com

Corresponding author:

Bartosz Szepietowski, Heliodor Swiecicki Clinical Hospital, ul. Przybyszewskiego 49, 60-355 Poznan, Poland

https://orcid.org/0009-0001-6945-3871

bartosz.szepietowski@gmail.com

Affiliations:

1. Heliodor Swiecicki Clinical Hospital, ul. Przybyszewskiego 49, 60-355 Poznan, Poland
2. Saint Lucas Hospital, ul. Gimnazjalna 41B, 26-200 Konskie, Poland
3. Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Lodz, Poland
4. Provincial Hospital in Bielsko-Biała, Al. Armii Krajowej 101, 43-316 Bielsko-Biala, Poland
5. Provincial Multidisciplinary Center of Oncology and Traumatology named after M. Copernicus University, ul. Pabianicka 62, 93-513 Lodz, Poland

Abstract

Introduction: Brugada Syndrome (BrS) is a rare genetic cardiac disorder that predisposes individuals to ventricular fibrillation and sudden cardiac death, often without structural heart disease. The condition, first described in 1992, is characterized by a distinct electrocardiographic (ECG) pattern and remains a diagnostic and therapeutic challenge.

Aim of the Study: This review aims to evaluate current literature on BrS, focusing on diagnostic criteria, risk stratification, and treatment options. By analyzing recent findings from electrophysiological studies, genetic research, and clinical trials, the study seeks to provide a comprehensive understanding of the syndrome and its management.

Materials and Methods: The literature available in the PubMed database was reviewed using the following keywords: "Brugada Syndrome," "Brugada Syndrome diagnosis," "Brugada Syndrome treatment," "risk stratification in Brugada Syndrome," "sudden cardiac death and Brugada Syndrome," and "electrocardiographic patterns in Brugada Syndrome."

Conclusion: Brugada Syndrome remains a complex condition with ongoing challenges in risk stratification and treatment optimization. While ICDs are the primary intervention for high-risk patients, their use in asymptomatic individuals remains controversial. Pharmacological therapies and catheter ablation provide alternative treatment options but require further validation. Advances in genetic testing, electrophysiological studies, and noninvasive diagnostic tools hold promise for improving risk assessment and treatment precision. Future

research should focus on refining risk prediction models and enhancing personalized therapeutic strategies.

Keywords: Brugada Syndrome, sudden cardiac death, electrocardiography, risk stratification, implantable cardioverter-defibrillator, pharmacological therapy, catheter ablation

Introduction

Brugada Syndrome (BrS) is a rare genetic cardiac disorder that predisposes individuals to ventricular fibrillation and sudden cardiac death in the absence of structural heart disease. Initially identified by the Brugada brothers in 1992, the condition is characterized by a distinctive electrocardiographic pattern—J-ST segment elevation in the right precordial leads—which can be transient or concealed, requiring pharmacological provocation for detection.[1] BrS predominantly affects middle-aged adults, with a significantly higher prevalence in men despite its autosomal inheritance pattern. [2,3] Although the syndrome is relatively rare, with an estimated prevalence of approximately 5 in 10,000 people, its role in unexplained cases of sudden cardiac death remains an active area of research. [4] Current risk assessment strategies focus on identifying individuals at the highest risk of life-threatening arrhythmias; however, predicting adverse events in asymptomatic patients remains a significant challenge. Implantable cardioverter-defibrillators (ICDs) serve as the main therapeutic intervention for high-risk patients, though their use in asymptomatic cases remains controversial due to potential complications. [5]

Two predominant theories attempt to explain the pathophysiology of BrS: the conduction disorder theory, which attributes the condition to impaired electrical impulse propagation, and the repolarization abnormality theory, which suggests an uneven loss of the action potential dome. Advances in genetic testing and epicardial mapping have provided new perspectives on the underlying mechanisms of BrS, potentially reconciling these competing theories. [6,7]

This review aims to evaluate current literature on BrS, focusing on diagnostic criteria, risk stratification methods, and treatment options. By analyzing recent findings from electrophysiological studies, genetic research, and clinical trials, we seek to offer a comprehensive understanding of the syndrome and its management.

Pathophysiology and Genetic Basis

The first genetic link to Brugada Syndrome was identified as a loss-of-function mutation in the SCN5A gene, which encodes the cardiac voltage-gated sodium channel. This mutation is present in approximately 15-30% of BrS cases.[8] Additionally, mutations affecting calcium and potassium channels, associated channel proteins, and desmosomal proteins have been implicated in the condition. BrS follows an autosomal dominant inheritance pattern, yet individuals may exhibit variable expressivity and incomplete penetrance. Moreover, a range of genetic and environmental factors, including temperature fluctuations, medication use, electrolyte imbalances, and cocaine, can influence disease manifestation.[9]

Symptoms

A sudden cardiac arrest (SCA) can sometimes be the initial and sole manifestation of Brugada Syndrome (BS), affecting as many as one-third of diagnosed individuals. Episodes of arrhythmia tend to occur more frequently at night or during sleep. [10,11] Notably, in BS patients, SCA is typically not triggered by physical exertion.[12]

Patients with BrS may experience symptoms such as seizures, irregular breathing during sleep and syncope which are linked to polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF). If these arrhythmias persist, they can lead to SCD. The incidence of syncope or SCD ranges from 17% to 42%,[13] although this estimate may be inflated, as many asymptomatic patients are not diagnosed. Recent studies suggest a considerably lower rate of SCD as the initial symptom (4.6%) and a reduced occurrence of recurrent arrhythmias during follow-up (5%).[14] The widespread recognition of the BrS ECG pattern has expanded the pool of diagnosed patients, including many who are asymptomatic, which has contributed to the decline in the proportion of SCD in the overall BrS population.

The first symptoms typically occur in adulthood, with the average age of SCD onset being 41 ± 15 years. However, symptoms can also appear in children and older adults. [13]

Electrocardiography(ECG)

The presence of a spontaneous BrS pattern on an ECG has consistently been linked to a higher risk of sudden cardiac death (SCD) [3,15], with rates ranging from 0.81% per year in

asymptomatic patients to 2.3% per year in those with symptoms [3]. After Brugada Syndrome (BrS) was first described, there was considerable uncertainty regarding its ECG features and diagnostic criteria. To resolve these uncertainties, an expert consensus document was released in 2012, outlining two key ECG abnormalities for diagnosing BrS [16]:

- Type I - coved pattern: The coved pattern features ST-segment elevation followed by a symmetric negative T wave in the right precordial leads, typically seen in V1-V2, but sometimes extending to V3. It is characterized by a high take-off of at least 2 mm in V1, followed by a downsloping concave or rectilinear ST segment. In some cases, the high take-off may be between 1 and 2 mm. The ST segment at 40 milliseconds shows less than a 0.4 mV decrease in amplitude, which distinguishes it from right bundle branch block (RBBB). The QRS duration is longer in V1-V2 due to right ventricular conduction delay. Additionally, the ST segment is followed by an asymmetric T wave. This typical ECG pattern is considered diagnostic for Brugada Syndrome[17].
- Type II - saddle back pattern: his pattern is seen in V1 and V2 with a terminal positive wave, known as r', which is a mix of the final QRS and the start of repolarization. The r' has a high take-off of at least 0.2 mV, followed by an elevated ST segment (≥0.5 mm) that is convex relative to the isoelectric line, forming a saddle-back pattern. The T wave is positive in V2 (with peak amplitude greater than the minimum ST amplitude) and varies in V1, being mildly positive, flat, or slightly negative. The descending limb of r' sometimes ends abruptly, but in some cases, particularly in V1, no clear change in slope occurs, making it hard to pinpoint the start of the T wave. To confirm the pattern, it is useful to administer a sodium channel blocker (ajmaline, flecainide, procainamide, or pilsicainide), which may convert the type 2 pattern into type 1[17].

ECG patterns in a single patient can vary frequently, and at times, the classic ECG pattern may be absent on a particular day, resulting in concealed BrS[18]. Moreover, prolonged ECG monitoring has revealed spontaneous intermittent type 1 ECG patterns in 20% to 34% of patients who initially show only drug-induced type 1 ECG patterns[19,20].

Provocative drug testing

Provocative drug testing is a commonly used method to diagnose Brugada syndrome (BrS) by unmasking a type I Brugada ECG pattern, especially in patients who do not exhibit this pattern at baseline. This test typically involves the administration of Class I antiarrhythmic drugs such

as ajmaline, procainamide, or flecainide, which can induce the characteristic ST-segment elevation in the right precordial leads[21]. This test, performed under continuous ECG monitoring, is considered positive if a type I ECG pattern appears during drug infusion. If QRS widening exceeds 130% or if frequent ventricular arrhythmias occur, the test should be stopped to prevent further complications. Ajmaline and flecainide are the most common drugs used, but procainamide is available in some regions, and oral doses of flecainide or propafenone may be used where intravenous options are unavailable[22]. The ECG should be continuously monitored until it returns to baseline.

However, the use of these drugs to provoke the Brugada pattern remains controversial due to the potential for false positive results and the test's uncertain impact on patient outcomes. While the sensitivity of the test for detecting type I patterns is high [23,24], studies have shown a false positive rate ranging from 4% to 27% [25-27], complicating the interpretation of results. The choice of drug, dosing protocols, and individual patient factors, such as genetic predispositions, further influence the accuracy and reliability of the test. Despite these challenges, provocative drug testing remains a valuable diagnostic tool, especially when used in combination with clinical risk factors and family history, as outlined in expert consensus[28].

Genetic testing

Initial genetic studies linked familial BrS to loss-of-function variants in the SCN5A gene [29], which encodes the NaV1.5 sodium channel. These variants lead to defective gating and reduced trafficking of NaV1.5 channels, causing delayed activation and premature inactivation, which shortens the action potential duration. This results in a slower upstroke of the action potential and reduced peak INa. To date, over 500 pathogenic variations have been linked to Brugada syndrome, reinforcing its autosomal dominant inheritance pattern[30]. Most pathogenic variants identified in Brugada syndrome are found in SCN5A (Human Gene Mutation Database), accounting for nearly 30% of cases where a genetic variant is implicated. However, this figure may be an overestimate, as many variants once classified as pathogenic are now considered of uncertain significance according to recent guidelines from the American College of Medical Genetics[31]. Other genes, such as SCN10A and those related to NaV1.5 trafficking, potassium channels, and calcium channels, have also been implicated but their pathogenic role is debated[32-34]. Recent studies suggest that common genetic variations may influence BrS

expression, with multiple single nucleotide polymorphisms potentially explaining familial BrS without a single identifiable pathogenic variant[35].

Treatment Strategies

Risk assessment for sudden cardiac death

Identifying and treating high-risk BrS patients, particularly those at risk for sudden death, remains a significant challenge. Syncope is a well-recognized risk factor, with between 17% and 62% of BrS patients experiencing new arrhythmic events within 48 to 84 months, potentially leading to sudden death[13,36]. The combination of syncope with a spontaneous type 1 ECG pattern is a strong predictor of poor prognosis, with 6% to 19% of patients experiencing arrhythmic events within 24 to 39 months[36]. In asymptomatic patients, risk stratification remains uncertain, but studies show a non-negligible arrhythmic event rate of 0.5% to 1.2% annually, with a 12% malignant arrhythmia rate over 10 years[37,38]. Fever-induced type 1 ECG patterns indicate an intermediate risk for sudden death[39]. While some studies suggest symptomatic patients are more prone to arrhythmias during electrophysiological studies (EPS), guidelines do not provide clear recommendations for EPS use in risk stratification[40]. Genetic analysis alone has not been conclusive in predicting prognosis, though combinations of risk factors, such as SCN5A mutations with a family history of sudden death, may be predictive[41]. Noninvasive markers like QRS fragmentation, late potentials, and early repolarization patterns also show potential for risk assessment, though further validation is needed[42-44].

Implantable cardioverter-defibrillators

ICD implantation is recommended for BrS patients with a history of resuscitated cardiac arrest, while primary prevention ICD decisions require balancing SCD risk against device complications[45]. Patients with cardiogenic syncope face the highest risk, with an annual severe arrhythmic event rate over 1.4%[46]. However, inappropriate shocks (3.3% annually) and device-related issues (4.5%) complicate ICD use[47]. When implanting, transvenous ICDs may benefit those with atrial arrhythmias, while subcutaneous devices reduce infection risk but may fail initial sensing in ~15% of cases[48]. Epicardial approaches may be considered for young children.

Pharmacological interventions

Quinidine and its related compounds are valuable in BrS management due to their ability to prolong the effective refractory period[49]. Despite evidence supporting its role in reducing VF inducibility and managing recurrent ICD shocks or electrical storms, its use is hindered by significant side effects and limited availability[50]. Additional pharmacologic options include isoproterenol for electrical storms and phosphodiesterase III inhibitors like cilostazol or milrinone[51]. While pharmacologic therapy remains an important adjunct, its role is constrained by accessibility and side effect concerns.

Ablation

Radiofrequency ablation is an important option for BrS patients with serious arrhythmic events despite optimized medical therapy or medication intolerance[52]. A combined epicardial-endocardial approach targets arrhythmogenic substrates, with sodium channel blockers provocation aiding in substrate identification[53]. The goal is eliminating J-point elevation, even after drug provocation[53]. However, ablation is primarily used for patients with recurrent ICD shocks or those who refuse ICD implantation, with limited data supporting its use in asymptomatic individuals.

Conclusion

Brugada Syndrome (BrS) remains a complex condition with ongoing challenges in risk stratification and treatment optimization. While ICDs are essential for high-risk patients, their role in primary prevention is debated. Pharmacologic therapies and catheter ablation offer alternatives but require further validation. Emerging noninvasive diagnostic tools and biomarkers may enhance risk assessment and treatment precision. Future research should focus on refining risk prediction, expanding treatment options, and improving accessibility to personalized therapies.

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Author's contribution

Conceptualization: Bartosz Szepietowski, Michał Wijata, Jan Szustak

Methodology: Zuzanna Przybyłek-Stępień, Justyna Dutkiewicz, Wiktoria Mączyńska

Software & Check: Bartosz Szepietowski, Ryszard Bartosiński, Anna Wijata

Formal Analysis & Investigation: Jakub Kaźmierczak, Ewelina Rycerz, Piotr Pasek

Resources &Data Curation: Maria Kąpa, Justyna Dutkiewicz, Ryszard Bartosiński

Writing-Rough Preparation: Zuzanna Przybyłek-Stępień, Michał Wijata, Ewelina Rycerz

Writing-Review and Editing: Bartosz Szepietowski, Jan Szustak, Wiktoria Mączyńska

Visualization: Anna Wijata, Maria Kąpa, Jakub Kaźmierczak

Supervision & Project Administration: Bartosz Szepietowski, Piotr Pasek, Maria Kąpa

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