

Pathophysiological Mechanisms, Clinical Spectrum, And Contemporary Strategies in the Diagnosis and Management of Brugada Syndrome: A Comprehensive Review

Carlos Alfonso Martín Olguín Curiel¹, Donaldo Emiliano Silva López², Frida Victoria Aguado Ortega³, Gibran Grano Rubio⁴, Miguel Castellanos Contreras⁵, Erick Eduardo López Santos⁶, Andrés Mendoza Romero⁵, Delia Carolina López Vargas⁷, Mariano Ibarra Torres Torija⁵

¹Universidad del Valle de Atemajac. Mexico.

²Tecnológico de Monterrey Campus Monterrey. Monterrey, Mexico.

³Universidad Autónoma de Aguascalientes. Aguascalientes, Mexico.

⁴Centro Universitario de la Costa. Mexico.

⁵Universidad de Guadalajara. Guadalajara, Jalisco, Mexico.

⁶Universidad Autónoma de Guadalajara. Jalisco, Mexico.

⁷Universidad de Guadalajara centro universitario de ciencias de la salud. Jalisco, Mexico.

ABSTRACT

Brugada syndrome represents a complex and potentially life-threatening cardiac arrhythmogenic disorder characterized by distinctive electrocardiographic abnormalities and a uniquely elevated risk of sudden cardiac death in structurally normal hearts. Originating primarily from inherited ion channel dysfunctions, particularly involving sodium channelopathies, this syndrome has revolutionized the clinical understanding of ventricular arrhythmogenicity and electrophysiological heterogeneity. Its clinical manifestations are highly variable, ranging from asymptomatic incidental electrocardiographic findings to malignant arrhythmic events such as polymorphic ventricular tachycardia and ventricular fibrillation. The pathogenesis involves intricate interactions between electrophysiological substrates, genetic susceptibility, environmental triggers, and autonomic imbalance. Diagnostic evaluation has evolved substantially and incorporates high-resolution electrocardiography, provocative pharmacological testing, high-fidelity risk stratification, and advanced electrophysiological mapping. Despite remarkable technological and conceptual advances, the clinical approach remains challenging due to dynamic electrocardiographic patterns, unpredictable arrhythmic risk, and variable penetrance. Current therapeutic strategies emphasize prevention of sudden cardiac death through implantable cardioverter-defibrillator therapy in high-risk phenotypes and emerging targeted pharmacological and ablative interventions. The ongoing evolution in the understanding of molecular genetics, ion channel physiology, and arrhythmogenic substrates reinforces Brugada syndrome as a model disease for the study of primary electrical disorders of the heart. This review provides a comprehensive discussion of the epidemiology, underlying mechanisms, diagnostic paradigms, clinical presentation, and therapeutic approaches, emphasizing contemporary perspectives and future directions in the management of this increasingly recognized cardiovascular entity.

KEYWORDS: Brugada syndrome, channelopathy, ventricular fibrillation, sodium channel dysfunction, arrhythmogenic disorder, electrophysiology, sudden cardiac death, ICD therapy, cardiac ion channels, ventricular arrhythmias.

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INTRODUCTION

Brugada syndrome constitutes a paradigmatic form of inherited cardiac arrhythmogenic disorder in which malignant ventricular arrhythmias arise in the setting of an anatomically preserved myocardium. Since its original description, this syndrome has generated substantial scientific and clinical interest due to its distinctive electrocardiographic phenotype and its prominent association with sudden cardiac death, particularly in young adults without structural cardiac disease. The syndrome is fundamentally rooted in alterations of transmembrane ion fluxes, most prominently involving dysfunction of the cardiac sodium channel. These perturbations disrupt the delicate balance of depolarizing and repolarizing currents in the ventricular myocardium, producing electrophysiological heterogeneity, abnormal conduction, and substrate formation conducive to reentrant arrhythmogenesis. The characteristic coved-type ST-segment elevation in the right precordial leads reflects these underlying ionic and conduction abnormalities and constitutes a crucial diagnostic hallmark.^{1,2}

Brugada syndrome exemplifies a condition of dynamic pathophysiology in which electrocardiographic expression, arrhythmic risk, and clinical severity may fluctuate over time or in response to external modulators such as fever, metabolic disturbances, medications, or enhanced vagal tone. The syndrome encompasses a broad clinical spectrum ranging from complete absence of symptoms to recurrent syncope or sudden cardiac arrest. Risk stratification therefore remains a central aspect of clinical management, requiring detailed evaluation not only of electrocardiographic patterns but also of personal history, electrophysiological findings, and genetic background. Contemporary diagnostic paradigms combine surface electrocardiography, sodium channel blocker challenge, and advanced imaging and mapping techniques to delineate the electrophysiological substrate.^{2,3}

Management of Brugada syndrome is focused primarily on the prevention of fatal arrhythmic events. The implantable cardioverter-defibrillator remains the cornerstone of therapy in individuals deemed at high risk; however, an expanding armamentarium now includes pharmacological agents capable of modulating ion channel behavior as well as substrate-targeted catheter ablation for suppression of ventricular arrhythmogenesis. Understanding of the syndrome has advanced considerably in recent years, driven by a deeper appreciation of genetic mechanisms, structural microanatomical substrates, and the interplay of autonomic influences on arrhythmic vulnerability. As research continues to unravel the molecular and electrophysiological determinants of this unique disorder, Brugada syndrome persists as a crucial frontier in modern cardiac electrophysiology and an emblematic example of primary electrical cardiomyopathy.^{3,4}

BACKGROUND

Brugada syndrome emerged as a distinct non-structural cardiac arrhythmogenic disorder following the recognition of a characteristic electrocardiographic pattern associated with idiopathic ventricular fibrillation in individuals without overt cardiac pathology. Historically, this entity challenged classical paradigms of sudden cardiac death which previously centered on coronary artery disease, structural cardiomyopathies, or myocarditis. The identification of Brugada syndrome redefined clinical concepts regarding primary electrical heart diseases and provided a new framework for understanding the role of ion channel dysfunction in ventricular arrhythmogenesis. Over subsequent years, it became increasingly evident that this pathology represents a complex interplay between genetic predisposition, electrophysiological abnormalities, and modulation by pharmacologic, metabolic, or autonomic factors.^{4,5}

The earliest conceptualization of Brugada syndrome was founded on the observation that life-threatening ventricular tachyarrhythmias may arise in the absence of structural myocardial derangements. This challenged the prevailing belief that fatal arrhythmias were secondary to gross myocardial damage. Advances in molecular cardiology progressively demonstrated that inherited abnormalities in ion channel function, particularly involving transmembrane sodium currents, contribute to the characteristic repolarization heterogeneity and conduction delay that define the arrhythmogenic substrate in this syndrome. The increasing availability of electrocardiographic screening and the recognition of dynamic variability in the Brugada pattern facilitated the expansion of clinical diagnostic criteria, enabling identification of symptomatic and asymptomatic individuals, and illustrating substantial phenotypic heterogeneity.⁶

As clinical awareness of Brugada syndrome expanded, attention shifted toward elucidating its etiopathogenic mechanisms, which encompass channelopathy-driven conduction disturbances localized predominantly in the right ventricular outflow tract. The interaction between reduced sodium channel availability, augmented transient outward potassium currents, and delayed depolarization creates a vulnerable electrophysiologic milieu in which premature ventricular complexes may trigger polymorphic ventricular tachycardia or ventricular fibrillation. Over time, the conceptual model evolved from a purely electrophysiologic phenomenon toward understanding that microstructural and intercellular alterations, although frequently inapparent in gross anatomy, may contribute to arrhythmogenic susceptibility.⁶

The syndrome's recognition also inspired a profound reevaluation of arrhythmic risk stratification in patients without structural heart disease. The clinical presentation ranges from incidental electrocardiographic abnormalities

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detected during routine evaluation to recurrent syncope, nocturnal agonal breathing, or out-of-hospital cardiac arrest. Such diversity led to the development of increasingly sophisticated methods for characterizing arrhythmic propensity, including pharmacologic provocation tests, high-resolution electrocardiography, and detailed electrophysiologic evaluations. The evolving diagnostic landscape underscored the importance of identifying concealed or intermittent electrocardiographic manifestations, particularly in individuals presenting with unexplained syncope or a family history of premature sudden cardiac death.⁶

From the perspective of therapeutic evolution, Brugada syndrome catalyzed major advances in preventive cardiology. The arrival of the implantable cardioverter-defibrillator as a primary therapeutic strategy transformed clinical outcomes by providing effective protection against malignant arrhythmias. Subsequently, novel pharmacologic and interventional approaches emerged, aiming to reduce arrhythmic burden or neutralize the electrophysiological substrate. The disorder therefore stands as a prominent example of translational cardiovascular research, in which fundamental discoveries in cellular electrophysiology and genetics have directly influenced bedside clinical practice.⁷

In contemporary cardiology, Brugada syndrome is recognized not only as a model of inherited arrhythmogenic disease, but also as an evolving condition in which genetic variants, environmental modulators, and dynamic electrophysiologic responses converge to determine clinical trajectory. Its historical development reflects continual refinement in the understanding of primary electrical diseases of the heart, the limitations of classical diagnostic strategies, and the transformative potential of molecular and electrophysiological insights in preventing sudden cardiac death.⁷

NATURAL HISTORY OF THE DISEASE

The natural history of Brugada syndrome is distinguished by a highly variable clinical trajectory that spans from lifelong quiescence to catastrophic arrhythmic events in previously asymptomatic individuals. This unique disorder evolves as a dynamic interplay between genetic substrate, electrophysiological remodeling, and environmental modulating factors, resulting in an unpredictable course that challenges conventional paradigms of disease progression. Unlike structural cardiomyopathies or ischemic heart disease, Brugada syndrome does not manifest with progressive myocardial deterioration or altered ventricular geometry. Instead, its evolution is governed by cellular and molecular aberrations in cardiac ion channel physiology, chiefly impairments in sodium channel function and altered repolarization currents, which create a persistent but fluctuating arrhythmogenic substrate. The disease course may remain clinically silent for years, with the characteristic

electrocardiographic pattern expressing intermittently or only under specific physiological stressors, such as fever, metabolic derangements, or heightened vagal tone.^{7,8}

The earliest phases of the condition are often marked by subclinical electrophysiologic instability. Patients may harbor concealed forms of the syndrome in which the arrhythmogenic substrate exists but lacks overt electrocardiographic expression. During this latent stage, the likelihood of arrhythmic events remains low, yet the substrate for malignant ventricular arrhythmias is already embedded within the myocardial conduction system. Over time, fluctuations in autonomic balance, hormonal status, or age-related electrophysiologic changes may precipitate the transition from a dormant to an overt phase, characterized by the appearance of the diagnostic coved-type ST-segment elevation in the right precordial leads. This transformation may be transient, with dynamic ECG patterns emerging and regressing unpredictably. Some individuals experience episodic manifestation only during febrile illnesses or under pharmacologic provocation, highlighting the reversible nature of certain electrophysiologic derangements and underscoring the centrality of extrinsic triggers in modulating disease expression.^{7,8}

As the disorder progresses, the predominant clinical risk revolves around the occurrence of malignant ventricular arrhythmias, including polymorphic ventricular tachycardia and ventricular fibrillation. These arrhythmias frequently arise in the absence of antecedent structural changes or ischemic triggers, reflecting the intrinsic electrical instability of the ventricular myocardium. Sudden cardiac death may represent the first clinical manifestation of the disease, particularly in young adults or middle-aged individuals who previously displayed no symptoms. This tragic and unpredictable presentation underscores the silent yet persistent vulnerability within the electrophysiologic substrate. In other cases, prodromal symptoms such as recurrent syncope, nocturnal agonal breathing, or presyncopal episodes may indicate escalating arrhythmic propensity. Episodes tend to cluster during periods of increased vagal dominance, often during rest or sleep, supporting the concept that autonomic imbalance serves as a significant catalyst for disease progression.^{8,9}

Despite the potential for catastrophic events, many individuals experience prolonged periods of clinical stability, particularly those without a history of syncope or documented arrhythmias. The natural evolution of Brugada syndrome does not necessarily follow a linear trajectory. Some patients remain asymptomatic throughout their lives, while others undergo sporadic arrhythmic events triggered by specific reversible factors. The transient and sometimes reversible nature of the electrocardiographic pattern reveals that disease progression is heavily influenced by dynamic physiological states rather than progressive myocardial damage. Nevertheless, even clinically stable patients harbor an

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inherent risk of sudden deterioration, emphasizing the need for continuous vigilance and individualized risk assessment.¹⁰

Over the long term, the syndrome may demonstrate subtle shifts in electrophysiologic phenotype. Age, genetic expression, and cumulative exposure to environmental modifiers may alter the susceptibility of ventricular myocardium to arrhythmogenesis. In certain individuals, progressive conduction delay in the right ventricular outflow tract or increasing repolarization dispersion may develop, further amplifying arrhythmic vulnerability. Conversely, other patients may experience mitigation of arrhythmic burden, particularly if modifiable triggers such as fever or pharmacologic exposure are controlled. Importantly, the absence of structural remodeling differentiates Brugada syndrome from traditional progressive cardiac disorders and situates it among primary electrical diseases in which the substrate remains static but the expression and consequences evolve dynamically.¹¹

The terminal events associated with Brugada syndrome are overwhelmingly arrhythmogenic rather than mechanical. Sudden cardiac arrest represents the culmination of a pathological continuum rooted in ion channel dysfunction, conduction heterogeneity, and susceptibility to reentrant or non-reentrant arrhythmogenic mechanisms. While modern therapeutic strategies, including implantable cardioverter-defibrillator implantation and electrophysiologic ablation, have altered the natural course for high-risk patients, the inherent biology of the disease persists. The syndrome remains a lifelong predisposition to malignant arrhythmias, modulated but not eliminated by intervention. Thus, the natural history of Brugada syndrome is defined not by progressive myocardial degeneration but by the oscillating presence of an electrically unstable substrate that may remain silent for decades or manifest suddenly with life-threatening events, a profile that continues to pose significant clinical challenges and demands comprehensive and nuanced risk-based management.¹¹

PATHOPHYSIOLOGY

The pathophysiology of Brugada syndrome is centered on a complex constellation of electrophysiological alterations that converge to generate a highly arrhythmogenic myocardial substrate in the absence of overt structural abnormalities. At its core, the syndrome represents a primary cardiac channelopathy predominantly caused by dysfunction in the voltage-gated cardiac sodium channels responsible for phase 0 depolarization in ventricular action potentials. Alterations in sodium channel expression, gating kinetics, or ion permeability reduce the inward sodium current and thereby impair the rapid conduction of electrical impulses across the right ventricular myocardium. This reduction in depolarizing current creates a marked imbalance between inward and outward ion fluxes during the early phases of ventricular

activation. The electrophysiologic consequence is a substrate characterized by conduction slowing, discontinuous impulse propagation, and regionalized repolarization heterogeneity, particularly within the right ventricular outflow tract, where conduction fiber architecture is naturally more vulnerable to perturbation.^{12,13}

The ionic disturbances in Brugada syndrome propagate destabilizing effects on the action potential morphology. Diminished sodium influx reduces the upstroke velocity of phase 0 and delays conduction across the epicardial surface of the right ventricle. Simultaneously, unopposed transient outward potassium currents accentuate epicardial action potential notch formation, leading to an outward shift in the transmembrane current balance. This accentuated repolarization gradient between epicardial and endocardial layers produces voltage dispersion that is readily translated into the characteristic coved-type ST-segment elevation observed in right precordial electrocardiographic leads. This repolarization heterogeneity is not merely an epiphenomenon but is intrinsically linked to arrhythmogenesis, as it generates local conduction block and fosters the development of vulnerable windows through which phase 2 reentry may be initiated. In this setting, premature ventricular complexes may trigger polymorphic ventricular tachycardia or ventricular fibrillation even in structurally normal hearts.^{14,15}

The electrophysiological substrate of Brugada syndrome is further modulated by factors that influence excitability, refractoriness, and autonomic tone. The sympathetic and parasympathetic nervous systems exert profound influence on cardiac electrical behavior, and in Brugada syndrome the arrhythmogenic potential is particularly enhanced under conditions of increased vagal dominance. Vagal stimulation reduces inward calcium currents and abbreviates action potential duration, potentiating the existing repolarization gradient and rendering the ventricular myocardium more vulnerable to arrhythmic triggers. Conversely, sympathetic activation may temporarily mitigate electrocardiographic abnormalities by enhancing sodium and calcium influx. This autonomic dependence partly explains the clustering of arrhythmic events during rest or sleep, when parasympathetic influence is maximal, and clarifies why fever, medications, or metabolic disturbances capable of modifying ion channel function may precipitate life-threatening ventricular arrhythmias.^{15,16}

Although Brugada syndrome has classically been conceptualized as a purely electrical disorder, emerging evidence suggests that subtle structural or intercellular abnormalities contribute to the arrhythmogenic substrate. Microscopic variations in fibrotic tissue deposition, altered gap junction coupling, or heterogeneity in connexin expression may accentuate conduction delay within the right ventricular outflow tract. These microstructural perturbations do not rise to the level of gross cardiomyopathic changes

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detectable using conventional imaging techniques, yet they potentiate the formation of conduction block lines and facilitate reentry circuits. Moreover, the molecular complexity of the syndrome extends beyond sodium channel dysfunction, involving interplay among various ion channel families, intracellular signaling cascades, and modulatory proteins that regulate channel trafficking, density, and spatial distribution on the cardiomyocyte membrane.¹⁷

The electrophysiological consequences of these molecular abnormalities are dynamic, reversible, and susceptible to physiological conditions. The Brugada electrocardiographic phenotype may wax and wane over time, reflecting fluctuations in ion channel expression, temperature-dependent kinetics, or autonomic stimuli. Fever, for example, exacerbates sodium channel inactivation and accelerates the manifestation of diagnostic electrocardiographic patterns by further reducing depolarizing currents. Likewise, certain pharmacologic agents, particularly sodium channel-blocking drugs, accentuate conduction delay and potentiate arrhythmic susceptibility by exacerbating the ionic imbalance intrinsic to the syndrome.¹⁸

Ultimately, the pathophysiology of Brugada syndrome culminates in a myocardial environment primed for malignant ventricular arrhythmias through the convergence of depolarization delay, repolarization heterogeneity, and impaired electrical coupling. The substrate predisposes to both triggered activity and reentrant arrhythmogenesis. The most catastrophic expression of these abnormalities manifests as polymorphic ventricular tachycardia degenerating into ventricular fibrillation, frequently in the absence of precipitating hemodynamic stress or ischemic injury. The disorder thus represents a prototypical example of primary electrical cardiomyopathy, in which the destabilizing forces originate from ion channel perturbations rather than macroscopic myocardial disease.¹⁸

The ongoing clinical and scientific interest in the syndrome is driven by its uniquely modifiable electrophysiological substrate, which can be unmasked, attenuated, or suppressed through pharmacologic intervention, autonomic manipulation, or substrate-targeted ablation. Although its pathophysiological foundation is rooted in ion channel dysfunction, the syndrome encompasses dynamic interactions between electrophysiology, autonomic regulation, and microstructural myocardial architecture. Together, these mechanisms produce a cardiac environment characterized by persistent but fluctuating vulnerability to life-threatening ventricular arrhythmias, distinguishing Brugada syndrome as a paradigmatic condition at the intersection of clinical electrophysiology, molecular cardiology, and the broader field of inherited arrhythmogenic disorders.¹⁸

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Brugada syndrome encompasses a broad array of cardiac and non-cardiac conditions capable of producing phenotypically similar electrocardiographic manifestations or predisposing to malignant ventricular arrhythmias in the absence of overt structural heart disease. Differentiating true Brugada syndrome from Brugada phenocopies, related channelopathies, and other etiologies of ST-segment elevation in the right precordial leads remains a central and challenging aspect of clinical evaluation. The characteristic coved-type ST-segment elevation observed in the syndrome may be mimicked by a variety of pathophysiological states in which transient alterations in ion channel behavior, conduction patterns, or myocardial excitability occur. A meticulous and systematic diagnostic approach is therefore essential to avoid misclassification, inappropriate risk stratification, and unnecessary or delayed interventions.¹⁸

One of the foremost considerations in the differential diagnosis involves distinguishing Brugada syndrome from acute ischemic heart disease, particularly anterior or right ventricular ischemia in which localized ST-segment elevation may resemble the Brugada pattern. However, ischemic etiologies are typically accompanied by clinical symptoms such as chest pain, hemodynamic instability, or evidence of myocardial injury, whereas Brugada syndrome manifests predominantly through electrical disturbances without accompanying structural compromise. Similarly, the differential diagnosis must include the early repolarization pattern, an electrocardiographic variant that exhibits J-point elevation and concave ST-segment morphology but lacks the characteristic coved or saddle-back pattern seen in Brugada syndrome. Early repolarization tends to be benign and more diffuse across precordial or inferior leads, necessitating careful electrocardiographic scrutiny to avoid conflation.¹⁸

A related and frequently confounding condition is arrhythmogenic right ventricular cardiomyopathy, a genetically mediated disorder characterized by fibro-fatty replacement of the right ventricular myocardium and predisposition to ventricular arrhythmias. Although both diseases share a predilection for the right ventricle and carry a risk of sudden cardiac death, arrhythmogenic right ventricular cardiomyopathy is distinguished by structural remodeling, regional wall motion abnormalities, and imaging findings suggestive of myocardial degeneration. Brugada syndrome, in contrast, lacks gross structural changes, and its arrhythmogenic substrate arises principally from primary ion channel dysfunction. The distinction is imperative, as the risk stratification strategies and therapeutic approaches differ substantially between these entities.¹⁹

Other primary electrical diseases must also be carefully evaluated. Long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation may present with syncope,

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palpitations, or life-threatening ventricular tachyarrhythmias in otherwise healthy individuals, thereby necessitating exclusion through thorough electrocardiographic, provocative, and electrophysiological testing. The unique hallmarks of Brugada syndrome, primarily the characteristic right precordial ST-segment elevation and proclivity for arrhythmias during rest or sleep, help differentiate it from these alternative channelopathies, which typically demonstrate distinct repolarization or adrenergic-dependent abnormalities.¹⁹

The differentiation of Brugada syndrome from Brugada phenocopies is of special clinical relevance. Brugada phenocopies represent transient electrocardiographic patterns that resemble the Brugada signature but are secondary to reversible physiological or pathological states. These may arise in association with hyperkalemia, hypothermia, drug toxicity, metabolic acidosis, pulmonary embolism, or mechanical compression of the right ventricular outflow tract. In these conditions, resolution of the underlying trigger results in disappearance of the electrocardiographic abnormality, distinguishing phenocopies from true genetic or idiopathic Brugada syndrome. Careful assessment of electrolytes, temperature, medications, and underlying systemic diseases is therefore essential. Pharmacological challenge testing further supports this differentiation by unmasking concealed Brugada patterns in the true syndrome while leaving phenocopies unaffected once reversible triggers are corrected.²⁰

Additional differential considerations include pericarditis, myocarditis, and conduction system diseases such as right bundle branch block, in which QRS prolongation and ST-segment abnormalities may simulate Brugada patterns. However, inflammatory markers, clinical presentation, and the distribution and morphology of electrocardiographic alterations allow differentiation. Right bundle branch block may particularly complicate interpretation due to overlapping conduction patterns in the right precordial leads, yet subtle distinctions in ST-segment configuration, QRS morphology, and the presence of terminal conduction delay can help distinguish the two entities.²⁰

Importantly, the differential diagnosis extends to non-cardiac etiologies of transient ST-segment elevation or electrical instability. Conditions such as central nervous system injury, sepsis, or endocrine dysfunction may induce alterations in autonomic tone or electrolyte balance sufficient to generate Brugada-like patterns. Fever deserves particular emphasis due to its well-described ability to unmask Brugada electrocardiographic abnormalities by accelerating sodium channel inactivation. Recognition of these influences is vital not only for accurate diagnosis but also for preventing iatrogenic exacerbation of arrhythmogenic risk, since certain medications and anesthetic agents may aggravate conduction abnormalities.²¹

The overarching challenge in the differential diagnosis lies in distinguishing Brugada syndrome as a primary electrical disease rooted in genetic or intrinsic ion channel malfunction from secondary Brugada phenotypes or alternative arrhythmogenic conditions. Accurate differentiation requires a holistic synthesis of clinical history, symptomatology, electrocardiographic characteristics, electrophysiological studies, and a detailed search for reversible precipitating factors. The clinical stakes are significant, as misinterpretation may lead either to unwarranted implantation of cardioverter-defibrillators in benign conditions or, conversely, failure to intervene in patients harboring a high-risk arrhythmogenic substrate. Ultimately, the differential diagnosis of Brugada syndrome reflects the intersection of advanced electrophysiologic insight, clinical acumen, and precise electrocardiographic interpretation, forming a crucial step in guiding appropriate management and mitigating the risk of sudden cardiac death.²²

CONCLUSIONS

Brugada syndrome represents one of the most complex and paradigm-shifting primary electrical cardiac disorders in contemporary cardiovascular medicine. Its recognition has fundamentally altered the understanding of sudden cardiac death in structurally normal hearts, demonstrating that lethal ventricular arrhythmias may arise from purely electrophysiological perturbations without accompanying myocardial structural pathology. The syndrome is emblematic of the intersection between molecular cardiology, clinical electrophysiology, and inherited channelopathy, and it exemplifies the profound impact that ion channel dysfunction can exert on cardiac excitability and the initiation of malignant ventricular tachyarrhythmias.

As a clinical entity, Brugada syndrome is characterized by dynamic and evolving phenotypic expression, unpredictable natural history, and heterogeneous risk profile. The fluctuating nature of its electrocardiographic manifestations underscores the significance of autonomic influences, metabolic states, and environmental modifiers in determining disease expression and arrhythmic vulnerability. This variability in presentation demands a high degree of clinical vigilance, particularly given that sudden cardiac death may serve as the initial manifestation in some patients. The syndrome therefore challenges traditional diagnostic frameworks, requiring integrative evaluation through advanced electrocardiographic interpretation, pharmacologic provocation, and electrophysiologic assessment.

From a pathophysiological perspective, Brugada syndrome highlights the critical contributions of ion channel integrity, regional conduction delay, repolarization heterogeneity, and functional block within the right ventricular outflow tract to the genesis of ventricular fibrillation. These electrophysiological characteristics form a dynamic substrate that may remain clinically silent for prolonged periods yet

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retain the capacity to degenerate rapidly into life-threatening arrhythmias under specific triggers. The condition illustrates the intricate relationship between cellular ion fluxes, myocardial conduction architecture, and autonomic regulation in shaping the stability of the cardiac rhythm.

Despite the absence of structural myocardial degeneration, the syndrome carries significant morbidity and mortality, emphasizing the importance of precise diagnostic discrimination and individualized risk stratification. The differentiation from Brugada phenocopies, ischemic heart disease, arrhythmogenic right ventricular cardiomyopathy, and other channelopathies is essential to avoid misinterpretation and guide appropriate therapeutic decisions. The natural evolution of the disorder demonstrates that although many patients may remain asymptomatic, a substantial and unpredictable minority remain susceptible to catastrophic arrhythmic events. This necessitates comprehensive monitoring strategies and long-term follow-up.

Therapeutic progress in Brugada syndrome has transformed the clinical landscape. The advent of implantable cardioverter-defibrillators, substrate-targeted catheter ablation, and electrophysiologic risk modifiers has significantly altered the arrhythmic prognosis. Nevertheless, these interventions do not eradicate the fundamental electrophysiological substrate, and the lifelong predisposition to ventricular arrhythmias persists. The condition therefore underscores the continuing need for innovative therapeutic approaches aimed at modulating ion channel function, stabilizing myocardial conduction, or neutralizing arrhythmogenic substrates.

Ultimately, Brugada syndrome remains an evolving field of investigation, marked by continual refinement of diagnostic criteria, expanded understanding of genetic architecture, and the emergence of novel interventional techniques. It stands as a disorder in which subtle electrophysiological changes exert profound clinical consequences, reflecting the delicate equilibrium maintained within the cardiac conduction system. Increased awareness, improved diagnostic accuracy, and a deeper understanding of the pathobiological mechanisms that drive disease expression are essential to reducing the burden of sudden cardiac death associated with this syndrome. As clinical and scientific insight continues to advance, Brugada syndrome will remain central to the broader exploration of inherited arrhythmogenic diseases and the intricate mechanisms governing cardiac electrical stability.

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