Management of Ventricular Arrhythmias in Suspected Channelopathies
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Although structural heart disease remains the predominant substrate for ventricular arrhythmia, channelopathies including long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and early repolarization syndrome (ERS) are less common but important contributing entities. These etiologies require specific therapies potentially contrary to empirical management of arrhythmias associated with structural heart disease. Conventional therapy including antiarrhythmic drug therapy may not only fail to resolve unstable arrhythmias but worsen them. Additionally, channelopathy patients with implantable cardioverter defibrillators (ICD) and arrhythmic storms represent a major challenge, and the acute care team needs to be cognizant of unique circumstances that require specific acute therapies beyond empirical advanced life support algorithm recommendations.

Successful and considered acute management of ventricular arrhythmias is contingent on a number of variables, including knowledge of the cardiac substrate or potential substrate; form, mechanism, and precipitants of ventricular arrhythmias; and acute effect of potential therapies. In the longer term, an understanding of the natural history of the channelopathy along with the efficacy of long-term therapy will lead to superior outcomes. This review will present the risk of ventricular arrhythmias associated with these uncommon entities, the evolving understanding of the mechanism of arrhythmia, and the mechanistic basis of therapies along with a clinical approach to summarize the evidence pertaining to acute and long-term management.

Long QT Syndrome
Patients with a prolonged QT interval are at risk of sudden cardiac death (SCD) due to Torsade de Pointes (TdP; Figure 1). Most patients with congenital LQTS are asymptomatic and diagnosed incidentally on electrocardiogram screening or following family screening. However, syncope, aborted SCD, or SCD may be the first presentation. Most arrhythmic events in congenital LQT1 occur during physical or emotional stress, at rest or in association with sudden auditory stimulation in LQT2, and during sleep or rest in LQT3 patients. Although typical presentations can assist in raising the suspicion of LQTS, the history alone remains insufficient to diagnose the genotype and guide management.

Although numerous variables have been reported to increase the risk of TdP in patients with LQTS, the degree of QTc prolongation remains foundational. SCD in patients with congenital LQTS and a normal QTc (<440 ms) is low (4% at 40 years and 10% at 70 years). This is significantly lower compared with patients with LQTS with prolonged QTc (>440 ms, 15% at 40 years and 24% at 70 years). However, the risk of death in patients with LQTS and a normal QTc is still 10-fold compared with unaffected family members (0.4% at 40 years and 1% at 70 years). Risk of TdP is directly related to QTc with QTc values >500 ms requiring prompt attention even in the absence of arrhythmias.

Mechanism of Arrhythmia
QT prolongation can be due to common genetic variants or acquired, commonly due to QT-prolonging medications. Decreased outward potassium current mediated by loss-of-function mutations in Ina (slowly activating delayed rectifier potassium current) channels leads to LQT1 (Figure 2). Decreased potassium current, mediated by loss-of-function mutations in Ina (rapidly activating delayed rectifier current) channels, leads to LQT2. Increased inward sodium current, mediated by gain-of-function mutations in the cardiac sodium channel, causes slowed or incomplete channel inactivation leading to LQT3.

The dysfunction of the ion channels results in prolonged repolarization and can lead to development of early after depolarizations due to inward shift in the balance of current flowing during phases 2 and 3 of the cardiac action potential (AP). When the early after depolarizations reach the threshold for activation of the inward calcium current, they generate triggered extrasystoles. Differences in the degree of AP prolongation among the 3 cell types that comprise the ventricular wall lead to development of transmural dispersion of repolarization (TDR), thus creating a vulnerable window across the ventricular wall and other regions of the ventricular myocardium, which can lead to development of reentrant arrhythmias. When an early after depolarization–induced triggered response falls within this vulnerable window, the result is an atypical polymorphic ventricular tachycardia (PMVT), known as TdP. To date, mutations in 15 different genes have been identified in patients clinically diagnosed with LQTS.
LQT1 to LQT3 account for an estimated 85% to 95% of genotype-positive LQTS cases. Medications that prolong the QT interval are the best-characterized risk factors for acquired LQT, which is far more common than congenital LQTS. The vast majority of QT-prolonging drugs act by blocking IKr (Figure 2). Some IKr blockers can augment late INa via inhibition of the phosphoinositide 3-kinase pathway. Thus, the torsadogenic actions of these IKr blockers are mediated by both a reduction in outward current and an increase in inward current. An up-to-date list of drugs associated with QTc prolongation and cardiac arrhythmias can be found at www.qtdrugs.org. Pharmacodynamic and pharmacokinetic drug–drug interactions may also lead to QTc prolongation.

Acquired LQTS is commonly associated with multiple risk factors. In 1 series of 11 patients with acquired LQT (9/11 with TdP), there were ≥2 risk factors for the development of LQT, which always included ≥1 known QT-prolonging medication and ≥1 electrolyte disturbance (hypokalemia, hypocalcemia, and hypomagnesaemia). Patients were taking an average of 2.8±0.3 QT-prolonging medications in this series. Average QTc interval at presentation was 633.8±29.2 ms. A QTc >500 to 550 ms should prompt clinicians to assess the risk/benefit ratio of continuing QT-prolonging pharmacotherapy, depending on contributing arrhythmic variables and competing clinical indications for QT-prolonging pharmacotherapy.

**Therapeutic Strategies**

The management principles hinge on pharmacological and nonpharmacological attempts to produce an outward shift in the balance of currents to overcome the abnormally prolonged repolarization and suppress triggers. Acutely, correction of electrolyte abnormalities, such as hypokalemia and hypomagnesaemia, is essential in both acquired and congenital LQTS. Studies have reported the safety and utility of intravenous magnesium sulfate for the treatment of TdP associated with acquired and congenital LQTS.

β-blockers are considered first-line therapy for patients with LQT1 and LQT2, but remain controversial in LQT3. Metoprolol seems to be less effective than propranolol and nadolol. The longer half-life of nadolol also allows twice-a-day administration and is preferable. Similarly sustained release propranolol should be preferred. Limited data suggest that atenolol may be less effective compared with propranolol.

**Figure 1.** Long QT syndrome with resultant Torsade de Pointes (TdP) (**top**, exercise-induced TdP; **bottom**, bradycardia-induced TdP).

**Figure 2.** The ionic currents of the action potential (AP). Epicardial (Epi) AP and current are shown by dotted lines and endocardial (Endo) by solid lines. Depolarizing inward currents are depicted downward and repolarizing outward currents upward. The Epi AP has a characteristic notch caused by larger phase 1 Ito compared with Endo. ECG indicates electrocardiogram; ICaL, inward calcium currents; IK1, inward rectifier current; IKACh, acetylcholine-activated current; IKATP, adenosine triphosphate–sensitive current; IKr, rapid delayed rectifier current; IKs, slow delayed rectifier current; INa, inward sodium current; INa/Ca, sodium calcium exchange; and Ito, transient outward current.
Additional data suggest that in LQT1, the risk reduction is similar among atenolol, metoprolol, propranolol, and nadolol, but in LQT2, nadolol provided the only significant risk reduction.\textsuperscript{10} Currently evidence is lacking to recommend cardioselective β-blockers for LQT3.

Experimental data indicate β-blockade (propranolol) to be effective in preventing ventricular tachycardia (VT)/ventricular fibrillation (VF) in a validated LQT3 model.\textsuperscript{11} However, other experimental data suggest β-blockade may facilitate TdP in LQT3.\textsuperscript{15} The apparent lack of clinical efficacy in small populations of patients with LQT3 on β-blockers has been suggested to be due to analysis including patients with LQT3 who had suffered a cardiac arrest in the first year of life who remained at high risk compare with patients who did not have events early in life who appeared to remain protected by β-blockers.\textsuperscript{13} The largest clinical series from 9 registries worldwide (published in conference abstract form) included 403 patients with LQT3 and concluded β-blocker therapy to be effective in significantly reducing the risk of aborted cardiac arrest or SCD.\textsuperscript{14}

Preliminary data suggest that patients with LQT3 could benefit more from Na\textsuperscript{+} channel blockers, such as mexiletine, flecainide, and ranolazine, although long-term data are not available as yet.\textsuperscript{15}–\textsuperscript{17} Experimental data have shown that mexiletine reduces TDR and prevents TdP in LQT3, as well as LQT1 and LQT2, suggesting that agents that block late sodium current may be effective in all forms of LQTS.\textsuperscript{18} In rare cases, cautious use of mexiletine has been advocated due to reported prolongation of the QT interval by facilitating trafficking of mutant proteins in LQT3.\textsuperscript{19} Flecainide, a potent blocker of the open sodium channel, in low dose consistently shortened the QTc interval (565±60 ms to 461±23 ms; \(P<0.04\)) and normalized QTc in patients with LQT3 (\(n=5\)) with a DKPQ mutation.\textsuperscript{15} Class 1b and 1c agents may also be tried acutely intravenously in patients with TdP due to LQT3, although no study has reported safety or efficacy.

The late I\(_{Na}\) blocker ranolazine is effective in abbreviating QT interval and suppressing TdP in experimental models of LQT\textsuperscript{3}\textsuperscript{17} and in significantly abbreviating QTc in patients with LQT3.\textsuperscript{20} In patients with DKPQ-mediated LQT3, ranolazine has been shown to cause a dose-dependent abbreviation of the QTc interval with no change in PR or QRS intervals.\textsuperscript{20} The lack of effect of ranolazine on PR interval and QRS duration is consistent with the finding that ranolazine does not significantly inhibit peak I\(_{Na}\) in the ventricle at therapeutic concentrations.\textsuperscript{20} Clinical trials of ranolazine in LQT1 and LQT2 are not as yet available.

Adrenergic stimulation may be of benefit in the case of acquired LQTS associated with bradycardia and long pauses. Isoproterenol or epinephrine may exacerbate arrhythmias in patients with acquired LQT with a concurrent congenital defect but may be beneficial in patients with acquired LQT with no concurrent gene mutation by recruiting functional I\(_{Ks}\) channels and accelerating heart rate\textsuperscript{21} (Table 1; Figure 3). β-adrenergic stimulation induces TdP by increasing TDR in canine models of LQT1 and 2 but suppresses TdP by reducing dispersion in the LQT3 canine model.\textsuperscript{12} Thus acutely, β-adrenergic stimulation can be beneficial in LQT3 and β-blockers in LQT1 and LQT2. Acute temporary pacing can minimize pause-dependent TdP in both acquired and congenital LQT patients.\textsuperscript{22}

The implantation of an ICD is pivotal secondary prevention in LQTS and a reasonable primary prevention approach in select cases.\textsuperscript{2} Thoughtful ICD programming to prevent inappropriate shocks is important and usually requires a VF-only zone (detect rate, >220–240 beats per minute).

Left cardiac sympathetic denervation (LCSĐ) is generally limited to the treatment of patients with LQT1 or LQT2 with recurrent syncope despite β-blocker therapy, in patients who experience arrhythmic events with an ICD, and considered in patients intolerant to β-blocker therapy.\textsuperscript{23} LCSĐ has been performed both as primary and secondary prevention in LQTS with excellent outcomes in select patients.\textsuperscript{33} Marked reduction in number of cardiac events is usually seen following LCSĐ. However, nearly 50% of patients with high-risk LQTS continue to experience breakthrough events. Thus, LCSĐ should not be viewed as curative or as an alternative to ICDs for high-risk patients. Furthermore, in appropriate patients, LCSĐ is initially favored, with subsequent right cardiac sympathetic denervation if there is arrhythmia recurrence.\textsuperscript{24}

### Short QT Syndrome

The SQTS is characterized by an abbreviated QTc interval (<330 ms), with J-point to T-wave peak <120 ms (measured in the precordial leads with the T-wave of greatest amplitude), with a relatively large amplitude peaked T-wave with a steep downward slope, ventricular and atrial arrhythmias (due to short atrial and ventricular effective refractory periods), and SCD/syncope.\textsuperscript{2} The majority of affected individuals typically

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**Table 1. Gene Defects Responsible for Long QT Syndrome**

<table>
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<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Ion Channel</th>
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<tbody>
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<td>7</td>
<td>KCNH2, HERG</td>
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<td>3</td>
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<tr>
<td>LQT15</td>
<td>2</td>
<td>CALM2, Calmodulin</td>
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</table>

\*Andersen–Tawill syndrome.

†Timothy syndrome.
have a personal or family history of syncope or autopsy-negative SCD in a first- or second-degree young relative. SQTS is relatively rare with <60 cases reported in a recent expert consensus statement. There are no validated diagnostic criteria, although a scoring system for diagnosis has been proposed. It is likely that the severity of QT abbreviation is related to prognosis, although this has not been validated.

In contrast to the mutations that underlie LQTS, SQT1 is caused by mutations that cause a gain of function of outward currents or loss of function of inward currents. The increased net outward current accelerates repolarization of the AP, thus abbreviating the QT interval. Gain-of-function mutations in the KCNH2 (IKr), KCNQ1 (IKs), and KCNJ2 (IK1) genes account for SQT1, 2, and 3, respectively. Loss-of-function mutations in the CACNA1C, CACNB2, and CACNA2D1 genes encoding for the a1, b, and a2δ subunits of the cardiac L-type calcium channel account for SQT4, 5, and 6, respectively (Figure 2).

**Mechanism of Arrhythmia in SQTS**

Abbreviation of the AP in SQTS is heterogeneous, most commonly displaying preferential abbreviation in epicardium, thus giving rise to an increase in TDR. Augmented TDR as the basis for arrhythmogenesis in SQTS has been demonstrated in experimental models in which repolarization is abbreviated using the IKr agonist, PD-118057, thus mimicking the cellular conditions created by the genetic defect associated with SQT1. Dispersion of repolarization and refractoriness serve as substrates for reentry by promoting unidirectional block. Marked abbreviation of wavelength (product of refractory period and conduction velocity) is an additional factor promoting the maintenance of reentry. Tpeak–Tend and Tpeak–Tend/QT ratio, an electrocardiographic index of spatial dispersion of repolarization, including TDR, are significantly augmented in cases of SQTS. This ratio is greater in symptomatic patients.

**Therapeutic Strategies**

Isoproterenol has been reported to suppress VF due to SQTS in 1 case report. This beneficial action was secondary to a reduction of Tpeak–Tend, suggesting a reduction in TDR. However, this observation is in contrast to some experimental models of SQTS, which have shown a significant further abbreviation of QT interval and increase in TDR with isoproterenol, leading to more inducible PMVTs. Thus, strong evidence is lacking regarding isoproterenol in SQTS.

Fifty-three patients from the European Short QT Registry were followed up for 64 months and found to have an incidence of arrhythmic events of 5% per year in patients without pharmacological prophylaxis compared with no arrhythmic events in those administered hydroquinidine, suggesting patients with SQTS should be considered for pharmacological prophylaxis at the least. Quinidine can normalize the QT interval but has not been evaluated in large long-term or comparative studies. Flecainide, sotalol, ibutilide, and quinidine were studied in 6 patients with SQTS. Only quinidine was associated with significant QT prolongation (263±12 ms to 362±25 ms), resulting in a longer ventricular effective refractory period and noninducibility of VF during provocative testing.

There are no data to support implantation of ICDs in asymptomatic patients. An ICD may be considered in patients with a genotype or phenotype diagnosis of SQTS and a family history of SCD with evidence of a short QTc in relative/s with SCD (class IIb). Appropriate programming is needed to prevent inappropriate shocks from T-wave over sensing.

**Brugada Syndrome**

The majority of patients with a Brugada electrocardiogram pattern are asymptomatic, diagnosed incidentally, and may remain asymptomatic for life. Others may present with VF or SCD (particularly at night), nocturnal agonal breathing, syncope, and palpitations. Patients with a Brugada type-1
electrocardiogram (Figure 4) have an approximate cardiac event-rate per year of 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients.35

**Mechanism of Arrhythmia**

Mutations in 19 genes have been associated with the Brugada electrocardiogram, and in each, a decrease in the inward sodium or calcium current or an increase in an outward potassium current has been demonstrated, resulting in an outward shift in the balance of current during the early phases of the AP (Table 2). The reduction in $I_{Na}$ allows the transient outward ($I_{to}$) current to repolarize the cell during phase 1 beyond the voltage range at which L-type $Ca^{2+}$ channels activate. Failure of the $Ca^{2+}$ channels to activate results in loss of the AP plateau, predominantly in the subepicardial cells where $I_{Na}$ is most prominent. Conduction of the AP dome from epicardial sites at which it is maintained to sites at which it is lost results in the development of phase 2 reentry, giving rise to a closely coupled extrasystole.

Interestingly, these repolarization abnormalities give rise to low-voltage fractionated electrogram activity and high-frequency late potentials when a bipolar electrogram is recorded in the epicardial region of the right ventricle (RVOT) in an experimental model.36 The low-voltage fractionated electrogram activity, initially thought to be due to delayed conduction in the RVOT,37 has more recently been shown in an experimental model to be due to dyssynchrony in the appearance of the epicardial AP dome secondary to accentuation of the AP notch, and the high-frequency late potentials are due to concealed phase 2 reentry, both the result of repolarization abnormalities in the RVOT epicardium.36

Figure 4. Brugada electrocardiogram types and precipitants of ventricular arrhythmia in Brugada syndrome. Type 1 is characterized by a coved-type ST-segment elevation of ≥2 mm in the right precordial leads (V1–V3) followed by a negative T-wave. In type 2, ST-segment elevation has a saddleback appearance with a high takeoff ST-segment elevation of >2 mm, a trough displaying >1 mm ST-elevation followed by a positive or biphasic T-wave. Type 3 has an ST-segment morphology that is either saddleback or coved with an ST-segment elevation of <1 mm. PMVT indicates polymorphic ventricular tachycardia; PVC, premature ventricular contraction; and VF, ventricular fibrillation.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Ion Channel</th>
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<tr>
<td>BrS1</td>
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**Therapeutic Strategies**

Fever should be treated promptly with antipyretics, and drugs that unmask or aggravate BrS (www.brugadadrugs.org) should be avoided. A number of precipitants for ventricular arrhythmias have been reported (Figure 4) and should be addressed acutely. Isoproterenol has been used successfully to control VF storm.38 The occurrence of spontaneous VF in patients with BrS is often related to increases in vagal tone, and correspondingly, electrical storm is sometimes treatable by the increase of sympathetic tone via isoproterenol administration (Figure 3).

Quinidine may have a role in asymptomatic patients; however, this has not been evaluated in large double-blinded clinical trials.39 Quinidine is effective as adjunctive therapy in symptomatic patients, with recurrent arrhythmias and frequent ICD discharges.40 Effectiveness of quinidine or hydroquinidine in doses ≥600 mg/d is 85% (median follow-up of 4 years).41 A prospective registry of empirical quinidine for asymptomatic BrS has been established (http://clinicaltrials.gov/ct2/show/NCT00789165?term_brugada&rank_2). Doses between 600 and 900 mg are recommended by the study, if tolerated.39

The relatively low annual rate of arrhythmic events in asymptomatic patients (0.5% versus 7.7%–10.2% in patients with VF and 0.6%–1.2% in patients with syncope) warrants careful consideration for ICDs in asymptomatic patients.42
HRS/EHRA/APHRS (Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society) guidelines, ICDs are not recommended in asymptomatic patients. However, the ICD is first-line therapy for BrS patients with a history of VT/VF or arrhythmic syncope. Long detect durations and high detect rates along with careful programming of discriminators may minimize inappropriate ICD therapy.

In 9 patients with VF storm due to BrS, electroanatomic mapping has demonstrated abnormally low, prolonged voltages and fractionated late potentials clustering exclusively in the anterior aspect of the RVOT epicardium. Ablation at these sites rendered VT/VF noninducible and normalized the Brugada electrocardiogram pattern in the majority. Long-term outcomes (20±6 months) were excellent, with no recurrent VT/VF with only 1 patient on medical therapy with amiodarone. One recent study (10 patients) reports late activation within the RVOT endocardium normalized the electrocardiogram, suppressedVF storm, and reduced VF recurrence.

**Early Repolarization Syndrome**

Although early repolarization (ER; Figure 5) was historically considered benign, this perception changed in 2000 when experimental data in wedge models of ER were shown to be capable of generating rapid PMVT. Validation of this hypothesis came with the landmark study of Haïssaguerre et al and coworkers demonstrating a high prevalence of ER in patients with idiopathic VF. Numerous studies have shown a clear increased representation of the ER pattern in patients with idiopathic VF, with augmentation of the amplitude of ER preceding the development of ventricular arrhythmias. The early repolarization pattern should be viewed as largely benign. In some, ER is a modifier of risk of underlying cardiac conditions, and rarely ER represents as a primary arrhythmogenic disorder (ie, the ERS when other etiologies have been systematically excluded and when ER is associated with otherwise unexplained VF). The risk of arrhythmia is reported to depend on the location, pattern, and magnitude of ER. A relatively high risk is associated with ER in the inferior limb leads with a high amplitude J-point/wave (>0.2 mV) and a horizontal or descending ST segment after the J-point (compared with rapidly ascending/upslping ST segments). These high-risk features are observed in <0.3% of the population. In the general population, ER is associated with a 1.3- to 6-fold increased relative risk of death. The highest risk is associated with global ER, in which ER is apparent in inferior, lateral, and anterior (right precordial) leads. Despite the high overall prevalence of ER in the general population (6%–13%) and the even higher prevalence of ER in patients with idiopathic VF (>20%–30%, ≤50%–60%), VF itself is rare (ER is estimated to increase VF risk from 3.4 per 100,000 to 11 per 100,000). The ideal method to accurately identifying individuals with ER with an increased risk of death or VF compared with the benign ER observed in a substantial proportion of the population remains elusive.

**Mechanism of Arrhythmia**

ER is reported to be due to steep transmural AP gradients that predispose to arrhythmogenesis. The normal epicardial AP differs from the endocardial in having a prominent phase 1 notch or spike-and-dome morphology (Figure 2). The difference is due primarily to a larger \( \frac{dV}{dt} \) in the epicardium, which results in greater net repolarizing (outward) current flow.
during phase 1. In ER, a further enhancement in epicardial net outward current results in an enhancement of the endocardial-to-epicardial AP differences that manifests as J-waves, which reflects current flow resulting from transmural voltage gradients generated by the presence of a prominent AP notch in epicardium but not endocardium.  

Recent studies have provided insight into how the repolarization gradients in ER translate into arrhythmogenesis. The study by Koncz et al suggest that the AP dome of cells within LV epicardium become accentuated giving rise to phase 2 reentry and PMVT. This study showed that repolarization defects can be accentuated by acetylcholine, explaining the deleterious influence of elevated vagal tone, and that relatively high intrinsic levels of Ito account for the greater sensitivity of ERS. This study showed that repolarization gradients in ER translate into arrhythmogenesis. The mechanism underlying development of arrhythmias in these models of ERS has been shown to be nearly identical to those of BrS.  

**Therapeutic Strategies**

Because of their similar pathophysiological mechanism, it is not surprising that the approach to therapy of ERS is similar to that of BrS. β-adrenergic activation with isoproterenol is effective in suppressing ER arrhythmias by enhancing inward calcium current (Figures 2 and 5). Quinidine via its effects to inhibit Ito is effective as well. A multicenter observational cohort study has demonstrated that isoproterenol in acute cases and quinidine in chronic cases is effective for suppression of VF related to ERS. In this study (n=122; 90 male patients; mean age, 37±12 years), patients with ER in the inferolateral leads with ≥3 episodes of idiopathic VF (including those with electrical storms) had empirical antiarrhythmic drug therapy prescribed by the treating physicians. Follow-up data were obtained for all patients using an ICD. Isoproterenol infusion immediately suppressed electrical storms in 7 of 7 patients. Quinidine decreased recurrent VF from an average of 33 episodes to none over ≥2 years of follow-up. In addition, quinidine restored a normal electrocardiogram. Although this was a case series with empirical drug therapy, there was no suggestion of benefit from a number of antiarrhythmic drugs (ie, β-blockers, verapamil, mexiletine, amiodarone, and class 1C agents). In 7 patients with J-wave syndromes (5 patients with BrS and 2 patients with ERS) who experienced ICD shocks due to recurrent VF after ICD implantation, combination therapy of cilostazol and bepridil has been effective in suppressing VF recurrence.  

An ICD is indicated following cardiac arrest or documented VT/VF. There is no current risk stratification strategy for asymptomatic patients with ER in the general population and within families with ER. Syncope attributed to ER seems clinically uncommon and warrants an aggressive attempt to verify that syncope is related to arrhythmia.  

**Catecholaminergic PMVT**

Affected patients typically present with life-threatening (polymorphic or bidirectional VT or VF) associated with adrenergic stress (physical or emotional; Figure 6). CPVT is rare (estimated at 1/10000), with SCD as the first presentation in ≤30% of cases. Mortality is high when untreated, reaching 30% to 50% by age 30. CPVT-related symptoms occur early in life and are reported to occur in ≈35% and 72% by the age of 10 and 20, respectively. The mean age at presentation is between 7 and 9 years. An atypical form of CPVT (typically gene negative) may be observed in older patients and seems to be more sporadic.  

**Mechanism of Arrhythmia**

CPVT is caused by mutations in genes involved in the intracellular calcium homeostasis of cardiac cells. Excitation contraction coupling is mediated by calcium-induced calcium release at the time of cardiac depolarization. A gain-of-function mutation of the (ryanodine receptor-2) RyR2 receptor leads to a premature release of calcium. With cellular depolarization, a small influx of calcium into the cytosol binds the RyR2 channel on the sarcoplasmic reticulum and opens the channel, leading to a larger release of calcium from the sarcoplasmic reticulum. This calcium binds to contractile proteins within the cardiac cell with resultant muscle contraction. Mutations in (calsequestrin-2) CASQ2, a regulatory protein, also contributes to abnormal calcium regulation. Thus, an increase in diastolic calcium is thought to cause delayed afterdepolarizations and the subsequent arrhythmia by activating a calcium-dependent inward current.  

Mutations in 2 other genes (KCNJ2 and ANKB) may cause catecholamine-induced ventricular arrhythmia (including bidirectional VT) and may resemble CPVT.
Therapeutic Strategies

Treatments for CPVT include medical and surgical efforts to suppress the release and effects of epinephrine at the myocardial level or modulate calcium regulation by inhibiting RYR2 function. ICDs seek to treat the ventricular arrhythmia when the aforementioned measures fail.

β-blockers are considered first-line therapy and should be prescribed in every patient with CPVT. Urgent management of unstable patients typically involves bolus or continuous infusion of intravenous β-blockers. Conscious sedation and even general anesthetic may reduce the adrenergic state that occurs in unstable CPVT patients, particularly with flurries of ventricular arrhythmias while taking conventional therapy, although this approach is unproven. Arrhythmic event rates on β-blockers remain significant. In a review combining 11 studies (mean follow-up range, 20 months to 8 years), totaling 403 patients with 88% on a β-blocker, the estimated 8-year arrhythmic event-rate was 37.2% (95% CI, 16.6%–57.7%), with a near-fatal event-rate of 15.3% (95% CI, 7.4%–23.3%) and a fatal event-rate of 6.4% (95% CI, 3.2%–9.6%). This review demonstrated that suppression of exercise-induced ventricular arrhythmias with β-blockers does not necessarily translate into long-term effectiveness of therapy. Studies have also demonstrated the occurrence of SCD despite a negative exercise stress test in asymptomatic genotype-positive CPVT patients in the absence of β-blockers.

Flecainide may offer clinical benefit as a first-line therapy and has been demonstrated efficacious in combination with β-blocker therapy as a second-line agent in genotype-positive and genotype-negative patients. Flecainide directly targets the molecular defect in CPVT by inhibiting RYR2 channels and preventing arrhythmogenic calcium waves. In the aforementioned recent multicentre international study, prior to flecainide therapy, all genotype-positive patients had persistent physical or emotional stress-induced ventricular arrhythmias while taking β-blockers. Twenty-two of 33 patients had either partial (n=8, 24%) or complete (n=14, 48%) suppression of exercise-induced ventricular arrhythmias with flecainide (P<0.001). In the subset of patients already on optimal β-blocker therapy (n=15), flecainide further significantly suppressed ventricular arrhythmias compared with β-blocker therapy alone (P<0.003). Patients without suppression of exercise-induced ventricular arrhythmias (24%, n=7) received a significantly lower dose of flecainide compared with patients with ventricular arrhythmia suppression. During follow-up (median, 20 months), VT recurred in a single patient who experienced several ICD shocks for PMVT after 8 months of flecainide treatment. The serum flecainide level was low, suggesting noncompliance. The optimal dose of flecainide was reported to be 150 to 200 mg/d (range, 100–300 mg/d). Daily doses <100 mg were associated with a lack of therapeutic response. These findings suggested that flecainide should be considered for CPVT patients with refractory ventricular arrhythmias on β-blocker therapy, and the combination could even be considered a first-line therapy. Patients with CPVT treated with flecainide were limited to patients with predominantly RvR2 (RvR2, n=32; CASQ2, n=1) mutations. The efficacy of flecainide in patients with genotype-negative CPVT was also recently reported. Twelve patients with genotype-negative CPVT were treated with flecainide. Flecainide was initiated because of significant ventricular arrhythmias (n=8), syncope (n=3), or cardiac arrest (n=1), despite conventional therapy. At the baseline exercise test before flecainide, 6 patients had ventricular tachycardia and 5 patients had bigeminal or frequent ventricular premature beats. Flecainide reduced ventricular arrhythmias at the exercise test in 8 patients compared with conventional therapy, similar to that in patients with genotype-positive CPVT. During a follow-up of 48±94 months, arrhythmic events (SCD and aborted cardiac arrest) associated with noncompliance occurred in 2 patients. Flecainide was not discontinued owing to side effects in any of the patients.

LCSD interrupts the major source of norepinephrine released to the heart and is an effective and safe therapeutic option when symptoms persist despite pharmacological therapy. However, it requires at least minimally invasive endoscopic surgery, is not universally available, and has only been tested in small cohorts. The procedure increases the threshold for VF and increases ventricular refractoriness. LCSD has been reported as a primary prevention strategy in a single patient with CPVT and patients with LQTS. Most

Figure 7. A short-coupled (200 ms) premature ventricular contraction initiating ventricular fibrillation in the absence of electrocardiogram features of early repolarization, long QT, short QT, or Brugada pattern.
patients have a significant improvement in symptoms post LCSD, which should likely be considered early in the course of therapy in high-risk patients.66

ICD therapy has been studied in a multicenter, retrospective review of young patients with CPVT (n=24).67 Freedom from appropriate shocks at 1 year was 75%. Of appropriate shocks, only 57% demonstrated successful primary (or immediate) termination (all for VF). No episodes of PMVT or bidirectional VT demonstrated successful primary termination. There were no deaths in this study. Forty-six percent of patients received 65 inappropriate shocks at 1 year. Despite the role for ICDs, ICD shocks may also be proarrhythmic in patients with CPVT because they induce an adrenergic state in the patient.68 The ICD should be programmed with long delays before shock delivery and high cutoff rates.

All symptomatic CPVT patients should avoid intensive sports and exercise. Asymptomatic patients may undertake low-intensity exercise. Exercise restriction can be guided by response observed during exercise stress testing. However, suppression of exercise-induced ventricular arrhythmias with β-blocker therapy does not necessarily translate into long-term effectiveness of therapy.69

Idiopathic VF
PMVT is usually initiated by a short-coupled relatively narrow complex premature ventricular contraction (PVC) (often from the Purkinje network; Figure 7) in the absence of an identifiable arrhythmic substrate including the aforementioned channelopathies.70 PMVT/VF can also be triggered from RVOT PVCs.70 The distinction from benign RVOT ectopy seems to relate to a shorter coupling interval that initiates ventricular arrhythmias.71

Mechanism of Arrhythmia
The underlying mechanism for sustained VF that follows an initiating short-coupled PVC remains unknown.72

Therapeutic Strategies
Isoproterenol has been shown to be effective in suppressing VF, and quinidine has also been reported for acute suppression and for long-term prophylaxis.54,73 Verapamil has been reported to be acutely effective in patients with idiopathic Purkinje-related VF but does not prevent SCD with long-term use.73 Although the efficacy of quinidine has been attributed to its ability to inhibit Ik1, suppression of arrhythmias in J-wave syndromes by minimizing transmural electrical inhomogeneity, in patients with idiopathic VF, the mechanism of efficacy is unknown.71

Catheter ablation of the triggering PVC has been reported and has demonstrated a cure rate as high as 89%.70 Reported long-term outcomes are also relatively favorable with an 18% rate of recurrent VF postablation. Recurrences may be caused by a different PVC trigger highlighting the underlying arrhythmic substrate.75 An ICD is recommended for secondary prevention.

Conclusions
Knowledge of the pathophysiology of ion channel defects is essential to understand the acute and chronic suppression of ventricular arrhythmias. In contrast to conventional triggers and substrate for ventricular arrhythmias, defect-specific therapy is often crucial in the acute setting to prevent fatal outcomes, coupled to long-term effective prevention strategies. A careful history and electrocardiogram recognition of both repolarization patterns and onset patterns is crucial to directing tailored arrhythmia suppression.

Sources of Funding
This work was supported by grants HL74678 from the National Heart, Lung, and Blood Institute, National Institutes of Health (Dr Antzelevitch), CO26424 from the NYSTEM (New York State Stem Cell Science; Dr Antzelevitch), and the Masons of New York State, Florida, Massachusetts, Connecticut, Maryland, Rhode Island, and Wisconsin.

Disclosures
None.

References


Management of Ventricular Arrhythmias in Suspected Channelopathies
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_Circ Arrhythm Electrophysiol._ 2015;8:221-231
doi: 10.1161/CIRCEP.114.002321

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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