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CONTEMPORARY REVIEW

Cardiac Channelopathies: Clinical Diagnosis and Promising Therapeutics

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ABSTRACT: Cardiac channelopathies, also known as primary electrical heart diseases, are inherited genetic abnormalities of cardiomyocyte electrical behavior. Notable for their absence of structural heart diseases, they include a diverse group of diseases such as long QT syndrome, short QT syndrome, Brugada syndrome, early repolarization syndrome, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation, and carry the risk of malignant arrhythmias leading to sudden cardiac death. The genetic and molecular foundations of these diseases are diverse and complex, with evolving research highlighting the multifactorial nature of their pathophysiology and the intricate interplay of various genes in the manifestation of arrhythmias. While advances in diagnostic techniques, such as genetic testing and electrophysiological studies, have improved the identification and management of these conditions, the relationship between specific genetic mutations and sudden cardiac death remains incompletely understood. This review provides an overview of the molecular and genetic mechanisms underlying those inherited arrhythmias, exploring both well-established and emerging data. Additionally, it discusses current diagnostic approaches and management strategies, aiming to enhance the understanding of these conditions and contribute to better sudden cardiac death prevention.

Key Words: cardiac electrophysiology ■ channelopathies ■ heart rhythm disorders ■ inherited arrhythmias ■ sudden cardiac death

Sudden cardiac death (SCD) refers to an unexpected death due to a cardiovascular event, occurring within 1 hour of symptom onset when witnessed or within 24 hours of last being seen alive when unwitnessed.[1] SCD accounts for around half of all cardiovascular deaths, with up to half of these cases being the initial manifestation of heart disease.[2] It results in the loss of 250 000 to 300 000 lives in the United States annually.[3] Its incidence rises markedly with age, with the mean age of patients being in the mid-60s. Many risk factors have been associated with SCD including hypertension, diabetes, dyslipidemia, obesity, and family history of SCD.[1] SCD pathogenesis varies depending on the stage of life.[4] In younger individuals, primary electrical disorders, cardiomyopathies, myocarditis, and coronary anomalies predominate. However, by the fourth decade of life, approximately half of SCD cases is attributed to coronary artery disease, particularly acute coronary syndrome.[2] In older populations, chronic structural diseases such as coronary artery disease, valvular heart diseases, and heart failure become more prevalent. Nonetheless, primary electrical disorders of the heart, also called channelopathies, account for >50% of SCD cases in individuals aged <50 years.

Channelopathies encompass a diverse group of diseases characterized by abnormalities in ion currents without any structural defects in the heart. These diseases can arise from genetic polymorphisms or environmental factors, resulting in gain or loss-of-function mutations that affect the calcium, sodium, and potassium channels. These mutations can alter the cardiac action potential (AP), predisposing patients to life-threatening arrhythmias.[5] Among these

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Nonstandard Abbreviations and Acronyms

AP	action potential
BrAID	Brugada Syndrome and Artificial Intelligence Applications to Diagnosis
BrS	Brugada syndrome
CPVT	catecholaminergic polymorphic ventricular tachycardia
ERS	early repolarization syndrome
I_{Kr}	rapid delayed rectifier current
IVF	idiopathic ventricular fibrillation
LCSD	left cardiac sympathetic denervation
LQTS	long QT syndrome
QTc	corrected QT
SCD	sudden cardiac death
SQTS	short QT syndrome

channelopathies are long QT syndrome (LQTS), short QT syndrome (SQTS), idiopathic ventricular fibrillation (IVF), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and early repolarization syndrome (ERS). While recent progress has been achieved in the diagnosis and treatment of channelopathies, the link between these conditions and SCD remains unclear. This review provides an overview of the pathophysiology, genetic basis, clinical manifestations, and available management of these channelopathies (Figure 1). A comprehensive understanding of these mechanisms may help bridge the knowledge gaps surrounding channelopathies as a cause of SCD, thereby enhancing treatment and prevention strategies.

LONG QT SYNDROME

LQTS is among the most prevalent channelopathies with at least 1:2500 on the basis of the prospective study by Schwartz et al.[6] This study was based on ECG readings and genetic analysis of 7 LQTS genes in individuals with corrected QT (QTc) >470 milliseconds.[6] Consequently, it is suggested that the prevalence may be higher (around 1:2000) as the genetic screening overlooked silent carriers.[6] However, such estimate remains far below the 1:80 ratio based on the "pathogenic" LQTS genotype according to the data from the Exome Sequencing Project.[7]

Congenital LQTS is the prolongation of phase 1 of the cardiac AP and is due to abnormalities in cardiac ion channels leading to aberrant repolarization of the heart.[7] Assuming monogenic mutations, LQTS can be categorized into 17 subtypes (Table 1) where the genes *KCNQ1*, *KCNH2*, and *SCN5A* are definitive contributors to the major, typical forms of LQTS: LQT1, LQT2, and LQT3, respectively.[8] Among these genes, loss-of-function mutations in the *KCNQ1* and *KCNH2* lead to decreased activity of the slow delayed rectifier current and rapid delayed rectifier current (I_{Kr}) during phase 3 of the AP, thereby affecting potassium channels functioning.[8] In contrast, gain-of-function mutation in the *SCN5A* gene leads to persistent influx of sodium ions from phase 0 to the plateau of the AP.[8] These abnormalities may lead to torsades de pointes, which is a polymorphic ventricular tachycardia (VT) that worsens into ventricular fibrillation (VF) ultimately causing SCD.[9] Other genes as *CALM1*, *CALM2*, *CALM3*, and *TRDN* have been considered to be involved in calmodulinopathy and triadin knockout syndrome.[10] Mutations in the *CACNA1C* gene are key to the Timothy syndrome (LQT8), a rare and highly malignant variant of LQTS.[8] Jervell and Lange–Nielsen syndrome is an autosomal recessive disorder that arises from homozygous or compound heterozygous mutations in either *KCNE1* or *KCNQ1* and is associated with congenital sensorineural hearing loss and marked QTc prolongation.[11] Andersen–Tawil syndrome (LQT7) is notable for the clinical triad of ventricular arrhythmias, periodic paralysis, and prolonged QT interval in association with dysmorphic anatomic features.[12]

The risk of life-threatening arrhythmic events in patients with LQTS seems to be highest in childhood and gradually decreases over time[13] with patients aged >60 years at an attenuated risk for cardiac events from LQTS compared with younger patients.[14] Moreover, patient sex appears to have an impact on the varying incidence of adverse cardiac events in patients with LQTS. Based on a study done by Hobbs et al, male sex was associated with a 4.0-fold higher relative risk of life-threatening arrhythmic events for male patients between the ages of 10 and 12 years.[15] The risk in both sexes seems to be similar during mid to late adolescence,[15] while between the ages of 18 and 40, the gap widens with a rate of life-threatening arrhythmic event of 11% in women compared with 2% in men.[16] These observations could be explained by the impact of sex hormones on potassium channels whereby estrogen inhibits I_{Kr}, whereas progesterone and testosterone potentiate slow delayed rectifier current.[17,18] In women, the potential competing effects of estrogen and progesterone, which may increase and decrease the QT interval, respectively,[19] and their relative differences during pregnancy and the postpartum period may explain the higher risk of cardiac events during the latter compared with the former.[20] On the other hand, increased levels of testosterone in postpubertal male patients result in a reduced QT interval.[19]

A comprehensive approach should be adopted when initially assessing for congenital LQTS to rule out secondary causes of LQTS and distinguish it from acquired LQTS. This is achieved by adequate history

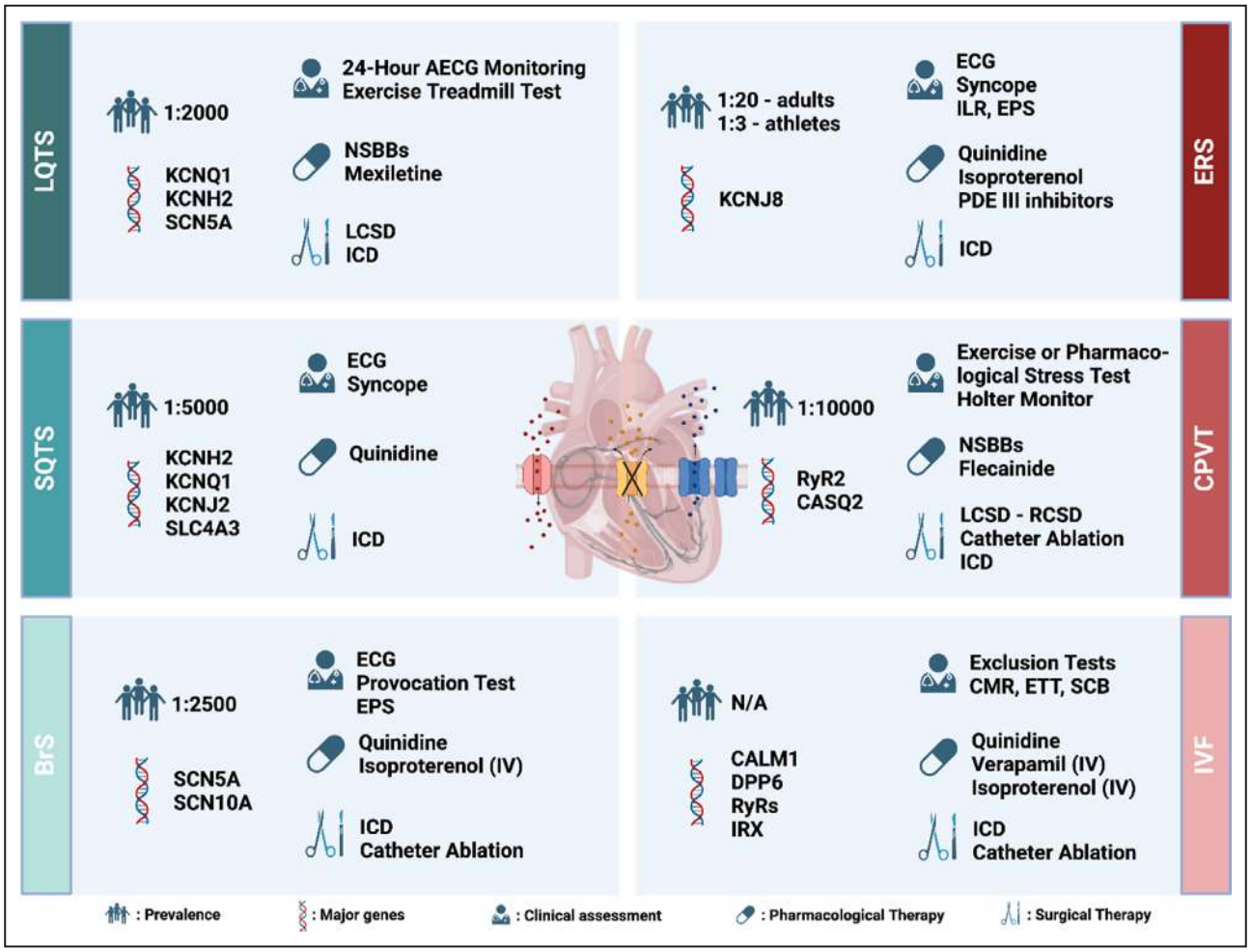

Figure 1. Overview of most common channelopathies.
This figure presents a comprehensive summary of the 6 most common channelopathies. Each channelopathy is presented with key details including prevalence in the general population, major genes responsible for the development of the disease, clinical assessment with common and channelopathy-specific diagnostic methods, along with available pharmacological and surgical interventions for the management of these disorders. This figure was created with BioRender.com. AECG indicates ambulator ECG; CMR, cardiac magnetic resonance imaging; EPS, electrophysiological study; ETT, exercise treadmill test; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; IV, intravenous; LCSD, left cardiac sympathetic denervation; NSBBs, nonselective β blockers; PDE, phosphodiesterase; RCSD, right cardiac sympathetic denervation; and SCB, sodium channel blockers.

taking to evaluate for prior seizures, syncope, and sudden cardiac arrest[21]; and elaborate physical examination, 12-lead ECG recordings for QTc calculation, and evaluation using the Schwartz scale (Table 2).[8] Additional workup is needed if congenital LQTS is highly likely and includes exercise treadmill test, 24-hour ambulatory ECG monitoring, and, finally, genetic testing in cases of high clinical suspicion with negative workup.[8] In fact, as the understanding of the genetics of LQTS has expanded, there seems to be considerable variation in the overall risk of cardiac events across different long QT genotypes, superseding the isolated identification of long QT subtype.[22] For example, Moss et al show that patients with variants affecting the transmembrane pore within the human ether-à-go-go–related gene potassium channel carry the greatest relative risk of cardiac events compared with those with variants affecting remaining non–pore-related transmembrane domains.[23] Additionally, numerous single nucleotide variation appears to affect the risk of cardiac events in LQTS.[24]

Management of LQTSincludes lifestyle modifications, drug therapy, device therapy, and surgical interventions. Nonselective β blockers are used as a first-line therapy to prevent a sudden surge in sympathetic activity.[7] Specifically, the nonselective β blocker nadolol is recommended over other selective and nonselective β blockers for its superior efficacy in decreasing the risk of life-threatening cardiac events.[25,26] If β blockers are insufficient or intolerable, left cardiac sympathetic denervation (LCSD) and mexiletine therapy are considered. The former is recommended as

Table 1. Long QT Syndrome by Genetic Subtypes

Type	Gene	Protein	Locus	Mechanism	Effect	Frequency among LQTS, %	Inheritance
LQT1	*KCNQ1*	Kv7.1 α subunit	11p15.5	Loss-of-function	Reduced I_{Ks}	30–35	AD, AR
LQT2	*KCNH2*	Kv11.1 α subunit	7q35-46	Loss-of-function	Reduced I_{Kr}	25–30	AD
LQT3	*SCN5A*	Nav1.5 α subunit	3p21-p24	Gain-of-function	Increased I_{Na}	5–10	AD
LQT4	*ANK2*	Ankyrin B	4q25-q26	Loss-of-function	Abnormal ion channel localization	<1	AD
LQT5	*KCNE1*	Kv7.1 β subunit	21q22.1	Loss-of-function	Reduced I_{Ks}	1–3	AD, AR
LQT6	*KCNE2*	Kv11.1 β subunit	21q22.1	Loss-of-function	Reduced I_{Kr}	<1	AD
LQT7	*KCNJ2*	Kir2.1 α subunit	17q23	Loss-of-function	Reduced I_{K1}	<1	AD
LQT8	*CACNA1C*	Cav1.2 α1c subunit	12p13.3	Gain-of-function	Increased $I_{Ca,L}$	Very rare	AD
LQT9	*CAV3*	Caveolin 3	3p25	Loss-of-function	Increased I_{Na}	<1	AD
LQT10	*SCN4B*	Nav1.5 β4-subunit	11q23.3	Loss-of-function	Increased I_{Na}	<1	AD
LQT11	*AKAP9*	Yotiao	7p21-q22	Loss-of-function	Reduced I_{Ks}	<1	AD
LQT12	*SNTA1*	Syntrophin α1	20q11.2	Loss-of-function	Increased I_{Na}	<1	AD
LQT13	*KCNJ5*	Kir3.4	11q24	Loss-of-function	Reduced $I_{K,ACh}$	<1	AD
LQT14	*CALM1*	Calmodulin 1	14q32.11	Gain-of-function	Abnormal calcium signaling	<1	Sporadic
LQT15	*CALM2*	Calmodulin 2	2p21.1-p21.3	Gain-of-function	Abnormal calcium signaling	<1	Sporadic
LQT16	*CALM3*	Calmodulin 3	19q13.32	Gain-of-function	Abnormal calcium signaling	<1	Sporadic
LQT17	*TRDN*	Triadin	6q22.31	Loss-of-function	Unknown	Very rare	AR

AD indicates autosomal dominant; AR, autosomal recessive; I_{Ks}, slow delayed rectifier potassium current; I_{Kr}, rapid delayed rectifier potassium current; I_{Na}, sodium channel current; I_{K1}, inward rectifier potassium current; $I_{Ca,L}$, long QT calcium current (L-type calcium current); and $I_{K\text{-}Ach}$, acetylcholine-activated potassium current.

an additional treatment for patients who do not respond to β blocker therapy and has been shown to notably reduce cardiac events. While a post-LCSD QTc of <500 milliseconds predicts the procedure's effectiveness in patients with history of syncope, those with persistent QTc prolongation (>500 milliseconds) have an increased risk of SCD and are candidates for an implantable cardioverter-defibrillator (ICD).[27] The latter has mutation-specific effects, particularly for LQT3 patients,[27] and has been recently shown to reduce QTc in patients with LQT2.[28] In cases of recurrent major events and documented cardiac arrests, ICDs play an important role in patient management as a last resort.[29] Primary ICD therapy is advised for high-risk patients with LQT1 and LQT2 only if there are concerns about compliance or intolerance to β blocker therapy or if syncope or torsades de pointes happen during medical therapy. Secondary prevention with an ICD is recommended for all patients with LQTS who experience aborted cardiac arrest. Nevertheless, ICD comes with significant limitations that include inappropriate shocks, potential infection, broken leads, and battery replacement. Moreover, ICD treats rather than prevents the advent of potential fatal arrhythmias.[30]

Current advances have focused on precision medicine in LQTS, which has been enhanced by patient-specific, human-induced pluripotent stem cell–derived cardiomyocytes, which serve as effective models for disease mechanisms and drug screening.[31,32] Additionally, in silico models and systems biology approaches such as genomics, transcriptomics, proteomics, and metabolomics contribute to a deeper understanding of disease severity, progression, prognosis, and treatment.[33] Building on these advancements, high-throughput automated clamp assays have been used for the evaluation of variants of uncertain significance in cardiac ion channels.[34] As highlighted by Zhao et al, ion channel variants can alter channel gating, conformation, drug-binding sites, trafficking, and interactions with intracellular regulators, which subsequently influence how the channel responds to drugs.[35] As a result, drug effects may differ in patients with LQTS with distinct variants, and performing variant-specific drug testing could be beneficial in identifying the most appropriate treatments for patients with LQTS, especially in the context of genotype-guided therapy. Introducing clustered regularly interspaced short palindromic repeats and associated protein 9 in human-induced pluripotent stem cell–derived cardiomyocytes enables us to compare the properties of different variants, a single variant in different cell models, and differences between homozygous or heterozygous mutation.[36]

Table 2. Schwartz Score for LQTS Diagnostic Criteria

Category	Criteria	Points
Clinical history	Syncope with stress	2
	Syncope without stress	1
	Congenital deafness	0.5
Family history	Family member with known LQTS	1
	Family member with unexplained cardiac death before age 30	0.5
Electrocardiography	QTc ≥480 ms	3
	QTc 460–479 ms	2
	QTc 450–459 ms (male patients only)	1
	Torsades de pointes arrhythmia	1
	T-wave alternans	1
	Notched T wave in 3 leads	1
	Bradycardia	0.5

Interpretation: ≤1 point, low probability of LQTS; >1 to 3 points, intermediate probability of LQTS; ≥3.5 points, high probability of LQTS. LQTS indicates long QT syndrome.

The Istituto Auxologico Italiano is currently investigating LQTS acquired from exercise training that could be acting as a trigger in athletes with genetic predisposition (NCT05759260). Additionally, this institute is running the phase II of a clinical trial assessing the use of lumacaftor in shortening the QTc of patients with LQT2 after lumacaftor was shown to rescue in vitro the LQTS phenotype in human-induced pluripotent stem cell-derived cardiomyocytes from patients with LQT2 (NCT04581408).[37] The Bordeaux University Hospital is prospectively evaluating the use of electromechanical window, following a phonographic method, as a means of diagnosing LQTS compared with routine tests (NCT04328376). The Tel-Aviv Sourasky Medical Center has completed but not yet posted the results of a study aimed at assessing whether pink grapefruit should be forbidden to patients with LQTS because of its interference with the I_{Kr} channel and their potential QT prolongation (NCT02680080).

SHORT QT SYNDROME

SQTS belongs to the spectrum of early repolarization syndrome and is diagnosed as a QTc interval of <340 milliseconds due to acquired or innate factors.[38,39] The prevalence of SQTS in the general population is estimated to be 0.02% to 0.1% in the adult population with a male predominance.[40] SQTS is an autosomal dominant primary electrical disorder with low penetrance.[41] The SQT1-3 genotypes are attributed to gain-of-function mutations in the potassium channel genes *KCNH2*, *KCNQ1*, and *KCNJ2*. On the other hand, the SQT4 to SQT6 genotypes are attributed to loss-of-function mutations in L-type calcium channel subunits *CACNA1C*, *CACNB2*, and *CACNA2D1*. Biophysical analysis of the SCN5A (sodium channel protein type 5α) protein containing the R689H mutation showed a loss-of-function mutation that could not facilitate sodium channel current in the SQT7 genotype.[42–44] The SQT8 genotype was added after the description of a loss-of-function mutation in the *SLC4A3* gene impacting the solute carrier family 4 member 3 anion exchanger Cl^-/HCO_3^-.[45]

Diagnosis of SQTS is done on the basis of QTc shortening and ≥1 of the following criteria: survival of a VF/VT episode in the absence of heart disease, a confirmed pathogenic mutation, and a family history of SQTS.[2] Moreover, SQTS diagnosis is considered when a QTc ≤320 milliseconds is noted or when the QTc falls within the range of 320 to 360 milliseconds, along with a history of arrhythmic syncope.[8] Additionally, Schwartz's score has been used to categorize the probability of SQTS in patients (Table 3).[46] Moreover, the use of implantable loop recorders in young adults can enhance the risk assessment of SQTS complications.[47] Finally, genetic testing can be used as a diagnostic tool, especially when cases of sudden death with no apparent causes occurred in the patient's family. However, common protocols cannot screen for undiscovered genetic mutations and some

Table 3. Schwartz Score for SQTS Diagnostic Criteria

Category	Criteria	Points
Clinical history*	Documented PVT or VF	2
	History of sudden cardiac arrest	2
	Unexplained syncope	1
	Atrial fibrillation	1
Family history*	High probability of SQTS in first- or second-degree relative	2
	Autopsy-negative SCD in first- or second-degree relative	1
	Sudden infant death syndrome	1
Electrocardiography	QTc Interval<330 ms	3
	QTc Interval<350 ms	2
	QTc Interval<370 ms	1
	J-point–T-peak interval<120 ms	1
Genetic factors*	Genotype positive	2
	Mutation of unknown significance in a culprit gene	1

Interpretation: ≤2 points, low probability of SQTS; =3 points, intermediate probability of SQTS; ≥4 points, high probability of SQTS. PVT indicates polymorphic ventricular tachycardia; SCD, sudden cardiac death; SQTS, short QT syndrome; and VF, ventricular fibrillation.

*Requires at least 1 ECG finding.

genotype–phenotype associations are not clearly understood. Prophylactic treatment should be based on the patient's phenotype.[48]

ICD is the primary therapeutic choice for symptomatic SQTS patients at risk of SCD and with a life expectancy surpassing 30 years.[49] Suitable candidates for ICDs to prevent cardiac arrest include individuals with documented situations of spontaneous sustained VTs, with or without syncope, and those who successfully overcame a prior cardiac arrest.[2] In young patients or patients with contraindications to ICD therapy, pharmacological therapy can be used. Quinidine is the first-line pharmacologic intervention for treating SQTS.[50] Hydroquinidine can be used to prolong the QT interval as it acts as a multichannel blocker, prolonging the AP length by interfering with the I_{Kr} channel. However, hydroquinidine's role in decreasing cardiac events is unclear. On another hand, amiodarone and sotalol are ineffective in treating patients with SQTS1 even though they are QT-prolonging drugs that block the I_{Kr} channel.[51,52] This may be attributed to ion channel mutations affecting drug effects and channel gating properties.[53] Currently, data on pharmacologic therapy in SQTS is limited, primarily focusing on patients with SQTS1, and necessitates further research on targeted drug interventions for specific SQTS gene variants.[35]

BRUGADA SYNDROME

BrS is an inherited channelopathy that predisposes patients to fatal cardiac arrhythmias.[54] Its prevalence is around 3 to 5 per 10 000 people, and it is 8 to 10 times more frequent in male patients.[55] The clinical manifestations of BrS vary, with approximately two thirds of patients being asymptomatic and one third presenting with syncope or palpitations and dizziness.[54] Nonetheless, SCD can be the first manifestation of the disease, with BrS being involved in 4% to 12% of all SCD cases and up to 28% of SCDs in individuals with structurally normal hearts. SCD and arrythmias tend to occur during periods of rest, sleep, or after consuming large meals, which are associated with episodes of enhanced vagal tone and bradycardia.[56] BrS is also associated with other conduction abnormalities, including first-degree atrioventricular block, right bundle branch block, intraventricular conduction delay, and sick sinus syndrome.[8]

Initially, BrS was believed to follow a monogenic autosomal dominant inheritance pattern. Current understanding suggests that it involves polygenic inheritance, with multiple genes implicated in its development.[56] More than 250 pathogenic variations linked to BrS have been documented across multiple genes, which primarily encode for sodium, potassium, and calcium channels or proteins associated with them.[55] Nonetheless, among these genes, only *SCN5A* stands out as the most causative gene, with the others having a less defined association. In fact, *SCN5A* loss-of-function mutations are implicated in 15% to 30% of known cases of BrS and are also associated with a more severe disease phenotype (Table 4).[56,57]

Experimental models such as human-induced pluripotent stem cell-derived cardiomyocytes are frequently used in BrS studies.[58] Currently, the exact cellular mechanism underlying BrS remains controversial. Two main hypotheses exist: the depolarization disorder hypothesis and the repolarization disorder hypothesis. Another less common theory proposes that BrS might be linked to abnormalities in neural crest development. These theories are not mutually exclusive and may have a synergistic role in the development of BrS.[56] The repolarization hypothesis suggests that genetic variations affecting ion currents alter the balance during the repolarization phase of the right ventricular (RV) epicardial AP. Mutations decrease inward sodium and calcium currents or increase outward potassium currents, causing an outward current shift and thereby increasing the risk of arrhythmias and SCD. These abnormalities may also facilitate phase 2 reentry, triggering VT or VF.[56,59] The depolarization hypothesis attributes BrS features to slow conduction in the RV outflow tract due to fibrosis and reduced sodium channels and gap junction proteins (eg, connexin 43) expression.[56,59] Finally, the neural crest theory states that abnormal cardiac neural crest cell expression leads to abnormal connexin expression, particularly Cx43, causing depolarization delay and repolarization heterogeneity in the RV outflow tract.[56,59]

Three possible types of BrS can be observed on an ECG. The typical type I is characterized by a J-point elevation of ≥2 mm followed by a gradually descending ST segment and a negative T wave in the right precordial leads V1 and V2 at either the second, third, or fourth intercostal spaces, also called coved-type ST-segment elevation.[56] Type 2, or saddleback ST segment, has a J-point elevation of ≥2 mm and a terminal ST-segment elevation of ≥1 mm, followed by a positive or biphasic T wave in lead V2. Type 3 also has a saddleback ST segment with a J-point elevation of ≥2 mm in lead V2, but the terminal ST-segment elevation is <1 mm.[56]

On top of an ECG, provocation testing is indicated in patients presenting with type 2 or 3 at baseline or those with a suspicion for BrS based on clinical or family history.[55] In fact, type 1 may be unmasked by intravenous administration of class IA antiarrhythmic drugs such as procainamide and ajmaline, and class IC antiarrhythmic drugs such as flecainide and pilsicainide that act as sodium channel blockers.[54] Some clinicians favor the use of ajmaline because its high sensitivity leads to a lower false-negative rate.[60] However, positive ajmaline tests do not necessarily confirm the diagnosis of BrS due to the potential for false positives, owing to the intricate mechanism of ajmaline. Therefore, based on

Table 4. Genes Associated With BrS

Gene	Protein	Locus	Mechanism	Channel	% of probands
SCN5A	Sodium channel protein type 5 subunit α	3p 21–23	Loss-of-function	I_{Na}	11–28
SCN10A	Sodium channel protein type 10 subunit α	3p22.2	Loss-of-function	I_{Na}	5–16.7
SCN1B	Sodium channel subunit β-1	19q13.1	Loss-of-function	I_{Na}	1.1
SCN2B	Sodium channel subunit β-2	11q23	Loss-of-function	I_{Na}	Rare
SCN3B	Sodium channel subunit β-3	11q23.3	Loss-of-function	I_{Na}	Rare
KCND2	Potassium voltage-gated channel subfamily D member 2	7p13	Unknown	I_{to}	Unknown
KCND3	Potassium voltage-gated channel subfamily D member 3	1p13.3	Gain-of-function	I_{to}	Rare
KCNE1	Potassium voltage-gated channel subfamily E member 1	21q22.12	Unknown	I_{to}	Unknown
KCNE2	Potassium voltage-gated channel subfamily E member 2	21q22.11	Unknown	I_{to}	Unknown
KCNE3	Potassium voltage-gated channel subfamily E member 3	11q13-14	Gain-of-function	I_{to}	Rare
KCNE5	Potassium voltage-gated channel subfamily E regulatory β subunit 5	Xq22.3	Gain-of-function	I_{to}	Unknown
KCNH2	Potassium voltage-gated channel subfamily H member 2	7q36.1	Gain-of-function	I_{to}	Unknown
HCN4	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4	15q24.1	Loss-of-function	I_f	Rare
KCNJ8	ATP-sensitive inward rectifier potassium channel 8	12p11.23	Gain-of-function	$I_{K\text{-}ATP}$	2
CACNA1C	Voltage-dependent L-type calcium channel subunit α-1C	12p13.3	Loss-of-function	I_{Ca}	6.6
CACNA2D1	Voltage-dependent calcium channel subunit α-2/δ-1	7q21-22	Loss-of-function	I_{Ca}	1.8
CACNB2	Voltage-dependent L-type calcium channel subunit β-2	10p12.33	Loss-of-function	I_{Ca}	4.8
ABCC9	ATP-binding cassette sub-family C member 9	12p12.1	Gain-of-function	$I_{K\text{-}ATP}$	Rare
FGF12	Fibroblast growth factor 12	3q28	Loss-of-function	I_{Na}	Rare
GPD1L	Glycerol-3-phosphate dehydrogenase 1–like protein	3p24	Loss-of-function	I_{Na}	Rare
PKP2	Plakophilin-2	12p11.21	Loss-of-function	I_{Na}	Rare
RANGRF	Ran guanine nucleotide release factor	17p13.1	Loss-of-function	I_{Na}	Rare
SEMA3A	Semaphorin-3A	7q21.3	Unknown	Unknown	Unknown
SLMAP	Sarcolemmal membrane-associated protein	3p14.3-p21.2	Loss-of-function	I_{Na}	Rare
TRPM4	Transient receptor potential cation channel subfamily M member 4	19q13.33	Both	NSC_{Ca}	Unknown
HEY2	Hairy/enhancer of split	6q22	Gain-of-function	I_{Na}	Rare
LRRC10	Leucine-rich repeat	11p15.5	Unknown	Unknown	Unknown
MOG1	Ran-binding protein family	17p13.1	Loss-of-function	I_{Na}	Rare

BrS indicates Brugada syndrome; I_{Ca}, calcium channel current; I_f, funny current, mixed sodium-potassium current; $I_{K\text{-}ATP}$, ATP-sensitive potassium current; I_{to}, transient outward potassium current; and NSC_{Ca}, calcium-activated nonselective cationic current.

the latest European Society of Cardiology guidelines, BrS diagnosis is indicated in patients without underlying heart conditions who demonstrate a spontaneous type 1 pattern on their ECG, regardless of symptoms, and in induced type 1 pattern provided there are other clinical features such as episodes of polymorphic VT/VF, arrhythmic syncope, or pertinent family history.[2]

A novel diagnostic tool called the Shanghai Score System has been introduced for identifying BrS (Table 5).[61,62] This system allocates points on the basis of various criteria, including ECG changes, medical and family history, and genetic factors. A score of 2 to 3 indicates a potential BrS diagnosis, while a score of ≥3.5 confirms a definite diagnosis.

Risk stratification in BrS is essential for identifying patients at high risk of SCD and guiding appropriate management strategies. The presence of a spontaneous type I ECG pattern, a history of syncope, and documented ventricular arrhythmias are among the strongest predictors of adverse outcomes.[63] Symptomatic patients, particularly those with a history of polymorphic VT/VF, are at the highest risk and are typically recommended for ICD placement. In asymptomatic individuals, additional factors such as a family history of SCD, inducibility during electrophysiological study, and the presence of early repolarization patterns may help refine risk assessment. While electrophysiological study remains controversial, it can aid in identifying patients at intermediate risk. Those with a drug-induced type I ECG generally have a lower risk and are managed conservatively with lifestyle modifications and avoidance of arrhythmia triggers. Other therapeutic options include pharmacological treatment with quinidine and its related compounds quinine and

Table 5. Shanghai Score System for BrS Diagnostic Criteria

Category	Criteria	Points
Clinical history*	Cardiac arrest or documented VF/PVT	3
	Nocturnal agonal respirations	2
	Suspected arrhythmic syncope	2
	Unexplained syncope	1
	Atrial flutter/fibrillation in patients <30 y without alternative pathogenesis	0.5
Family history*	Definitive BrS in first- or second-degree relatives	2
	Suspicious SCD related to BrS in first- or second-degree relative	1
	Unexplained SCD in first- or second-degree relative aged <45 y	0.5
Echocardiography	Spontaneous type 1 Brugada ECG pattern	3.5
	Fever-induced type 1 Brugada ECG pattern	3
	Type 2 or 3 Brugada ECG pattern that converts with provocative drug testing	2
Genetic factors*	Presence of a pathogenic mutation associated with BrS	0.5

Interpretation: <2 points, nondiagnostic; 2–3 points, possible BrS; ≥3.5 points, probable or definite BrS. BrS indicates Brugada syndrome; PVT, polymorphic ventricular tachycardia; SCD, sudden cardiac death; and VF, ventricular fibrillation.

*Requires at least 1 ECG finding.

hydroquinidine, which should be considered in patients who are eligible for ICD implantation but have contraindications, decline the procedure, or experience recurrent ICD shocks.[8] In patients with BrS who experience electrical storms, intravenous isoproterenol should be considered. However, for patients experiencing recurrent ICD shocks that cannot be controlled with medications or patients who did not receive an ICD despite indications for one, radiofrequency ablation can be an effective treatment option. Radiofrequency ablation could potentially eliminate the arrhythmic consequences of BrS and therefore results in ECG normalization and VT/VF noninducibility.[64]

Several clinical trials are underway to enhance diagnosis and treatment of BrS. One is the prospective BrAID (Brugada Syndrome and Artificial Intelligence Applications to Diagnosis) multicenter clinical study (NCT04641585).[56] This initiative focuses on developing an integrated platform based on machine learning algorithms and transcriptomics to aid physicians in accurately diagnosing type 1 BrS.[65] Extensive research is also being conducted on RNA-based therapies for cardiovascular diseases.[66] This paves the way for novel noncoding RNA therapeutics for BrS. Further research into the role of noncoding RNA will aid in developing new diagnostic and therapeutic strategies.[56]

EARLY REPOLARIZATION SYNDROME

Early repolarization findings on ECG called early repolarization pattern (ERP) used to be considered benign or normal.[67] However, studies have identified a link between ERP and an increased risk of SCD. The prevalence of ERP is around 5.8% in adults and is even higher in the pediatric population.[2] It is also more common in

Table 6. List of Genes Linked to ERS

Gene	Protein	Locus	Mechanism	Channel	Mutation	% of probands
KCNE1	KCNE1	21q22.12	Unknown	I_{to}	Missense p.S38G	Unknown
KCND3	Kv4.3	1p13.3	Unknown	I_{to}	Missense p.G306A	Unknown
KCNH2/hERG	Kv11.1	7q36.1	Unknown	I_{to}	Missense p.V392I	Unknown
KCNJ8	Kir6.1	12p11.23	Gain-of-function	$I_{K\text{-}ATP}$	Duplication	Rare
ABCC9	SUR2A	12p12.1	Gain-of-function	$I_{K\text{-}ATP}$	Missense p.K801T	Rare
DPP6	DPP6	7q36.2	Unknown	$I_{K\text{-}ATP}$	Missense p.S422L	Unknown
CACNA1C	α1c subunit CaV1.2	12p13.3	Loss-of-function	I_{Ca}	Missense p.V734I	4.1
CACNB2	*Ca_vβ2b*	10p12.33	Loss-of-function	I_{Ca}	Missense p.R663C p.A665T, p.V1137I	8.3
CACNA2D1	*Ca_vα2σ1*	7q21.11	Loss-of-function	I_{Ca}	Missense p.L747P	4.1
SCN5A	α-subunit Nav1.5	3p21	Loss-of-function	I_{Na}	Missense p.G490R	Rare
SCN10A	α-subunit Nav1.8	3p22.2	Loss-of-function	I_{Na}	Missense p.P817S	Rare
SCN1Bβ	β1-subunit	19q13.11	NA	I_{Na}	Missense p.G37R	Unknown
PKP2	Plakophilin-2	12p11.22	NA	I_{Na}	Frameshift p.E850del	Unknown
GPD1-L	GPD1-L	3p21.31	NA	I_{Na}	Missense p.A170V, S503L	Unknown

DPP6 indicates Dipeptidyl aminopeptidase-like protein 6; ERS, early repolarization syndrome; GPD1-L, glycerol-3-phosphate dehydrogenase 1–like protein; I_{Ca}, calcium channel current; I_{Na}, sodium channel current; $I_{K\text{-}ATP}$, ATP-sensitive potassium current; I_{to}, transient outward potassium current; KCNE1, potassium voltage-gated channel subfamily E member 1; and NA, not applicable.

Table 7. Shanghai Score System for ERS Diagnostic Criteria

Category	Criteria	Points
Clinical history*†	Unexplained cardiac arrest, documented VF or PVT	3
	Suspected arrhythmic syncope	2
	Unexplained syncope	1
Family history*†	Definitive ERS	2
	II.A. ECG pattern in ≥2 first-degree relatives	2
	II.A. ECG pattern in a first-degree relative	1
	Unexplained SCD <45 y in a first- or second-degree relative	0.5
Echocardiography†	ER ≥0.2 mV in ≥2 inferior or lateral leads with horizontal/descending ST segment	2
	Dynamic changes in J-point elevation (≥0.1 mV) in ≥2 inferior or lateral leads	1.5
	≥0.1 mV J-point elevation in at least 2 inferior or lateral leads	1
Ambulatory ECG monitoring	Short-coupled PVCs with R on ascending limb or peak of T wave	2
Genetic factors	Presence of mutations in genes associated with ERS	0.5

Interpretation: <3 points, nondiagnostic; 3–4.5 points, possible ERS; ≥5 points, probable/definite ERS. ERS indicates early repolarization syndrome; PVC, premature ventricular contractions; and VF, ventricular fibrillation.

*Requires at least 1 ECG finding.

†Only award points once for highest score within this category.

physically active individuals, reaching a prevalence of up to 33.9%, and in Black as well as Southeast Asian individuals.[8,68] Several ion channel mutations have been linked to ERS, the most studied being a gain-of-function mutation in the *KCNJ8* gene that encodes the $K_{ir}6.1$ subunit of the K_{ATP} channel.[69] More recently, mutations in *ABCC9*, encoding the ATP-binding cassette transporter of ATP-sensitive potassium current, have been linked to ERS (Table 6).[8,69,70]

The initial presentation of ERS is often a life-threatening unexpected heart arrhythmia. It is frequently asymptomatic and discovered incidentally through ECG findings or following a cardiac event. Some patients may exhibit a history of syncope or have a family history of SCD at a young age, idiopathic VF, or ERP.[8] ERS is diagnosed in a patient who has been resuscitated from polymorphic VT or unexplained IVF, or in a patient with SCD with a negative autopsy report, along with an ECG displaying ERP characterized by J-point elevation ≥1 mm in ≥2 adjacent inferior or lateral leads.[2,8] The Shanghai Score System was proposed as a tool for diagnosing ERS; it takes into account the ECG findings, clinical history, family history, and presence of ERS susceptibility mutations (Table 7).[70]

Consensus guidelines state that asymptomatic patients with ERP do not require further testing or treatment.[67] However, in symptomatic patients such as those with unexplained syncope or a history of ventricular arrythmias, risk stratification is crucial. Patients with high-risk features, including inferolateral ERP with horizontal/downsloping ST segments, recurrent syncope, or a family history of SCD, may benefit from further evaluation with an implantable loop recorder or electrophysiological study to assess arrhythmia inducibility.[71] For patients with ERS who have survived a sudden cardiac arrest, an ICD is advised.[68] Pharmacological therapy may be considered in symptomatic patients with recurrent ventricular arrhythmias or electrical storms. Quinidine, phosphodiesterase III inhibitors, and isoproterenol have all demonstrated effectiveness in preventing or reducing arrhythmias.[70] Isoproterenol has been shown to counteract the repolarization abnormalities responsible for the disease phenotype by restoring the epicardial AP dome calcium channel current.[70,72] Phosphodiesterase III inhibitors such as cilostazol and milrinone have been shown to reduce the recurrence of VF.[2] They induce an inward shift in the current balance during the early phases of the epicardial AP by inhibiting the transient outward potassium current and augmenting the calcium channel current. This shift reverses the repolarization defects that contribute to the development of phase 2 reentry and VT/VF.[70,73] Quinidine has also been associated with a suppression of VF storm in patients with ERS by inhibiting the transient outward potassium current current.[69,73]

The VF Mapping in Brugada and Early Repolarization Syndromes trial (NCT03764592) aims to determine the value and limitations of noninvasive mapping using electrocardiographic imaging in identifying VF substrates. The goal is to target these sites for catheter ablations in patients with BrS and ERS. Moreover, this study seeks to provide risk stratification for these patients.[74] Recent advances in ERS basic research includes a recently published study led by the Lankenau Institute for Medical Research that revealed a potential pharmacological approach to treat the arrhythmic manifestations of J-wave syndromes, namely BrS and ERS, and hypothermia.[75] ARumenamide-787 was shown to have multiple effects on cardiac ion channels, primarily

Table 8. Major Genetic and Epidemiological Characteristics of CPVT Variants

Gene	Protein	Locus	Prevalence, %	Inheritance
RYR2	Ryanodine receptor 2	1q42-q43	60–70	AD
CASQ2	Calsequestrin-2	1p13.1	2–5	AR
TRDN	Triadin	6q22.31	<1	AR
TECRL	Trans-2,3-enoyl-CoA reductase like	4q13.1	<1	AR
CALM1	Calmodulin-1	14q31-q32	<1	AD
CALM2	Calmodulin-2	2p21	<1	AD
CALM3	Calmodulin-3	19q13.32	<1	AD
KCNJ2	Potassium voltage-gated channel subfamily J member 2	17q24.3	<1	AD
SCN5A	Sodium voltage-gated channel α-subunit 5	3p22.2	<1	AD
PKP2	Plakophilin-2	12p11.21	<1	AD
ANK2	Ankyrin-2	4q25-q26	<1	AD

AD, autosomal dominant; AR, autosomal recessive; and CPVT, catecholaminergic polymorphic ventricular tachycardia.

by inhibiting the transient outward potassium current and enhancing the sodium channel current. It also has lesser effects, such as inhibiting the I_{Kr} and augmenting the calcium channel current.[75] In canine RV and left ventricular experimental models of BrS and ERS and hypothermia, ARumenamide-787 significantly reduced the electrocardiographic J wave and prevented or suppressed all arrhythmic activity, making it a promising candidate for further research and potential therapeutic use.[75]

CATECHOLAMINERGIC POLYMORPHIC VT

CPVT is characterized by sudden episodes of syncope and sudden cardiac arrest, in the absence of structural heart defects.[76] CPVT is estimated to affect approximately 1/10 000 people[77] and is one of the most prevalent causes of sudden death in individuals aged <35 years with no structural heart defects, especially during exertional exercises such as swimming and running,[78] and is responsible for almost 15% of sudden cardiac deaths in youth.[79] The average age of onset of CPVT symptoms is 7 to 12 years, with almost 60% of patients having the first episode of syncope by 20 years of age.[80,81] If not recognized, CPVT is highly lethal, with up to a 50% mortality rate by the age of 35 years.[82]

The most common initial presentation is syncopal episodes that occur during exercise or emotional stress.[81] In some cases, the episode of VT self-terminates, but can transition to VF in almost one third of cases, causing SCD. A considerable proportion of patients with CPVT are misdiagnosed with epilepsy due to the similarity of symptoms, which include seizure-like activity. In addition, the episodes of syncope are often misattributed to vasovagal response or neurological triggers.[83]

The mutation in *RYR2* gene constitutes the predominant subtype of CPVT, known as CPVT1, which is autosomal dominant and prevalent in 60% to 70% of patients.[84] Genetic analysis has identified less prevalent mutations in the *CASQ2*, *TRDN*, *TECRL*, *KCNJ2*, *CALM1*, *CALM2*, *CALM3*, *SCN5A*, *PKP2*, and *ANK2* genes,[85] summarized in Table 8. The *RYR2* mutations are usually missense mutations, leading to a gain-of-function of the ryanodine receptor 2 channel. This results in excessive accumulation of calcium in the sarcoplasmic reticulum during diastole, followed by its sudden release into the cytoplasm.[86] This causes delayed afterdepolarizations, causing ventricular arrhythmias, especially under conditions of physical or emotional stress.[87]

Another mutation that is worth discussing is that of the *CASQ2* gene. Although mutations in this gene are less prevalent than *RYR2* mutations, accounting for <5% of cases, it remains the second most common mutation. There is emerging evidence of *CASQ2*-targeted gene therapy in CPVT.[88] It has been shown that patients with autosomal recessive, homozygous, loss-of-function mutations in *CASQ2* demonstrate a more severe phenotype of CPVT with earlier onset, compared with heterozygous carriers.[89] The most common mechanisms leading to *CASQ2* mutations include splice site alterations and stop codon insertion.[90] *CASQ2* mutations lead to CPVT via alteration of calcium signaling. *CASQ2* is known to form the calcium release unit by working alongside *RYR2* and the proteins junctin (gene *ASPH*) and triadin (gene *TRDN*).[91] The calcium release unit controls the release of calcium during excitation–contraction coupling. For proper coupling, calcium must be buffered so that precise release and reuptake into the sarcoplasmic reticulum occurs. *CASQ2* is the main calcium buffer and additionally modulates *RYR2* activity.[92] When calcium is released, it binds to calsequestrin 2 proteins,

which causes them to polymerize linearly. *CASQ2* mutations lead to both disrupted polymerization and decreased levels of calsequestrin 2 proteins. This disrupted assembly impairs calcium handling during increased physiological demands, explaining the CPVT phenotype.[93]

CPVT should be considered in patients with a structurally normal heart and a normal resting ECG, presenting with dizziness, palpitations, fainting, seizure-like episodes, or family history of juvenile sudden cardiac death during physical/emotional stress. During acute episodes, ECG presentations may exhibit 2 distinct types of polymorphic VT. The first type is the typical polymorphic VT with characteristic changing QRS morphology.[94] The other subtype is bidirectional tachycardia characterized by 180-degree rotation of the QRS complex between one beat and the other.[95] It is important to distinguish normal premature ventricular contractions (PVCs) from those seen in patients with CPVT. The PVCs in CPVT are typically late coupled and can exhibit a right bundle branch block pattern with a superior axis or a left bundle branch block pattern with an inferior axis. During exercise, the PVCs in patients with CPVT can be distinguished from normal heathy controls due to a variety of characteristics. These include a bigger number of PVCs that start appearing at high cardiac workload, left bundle branch block pattern with an inferior axis, bigeminy or trigeminy at peak stress, QRS > 120 milliseconds, coupling interval > 400 ms, or disappearance in the first minute of rest.[96] Of those characteristics, the most sensitive and specific one is the left bundle branch block pattern with an inferior axis.[97] This pattern suggests the presence of an RV outflow tract as an ectopic initiation site.

The primary diagnostic tool for CPVT is an exercise stress test. The test is done in a closely monitored environment and followed using a standard Bruce protocol.[98] As the duration and intensity of the test increases, the beats can transition into a bigeminal or trigeminal pattern and may become a ventricular arrhythmia.[99] A negative exercise stress test cannot rule out CPVT as it provokes a VT in around two thirds of patients only.[100] In such cases, a novel "burst" exercise protocol may be used. The hypothesis is that short intense bursts of exercise cause an abrupt surge in heart rate, predisposing to higher risks of calcium dysregulation and arrhythmogenesis.[101,102] In patients who cannot undergo exercise stress testing, a pharmacological stress test by epinephrine infusion is used. CPVT is diagnosed when the infusion triggers a polymorphic VT with >10 PVCs per minute or the presence of new T-wave alternations.[103]

In patients where neither the physical nor the pharmacological stress tests are feasible, such as young patients or patients with symptoms that are related to emotional rather than physical stress, a 24-hour Holter monitor can be used. However, the Holter monitor is less sensitive compared with stress testing.[100] In patients with clinical symptoms of CPVT or family history, genetic screening can be used to aid diagnosis and has the potential to identify individuals at risk before the onset of a life-threatening arrhythmia. The current Heart Rhythm Society and European Heart Rhythm Association guidelines both recommend genetic testing in all patients with clinically suspected CPVT, as well as screening all first-degree relatives at risk.[104,105]

The treatment of CPVT usually involves lifestyle modifications, medical treatment, surgical treatment, and ICD as a last resort.[38] In patients with symptomatic disease, pharmacological treatment is needed. If medical therapy fails to control the symptoms, nonpharmacological treatments should be considered on a patient-by-patient basis. These include device therapy with an ICD and even surgical sympathetic denervation.[106] Current recommendations by the European Society of Cardiology advocate restrictions on strenuous exercises in both symptomatic and asymptomatic patients with CPVT.[2] However, some observational studies have shown no difference in the incidence of arrhythmias between well-treated athletes and nonathletes.[107]

Medications used in the treatment of CPVT include antiarrhythmic agents, mainly β blockers and flecainide. β Blockers are considered the cornerstone of therapy.[38] It is recommended to initiate β blocker therapy for all symptomatic patients to minimize the proarrhythmogenic effects of catecholamines on the cardiac β-adrenergic receptor.[108] Nonselective β blockers are preferred over the β1-selective counterparts, potentially due to their favorable tolerability and superior effect on modulating the chronotropic response.[109,110] Despite optimal medical treatment, almost 30% of patients will require additional medical therapy.[111] In such patients, additional therapy with flecainide, a class IC antiarrhythmic agent, is warranted.[112] However, monotherapy with flecainide has been shown to be less effective than β blockers.[113] Suggested alternatives include propafenone, verapamil, ivabradine, and dantrolene. Propafenone, a class IC sodium channel blocker, has limited evidence for its use.[114] Verapamil, a non-dihydropyridine calcium channel blocker, is also rarely used in CPVT due to the lack of any significant benefits.[115] Ivabradine, a hyperpolarization-activated cyclic nucleotide-gated channel blocker, has limited use due to the lack of any significant evidence of its effectiveness.[116] Dantrolene, a ryanodine receptor 1 blocker, is conventionally used for the treatment of malignant hyperthermia, but no human studies have been conducted to check for its efficacy and safety in CPVT.[117,118]

Nonpharmacological treatment is indicated when lifestyle modifications and pharmacological treatments fail. The current nonpharmacological treatments

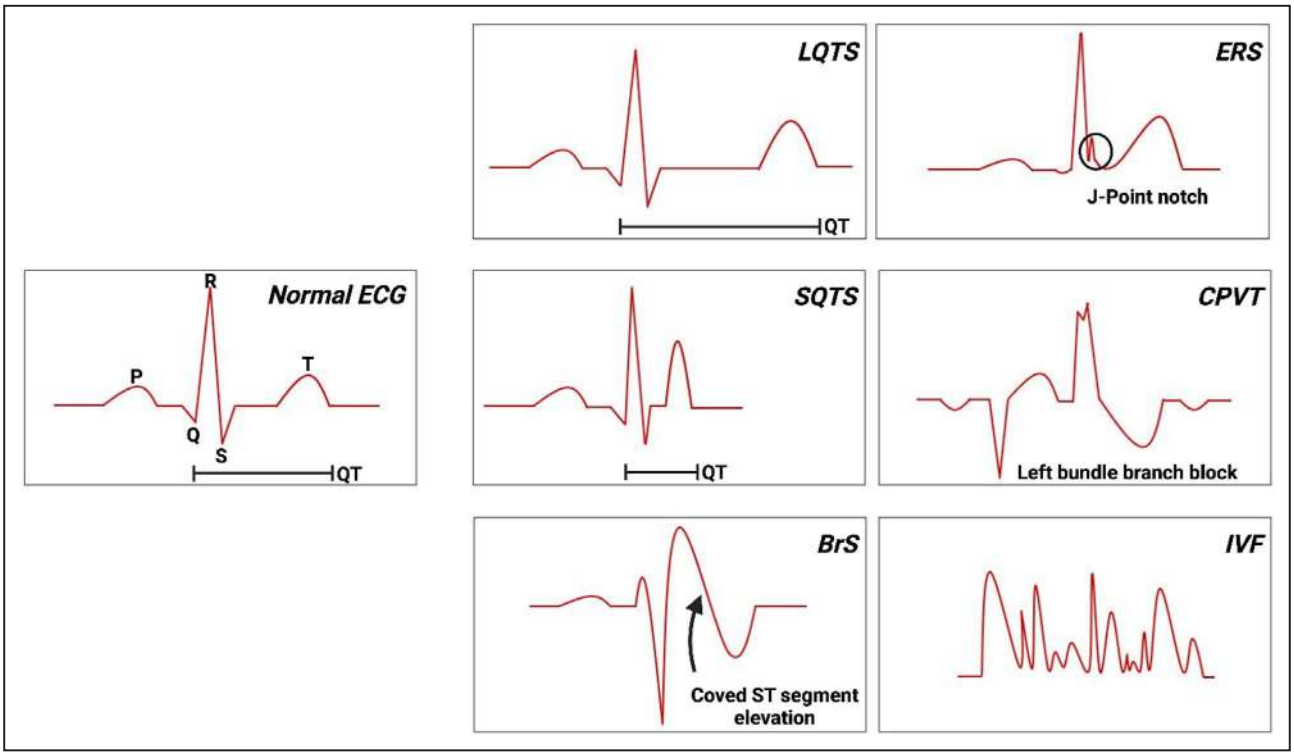

Figure 2. Typical and common arrhythmogenic channelopathies.
Shown are representative ECGs for normal cardiac function and most prevalent arrhythmogenic channelopathies. Panels are annotated to highlight specific abnormal feature characteristic of the respective channelopathy. This figure was created with BioRender.com. BrS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; and SQTS, short QT syndrome.

include left and right cardiac sympathetic denervation, ICDs, and catheter ablations.[76] LCSD has been described as an effective antiarrhythmogenic intervention in patients with CPVT refractory to pharmacological intervention.[119] The procedure includes thoracoscopic dissection of the lower two thirds of the left stellate ganglion with upper thoracic ganglia and is effective in disrupting the main sympathetic stimulation to the heart, decreasing the incidence of proarrhythmogenic events.[120,121] Although effective, LCSD is not always curative.[122] In cases of recurrence, right cardiac sympathetic denervation may be added, forming a complete bilateral sympathetic denervation to the heart.[121] LCSD is associated with complications including ptosis, Horner syndrome, pneumothorax, neuropathic pain, emotional excitement, and harlequin flushing following aerobic exercise.[123] Despite these possible complications, LCSD has shown improved quality of life in patients with CPVT.[124]

In patients with refractory CPVT who fail to respond to the previously mentioned pharmacological and nonpharmacological interventions, ICD can be considered as a last resort.[125] However, drawbacks of this therapy exist. One complication is that ICD shocks are associated with a risk of provoking or exacerbating an arrhythmia due to the catecholaminergic surge and pain/fear associated with the shock.[125] Inappropriate ICD shocks are more common in patients with CPVT compared with other channelopathies.[126] In addition, the efficacy of ICDs in patients with CPVT depends on whether the arrhythmia is VT or VF. In patients with VT, ICD conversion is generally unsuccessful, while in patients with VF the conversion is highly successful.[127,128]

Recently, subcutaneous ICDs emerged as possible replacements for current ICDs. However, subcutaneous ICDs were associated with a higher incidence of complications and inappropriate shocks compared with ICDs.[129] Previous guidelines endorsed the use of ICDs in CPVT; however, current expert opinions and guidelines advocate for the use of ICDs only as a last resort.[130] Catheter ablation of ectopic sites triggering arrhythmias in CPVT holds promise as a possible therapeutic intervention. This technique has not been studied extensively.[131] Multiple studies have shown short-term success of the procedure but high recurrence rates.[132] The mainstay treatment remains β blockers regardless of ablation, with the possibility of ICD or LCSD in refractory patients.[133]

A variety of gene therapies are currently under exploration for CPVT.[134] One proposed technique is via reconstitution of a functional wild-type *CASQ2* gene in

CASQ2-dependent CPVT, restoring the normal Ca^{2+} cascade.[135,136] Another is the use of clustered regularly interspaced short palindromic repeats and associated protein 9/Cas9-mediated genome to trigger DNA double-strand breaks in precise mutant genes.[137] This can be used to suppress the mutant genes in CPVT.[138,139]

IDIOPATHIC VENTRICULAR FIBRILLATION

IVF is an exclusionary diagnosis made after a patient with sudden cardiac arrest and a documented VF rhythm is rescued and other potential pathogeneses are excluded.[140] In young patients without structural or electrical heart disease, IVF is considered a major cause of SCD. IVF occurs due to Purkinje fiber–derived short-coupled premature ventricular complexes descending on the T wave, known as the R-on-T phenomenon.[141] There are many genes responsible for IVF; these include *CALM1*, *RyR*-encoded cardiac calcium channel, *IRX*-encoded Iroquois homeobox gene family transcription factor, and the promoter haplotype in *DPP6* locus on chromosome 7. Among them, the *DPP6* haplotype was shown to have diagnostic purposes as its level was found to be >20 times higher in patients with IVF than in healthy patients.[140]

To diagnose IVF, a workup including multiple tests should be done given that IVF is diagnosed by exclusion. Ruling out cardiac abnormalities such as early J-wave syndromes or QT syndromes requires a 12-lead ECG followed by Holter cardiac monitoring.[142] Other test options include an intravenous epinephrine test and a procainamide challenge test and invasive testing as electrophysiological testing or myocardial biopsy.[140] Currently, guidelines recommend diagnosis in patients with unexplained cardiac arrest to determine causality, but no strict diagnostic workup exists for IVF diagnosis. Cardiac magnetic resonance imaging, exercise treadmill test, and sodium channel blockers at least must be performed given their highest-performing quality.[143] Additionally, genetic variants related to cardiomyopathy could be involved in IVF occurrence and should be investigated as a possible risk factor.[144] According to the most recent guidelines from the American College of Cardiology, the American Heart Association, and the European Heart Rhythm Association/Heart Rhythm Society, genetic testing is advised for patients who survived SCD from unexplained causes, with IVF being the default diagnosis if clinical suspicion of genetic heart disease exists.[140] The higher incidence of variants of uncertain significance compared with that of pathogenic/likely pathogenic variants adds to the complexity of genetic testing analysis.[140]

There are multiple treatment options available for patients with IVF.[2] These guidelines recommend either an ICD or pharmacotherapy including infusion of isoproterenol, verapamil, or quinidine for acute treatment of electrical storm or recurrent ICD discharges. Chronic use of quinidine can also be used to suppress recurrent ICD discharges or electrical storms in IVF. The last option is percutaneous catheter ablation in patients with recurrent IVF with repeated episodes of VF with similar premature ventricular complexes, unresponsive to pharmacotherapy.[2]

There are several ongoing clinical trials pertaining to IVF. Among them, a pilot study by the University of Amsterdam Academic Medical Center will be conducted to provide insight into the advisability and feasibility of quinidine and verapamil in reducing IVF incidence (NCT05593757). Another study is being conducted by the Maastricht University Medical Center to evaluate the electrophysiological properties of the heart conduction system in patients at risk for apparent IVF (NCT03963271). One completed but unpublished study by the University of British Columbia aims to test for primary electrical disease and latent cardiomyopathy along with clinical genetics screening of affected individuals based on an evident or unmasked phenotype (NCT00292032).

CONCLUSIONS

SCD continues to pose a significant public health challenge, responsible for a substantial portion of cardiovascular death. Primary electrical heart diseases, or channelopathies, which are inherited genetic abnormalities affecting the function of cardiomyocytes without structural heart defects, account for many SCD cases. Recent advancements in genetic research, particularly in genomics, proteomics, and transcriptomics, have shed light on the underlying genetic mutations and complex pathophysiology of these conditions. Comprehensive clinical evaluations, detailed family histories, and genetic testing have significantly improved diagnostic accuracy and risk stratification. Moreover, diagnostic scores have been proposed for these conditions, with the 12-lead ECG remaining a fundamental tool in diagnosis (Figure 2). Continued research and clinical trials are essential to bridge remaining knowledge gaps, ultimately enhancing prevention and treatment strategies for SCD related to these channelopathies.

ARTICLE INFORMATION

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Disclosures

None.

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