Electrophysiological Interventions for Inherited Arrhythmia Syndromes

Elizabeth A. Stephenson, MD; Charles I. Berul, MD

Inherited arrhythmia syndromes are electrical myopathies with genetic origins and risk of sudden death. They may present from infancy through adulthood, although the specific diseases have stereotypic but variable phenotypic onset and severity. There is clinical and genetic overlap among the syndromes, with variable penetrance and expressivity. Although underlying mechanisms of arrhythmogenesis may differ between syndromes, the electrophysiological (EP), pharmacological, and interventional options overlap. Specifics of the genetics, pharmacological therapies, and lifestyle modifications have been reviewed recently and are beyond the scope of this article, which focuses on interventional electrophysiology for inherited arrhythmias.

Congenital Long-QT Syndromes

The congenital long-QT syndromes (LQTSs) are the prototypic group of inherited arrhythmias. They were initially described as autosomal-recessive LQTSs with congenital sensorineural hearing loss, Jervell and Lange-Nielson (JLN) syndrome, and the more common autosomal-dominant LQTS with normal hearing, Romano-Ward syndrome. LQTS is caused by mutations in ion channel (or related anchoring protein)–encoding genes, presenting with prolonged QTc, stress-induced syncope, ventricular arrhythmias, or sudden cardiac death (SCD). The diagnosis is ascertained from clinical symptom complex, family history, ECG manifestations (at baseline or with provocative stimulation), and genetic testing. The principal treatment is pharmacological for most LQTS patients.

Interventions for Congenital Long-QT Syndromes

Catheter Ablation

There is little role for diagnostic EP testing in LQTS. Studies have shown that programmed ventricular stimulation, QT interval response to pacing, and infusion of β-blocking medication in LQTS are of limited value. Monophasic action potential studies demonstrated afterdepolarizations but were not prognostic, and proarrhythmia can occur with ventricular stimulation.

Left Cardiac Sympathetic Denervation

Left cardiac sympathetic denervation (LCSD) can reduce cardiac events in LQTS but is not commonly performed at many institutions. Indications for LCSD include failure of medical therapy or frequent implantable cardioverter-defibrillator (ICD) shocks. Clinical results vary, likely because of the level of sympathetic denervation and operator experience. Left cervicothoracic sympathectomy involves resection of the left stellate ganglion and the first 4 or 5 thoracic ganglia, resulting in significant cardiac denervation but with an associated Horner’s syndrome. Stellectomy alone without removal of the upper thoracic ganglia provides inadequate sympathetic denervation and carries a high arrhythmia recurrence rate. High thoracic left sympathectomy, which removes the lower stellate ganglion portion along with the first 4 thoracic ganglia, may provide sufficient cardiac denervation without Horner’s syndrome. The invasiveness of LSCD has decreased with video-assisted thorascopic surgery.

No randomized trial has assessed the safety or efficacy of LCSD. A retrospective worldwide series reviewed 147 patients, most of whom had multiple cardiac events (syncope or aborted SCD), who underwent LCSD and demonstrated decreased symptoms and cardiac events. In patients with ICDs, LCSD reduced shock frequency. A QTc ≥500 ms after LCSD predicted a higher subsequent event rate. LCSD appeared more effective in LQT1 than LQT2.

Cardiac Rhythm Management Devices for LQTS

Permanent Pacemakers

Guidelines for pacemaker implantation were established by a joint American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) task force. The weight of evidence supported pacing (Class IIa indication) in high-risk congenital LQTS patients. Pacing is recommended for patients who remain symptomatic despite medication, particularly if bradycardia or pauses facilitate syncope or torsade de pointes. LQT3 patients may derive particular benefit because bradycardia is common, β-blockers are less effective, and repolarization dispersion worsens during bradycardia, potentiating pause-dependent arrhythmias.
Optimal pacing results are achieved with rates that reduce the QTc. Atrial pacing allows normal ventricular activation and avoids heterogeneous conduction if atrioventricular conduction is intact. Pacing should be programmed to limit bradycardia by setting an adequate lower rate limit and using algorithms that minimize pauses such as rate smoothing. Features that allow lower rates (hysteresis and sleep/rest algorithms that minimize pauses such as rate smoothing) should be avoided in LQTS patients with pauses.

The efficacy of combined therapy of β-blockade and permanent pacing was reported for 37 LQTS patients with recurrent syncope or ventricular tachycardia (VT) while on β-blockers or after LCSD. Pacing shortened the QTc, and over a 6-year follow-up, 76% remained asymptomatic. The SCD incidence was 24% overall, 17% if the patient was compliant with β-blocker therapy. Similarly, pacemakers were implanted in 21 LQTS patients with cardiac arrest, syncope, or polymorphic VT. Of these, 9 failed β-blocker therapy and 5 did not respond to LCSD. QTc shortening and symptom reduction occurred in most patients; however, 4 experienced syncope and 1 experienced SCD. One unique group of LQTS patients in whom pacing may be particularly efficacious is infants with 2:1 atrioventricular conduction resulting from markedly prolonged ventricular refactoriness (Figure 1). Standard programming may be ineffective, and high-rate atrial pacing rarely can be used to maintain adequate ventricular rates, albeit with 2:1 atrioventricular conduction.

Taken together, these data suggest that the combination of β-blockers and pacing is effective for many patients. However, risk of recurrent VT and SCD remains, particularly in noncompliant patients and those with persistent symptoms. This incomplete protection likely justifies the consideration of an ICD when pacemaker implantation is contemplated in LQTS patients. The rationale for choosing a pacemaker instead of ICD should be individualized and based on complex clinical decision-making interactions of multiple factors, including symptomatology, genotype, age, QTc, device features, and overall risk-to-benefit ratio.

**Implantable Cardioverter-Defibrillator**

Multicenter randomized trials have established that ICDs prevent SCD in adult heart failure patients. ICDs have become an important therapeutic component for LQTS patients with recurrent symptoms on β-blockers, pacing, or LCSD. The ACC/AHA/HRS and European Society of Cardiology (ESC) guidelines detail the expert consensus on ICD indications. Ongoing risk with β-blockers and pacing or LCSD suggests that an ICD be recommended for SCD survivors and patients with recurrent syncope or VT on β-blockers. The guidelines also recommend primary ICD therapy in selected high-risk patients, those with strong family SCD history, and those with medication intolerance or noncompliance. The potential efficacy of ICDs has been demonstrated in several LQTS series. In the International LQTS Registry, 125 ICD patients were compared with 161 clinically similar patients without ICD. This study found a 16% death rate without an ICD, versus only 1.3% among the ICD-treated cohort. In a similar retrospective study, 27 symptomatic LQTS patients with ICDs were compared with 81 genotyped LQTS patients treated medically. This study showed 37% appropriate shocks, which were more prevalent in SCD survivors and those with longer QTc. There were no sudden deaths among ICD recipients over a 5-year mean follow-up.

In a initial report of 14 LQTS children with ICDs, 8 subsequently had appropriate shocks. In a retrospective study of 35 young LQTS patients, aborted SCD was observed in 74%, syncope in 17%, and torsade de pointes in 9%, with no deaths and 3 device-related complications. Other pediatric ICD series are consistent: Children with LQTS experience high rates of both appropriate and inappropriate shocks.

JLN syndrome has a higher arrhythmia risk than does Romano-Ward syndrome, and because JLN syndrome is autosomal recessive, family history is less informative. A large retrospective study of 186 JLN patients found that most (86%) had syncope or aborted SCD. Symptom onset began early, during childhood in most patients, and half of the β-blocker–treated patients had persistent events, including 27% who experienced SCD. In a similar study, 44 JLN patients were compared with Romano-Ward type LQTS, demonstrating that JLN patients presented younger (5±7 versus 14±9 years) and had higher risk of cardiac events (93% versus 54%). JLN β-blocker–treated patients had a 35% death rate, whereas no patients with an ICD died during a 5±3-year follow-up. Both studies support ICD use in JLN presenting during childhood. However, ICD-related complications, including infection, lead fracture, inappropriate discharges, psychiatric sequelae, and electrical storm, are relatively common in younger patients. Many young LQTS patients outlive their devices and leads, necessitating complex extraction and multiple replacement procedures. Recognition of these issues led to the development of novel implantation techniques and leadless ICD systems. Multiple factors should be considered carefully when interventional options in LQTS are assessed. The risk-to-benefit ratio of each approach differs by age, size, symptoms, and specific mutation.

**Short-QT Syndrome**

A related inherited arrhythmia is the short-QT syndrome (SQTS). The symptom complex is similar to LQTS, including recurrent syncope and malignant ventricular arrhythmias. SQTS patients also are prone to paroxysmal atrial fibrillation (AF). Mutations in potassium channel–encoding genes that differ from those causing LQTS are responsible. Functional analyses revealed that SQTS mutations caused gain-of-function, rather than loss-of-function, mutations in LQTS. This leads to short atrial and ventricular refractory periods and increased susceptibility to fibrillation. The QTc is ultrashort (<330 ms) (Figure 1B). Resembling LQTS, penetrance and expressivity are variable, ranging from carriers who are asymptomatic to those who have AF, ventricular fibrillation (VF), and SCD. Age of presentation is relatively early, with symptoms developing during childhood and even prenatally. Pharmacological treatment is geared toward prolonging repolarization by blocking outward potassium currents. QT-prolonging medications avoided in LQTS may actually be
Figure 1. Congenital LQTS and SQTS. A, top left, Marked QT prolongation (QTc = 620 ms) in a neonate with 2:1 atrioventricular conduction caused by alternating beats falling in the ventricular refractory period. A, lower right, Rhythm strip from the same patient showing a short run of torsade de pointes. B, ECG from a child with an extremely short QT interval (QTc = 210 ms) who died suddenly in the neonatal period.
therapeutic for SQTS. Given the rarity of the disease, there are no randomized trials, but quinidine lengthens QTc, prolongs refractoriness, and reduces arrhythmia vulnerability.

**EP Studies and Catheter Ablation**

In small clinical series, EP studies have been performed in SQTS patients to determine refractoriness and arrhythmia inducibility. Analogous studies in LQTS were found to have little clinical utility; whether this is also true for SQTS requires further research. EP study may induce atrial and ventricular arrhythmias; inducible arrhythmias are suppressed, and the QT interval is normalized with quinidine or sotalol. No data are yet available on catheter ablation to treat SQTS-associated AF or VF.

**Cardiac Rhythm Management Devices**

The ICD is primary treatment for symptomatic SQTS, given the high SCD incidence. Indications are less clear for asymptomatic SQTS patients or affected family members. Reports involve small numbers of patients (some may be counted in several articles) but recommend ICD implantation in symptomatic SQTS. Pharmacological therapies are unproven and used as secondary measures to reduce shocks and to treat AF or when an ICD is contraindicated or unavailable. Several reports state that ICD implantation in young children is not feasible; however, novel implantation approaches allow safe and effective ICD placement even in infants when necessary (discussed above).

Unique problems with ICDs in SQTS are being identified, particularly oversensing of peaked T waves and short coupling intervals between QRS-T waves. Careful attention to programming sensitivity and refractory periods is necessary. Better understanding of the efficacy of ICDs for SQTS, as monotherapy or combined with potassium channel-blocking medications, and potential gene-specific therapies may be gained with clinical experience and investigations.

**Brugada Syndrome**

The Brugada syndrome is an inherited arrhythmia disorder characterized by a stereotyped ECG pattern of right bundle-branch block, right precordial ST-segment elevation, and vulnerability to SCD from ventricular arrhythmias. The Brugada brothers codified the syndrome in 1992 previously classified as idiopathic VF or “sudden unexpected nocturnal death syndrome.” Similar to patients with LQTS and SQTS, Brugada syndrome patients have a structurally and functionally normal heart and therefore are characterized as having an isolated electric myopathy. The ECG characteristics of Brugada syndrome can be evanescent or persistent. ECG morphology subtypes include the “coved-type” ST elevation with upward convexity and inverted T wave (type 1) and “saddleback-type” ST elevation with concave ST elevation and biphasic or upright T wave (type 2). Presence of the ECG pattern alone without ventricular arrhythmias, SCD, or family history is designated a Brugada ECG pattern but not the syndrome (analogous to a patient having a long QT interval without having LQTS).

At least some cases are due to genes encoding ion channels. Mutations in the sodium channel gene, SCN5A, have been identified (in \( \approx 20\% \) to 30\% of cases). Unlike mutations in this gene that cause LQT3 as a result of delayed sodium channel inactivation, SCN5A mutations causing Brugada syndrome decrease sodium channel current by various biophysical mechanisms. It is likely that additional Brugada syndrome genes will be identified. Although Brugada syndrome is autosomal dominant with variable expressivity, it is more commonly observed in adults, typically presenting between the ages of 16 and 40 years, and symptomatic presentation is far more common in young male adults.

**Provocation of Concealed Brugada Phenotype**

In affected patients without a manifest Brugada ECG, administration of a sodium channel–blocking drug can elicit a typical ECG pattern (Figure 2A). The most commonly used medications are ajmaline (in Europe), procainamide, and flecainide. This provocative drug challenge can be helpful in the diagnosis of patients and family members.

**Interventions for Brugada Syndrome**

**EP Studies and Catheter Ablation**

The role of EP testing in Brugada syndrome continues to evolve. Patients with clear Brugada phenotype and ventricular arrhythmias, arhythmic syncope, aborted SCD, or family history clearly are at risk for recurrent SCD; therefore, EP studies have little prognostic value. However, in less symptomatic or asymptomatic patients with Brugada syndrome or Brugada ECG pattern, programmed stimulation may have diagnostic utility to assess for inducible arrhythmias. These studies may be combined with pharmacological provocation to increase the sensitivity (albeit lower the specificity). In a series of 547 Brugada syndrome patients, EP testing demonstrated that inducible VT/VF was predictive of future SCD or spontaneous ventricular arrhythmias, especially in symptomatic patients. Additionally, a prolonged H-V interval predicted higher risk of ventricular arrhythmia. In a prospective study of 200 Brugada syndrome patients, EP study results did not correlate with spontaneous VT/VF. The diagnostic accuracy for determining future cardiac events was 63% with programmed stimulation and 68% on the basis of symptoms. In another study, 37 symptomatic adult Brugada syndrome patients underwent EP study and were classified as inducible versus noninducible for VF. Those with inducible VF had longer baseline QRS duration, right bundle-branch block, and longer conduction time from the right ventricular outflow tract to the left ventricle with programmed extrastimulation. However, these findings were not prognostic for spontaneous VF or SCD. The aggressiveness and specific programmed stimulation techniques can markedly affect the variability of predictive value.

There is only a small series on ablation of ventricular arrhythmia triggers. In 7 patients with recurrent VT/VF (4 with LQTS, 3 with Brugada syndrome), the foci of spontaneous ventricular ectopic activity were identified in the Purkinje arborizations or the right ventricular outflow tract. Focal catheter ablation abolished recurrent VT/VF during an average of 17 months of follow-up. This study follows a
Figure 2. Brugada syndrome. A, A 12-lead ECG at baseline and intracardiac unipolar monophasic ventricular electrogram converting to a Brugada ECG phenotype with prominent afterdepolarizations visible after administration of procainamide. B, Evidence of T-wave oversensing on ICD, leading to an inappropriate device discharge.
Figure 2. Continued.
larger series of 27 patients with idiopathic VF who underwent successful catheter ablation of the ventricular trigger foci.\textsuperscript{74} ICDs are recommended for symptomatic Brugada syndrome, with ablation a consideration for rare cases of recurrent arrhythmia with accompanying frequent ectopic activity.

**Cardiac Rhythm Management Devices**

No clear role exists for pacemakers in Brugada syndrome. The high incidence of SCD warrants ICD placement in symptomatic or otherwise high-risk individuals. ICD implantation indications are less clear for asymptomatic Brugada syndrome patients or affected family members, particularly those without a persistent ECG phenotype or malignant family history. Because pharmacological therapy is not nearly as effective as for LQTS, ICDs are advocated for primary prevention therapy. Brugada syndrome patients with ICDs receive appropriate shocks, many presumed to be potentially life-saving.\textsuperscript{75} Review of ICD-stored electrograms reveals VF, typically preceded by premature ventricular beats, occurring in \( \approx 30\% \) to \( 40\% \) of Brugada syndrome ICD patients.\textsuperscript{76} Several studies comparing the efficacy of ICD and medical therapy (or no treatment) revealed decreased death rate in the ICD groups and relatively frequent appropriate shocks.\textsuperscript{60,63} Additionally, patients with inducible ventricular arrhythmia during EP testing had a higher likelihood of receiving an appropriate shock. The Second Consensus Conference on Brugada Syndrome recommended an ICD for patients with spontaneous ECG pattern and aborted SCD (Class I), symptomatic patients without clear origin (Class I), and asymptomatic patients with either a positive family history or positive EP study (Class IIa).\textsuperscript{59} If the Brugada ECG pattern is elicited only with sodium channel blockade, ICD is recommended for aborted SCD (Class I), symptomatic patients without extracardiac cause (Class IIa), and asymptomatic patients with both a positive family history and positive EP study (Class IIb).
study (Class IIb). Recently, in a large French multicenter study of 220 Brugada syndrome ICD patients, only 8% received appropriate shocks over an average of 3 years of follow-up, and a 28% complication rate, including 20% inappropriate shocks, was observed.\(^{77}\) This retrospective report highlights several downsides of ICD implantation for Brugada syndrome, including inappropriate shocks resulting from T-wave oversensing (Figure 2B) and supraventricular arrhythmias. Some Brugada syndrome patients have high defibrillation thresholds, necessitating more complicated implantation techniques, subcutaneous arrays, or high-energy devices to ensure adequate defibrillation.\(^{78,79}\)

**Overlap SCN5A Syndromes**

Several hybrid diseases involve SCN5A genetic overlap syndromes. Specifically, certain SCN5A mutations are responsible for LQT3, Brugada syndrome, and progressive cardiac conduction system disease (Lenegre syndrome). The phenotype correlates with the functional effect(s) on the sodium channel. Several recent reports describe patients with overlapping phenotypic presentations such as bradyarrhythmias and tachyarrhythmias.\(^{80–82}\) In some cases, these relationships are unmasked by administration of a sodium channel blocker.\(^{83}\) Given the combination of bradycardia, conduction defects, and VT/VF, an ICD that can provide pacing is a rational therapeutic approach.

**Inherited Cardiomyopathies**

Multiple cardiomyopathies are genetically based, with both dilated and hypertrophic phenotypes. The risk of arrhythmias and SCD is significant in familial dilated cardiomyopathies, which are beyond the scope of this article; management of arrhythmias is predominantly symptom based, with medications and devices forming the basis of therapy.

**Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy**

Arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) is a myocardial disease characterized by gradual replacement of myocytes with fibrosis and adipose tissue, leading to cardiomyopathy and arrhythmias. It affects predominantly the right ventricle, especially in earlier stages. Several forms have been linked to desmosomal dysfunction resulting from mutations in one of at least 6 genes, including those encoding plakoglobin, desmoplakin, plakophilin 2, and desmoglein 2.\(^{84}\) Inheritance is usually autosomal dominant with variable penetrance, but many cases are sporadic.\(^{85}\)

ARVD/C can present with palpitations, syncope, heart failure, or SCD. In an autopsy-based study, one third of sudden deaths attributed to ARVD/C occurred in the fourth decade, with the age at sudden death ranging from 5 to 65 years.\(^{86}\) Definitive diagnosis can be challenging, particularly at early stages. Diagnostic criteria include structural, histological, familial, arrhythmic, and ECG factors (Figure 3A).\(^{87,88}\) Endomyocardial biopsy can establish the presence of fibrofatty changes, but the right ventricular septum, the area usually sampled because of concerns about perforation at other sites, may exhibit less disease involvement than other areas.\(^{89}\) Magnetic resonance imaging can demonstrate fibrofatty tissue, along with structural and functional abnormalities, but may have subjective interpretation. Repeat magnetic resonance imaging assessments and detection of fibrosis from delayed gadolinium enhancement may improve diagnostic accuracy.\(^{90,91}\) An insertable loop recorder also may be useful in patients with a high suspicion of arrhythmias that cannot be documented through noninvasive means. Risk stratification in ARVD can be difficult. A retrospective study found that history of VT, clinical signs of right ventricular failure, and left ventricular dysfunction were predictors of SCD and that any combination significantly increased risk.\(^{92}\)

**Interventions for ARVD/C**

**EP Studies and Catheter Ablation**

Programmed ventricular stimulation has been suggested for risk stratification, but only retrospective data are available. A multicenter analysis of patients with ARVD/C and ICDs found that programmed stimulation had a positive predictive value of 49%, a negative predictive value of 54%, and an accuracy of 49% (based on appropriate shocks).\(^{93}\) EP studies were performed on 111 of the 132 patients; 88% were positive, possibly suggesting an aggressive stimulation protocol that might decrease the specificity of a positive test. Although this suggests that programmed stimulation is of limited utility in this population, there were no data on patients who did not receive ICDs, and numerous clinical factors influence the decision to implant an ICD. A smaller multicenter retrospective study found a higher appropriate shock rate (78%) and that inducible VT was an independent risk factor for appropriate ICD therapy.\(^{94}\) In this study, all but 1 patient underwent programmed stimulation, with \(\approx 50\%\) being positive. The discrepant conclusions in these 2 studies may be due to differences in patient population, stimulation protocol, or clinical decision-making with regard to ICD placement. Another recent study looked specifically at predictors of appropriate ICD therapy in definite versus probable ARVD/C and again found inducible ventricular arrhythmia as a risk factor. No patients with probable ARVD/C and a negative EP study received appropriate shocks, which suggests that a lower-risk group might be identified. All others received appropriate shocks, although those with ARVD/C but without inducible VT/VF were less likely to experience a shock than those with inducible VT/VF.\(^{95}\) Therefore, a negative EP study should not preclude ICD placement in patients with definite (ie, meeting task force criteria) ARVD/C. These studies evaluated only patients with ICDs, a potential selection bias.

Ablation of VT foci may be undertaken when arrhythmias cannot be controlled or intolerance to medications exists. Early studies report success rates of 32%, 45%, and 66% after 1, 2, and 3 radiofrequency ablation attempts, respectively.\(^{96}\) Marchlinski et al\(^{97}\) reported ablation results in 21 patients with ARVD/C and VT. Electroanatomic mapping of voltage potentials demonstrated electrogram abnormalities in all patients thought to be affected by ARVD/C. In 19 patients, VT was successfully ablated, most frequently identified in perivalvar regions.\(^{97,98}\) Recurrences should be anticipated because ARVD/C is progressive and other arrhythmic foci may emerge over time. However, patients with multiple shocks...
Figure 3. ARVD/C. A, ECG from an ARVD/C patient illustrating conduction delay and ventricular ectopy. B, Electroanatomic map (EAM) displaying heterogeneous right ventricular voltages. Colors represent endocardial voltages, with low voltages (red-orange) near the tricuspid annulus and mid-range (yellow-green-blue) and highest (purple) voltages in normal tissue.
and frequent arrhythmias may benefit from ablation as a tachycardia-reduction strategy.

Cardiac Rhythm Management Devices for ARVD/C
Although not a common feature of the disease, ARVD/C can involve the conduction system, and complete heart block has been reported. In this situation, placement of a permanent pacemaker might be indicated if an ICD was not also necessary.

Defibrillator implantation in ARVD carries a Class I indication in those patients with sustained VT and a Class II indication for primary prevention according to both ACC/AHA/HRS and ESC guidelines. Studies specifically evaluating ARVD/C show a high rate (48% to 78%) of appropriate ICD therapy overall. Although more recent studies include a larger proportion of patients receiving ICDs for primary prevention, the appropriate therapy rate remains substantial. Piccini et al showed that patients receiving a primary-prevention ICD (who had not had spontaneous VT before implantation) had a 39% appropriate discharge rate, versus 85% in the secondary prevention group.

The myocardium in ARVD/C can be markedly abnormal, with heterogeneous, low-voltage regions on electroanatomic mapping (Figure 3B); this can make finding a site for lead placement with adequate ventricular sensing and pacing difficult. This problem may be present at implantation or occur later with disease progression. A coronary sinus lead can be used to sense the left ventricle when right ventricular electrograms are insufficient.

Familial Wolff-Parkinson-White Syndrome
Several mutations in adenosine monophosphate–activated protein kinase (PRKAG2) gene cause glycogen accumulation and pre-excitation, with or without ventricular hypertrophy and atrioventricular block (Figure 4). These patients also are susceptible to developing AF and therefore a probable higher risk of sudden death. The EP characteristics of these accessory pathways do not differ clinically from isolated Wolff-Parkinson-White syndrome, and ablation can be attempted with standard techniques, although there frequently are multiple pathways. Conduction system disease may be progressive, and a pacemaker may eventually be required.

As with all forms of Wolff-Parkinson-White syndrome, ablation is indicated in patients presenting with AF or syncpe because of the risk of sudden death. ICD implantation, even in Wolff-Parkinson-White patients with cardiac arrest, carries a Class III indication (ie, generally not recommended because of a treatable cause) if the substrate is ablatable.

Familial Hypertrophic Cardiomyopathy
Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder, occurring in 1 in 500 people. Age at onset and phenotypic spectrum are broad, ranging from asymptomatic to outflow tract obstruction, arrhythmias, and sudden death. Sudden death is most common in adolescents and young adults <35 years of age, but continued risk persists throughout adulthood.

The majority of HCM (≈60%) is due to mutations in genes that encode sarcomeric proteins. To date, >400 mutations have been identified in 11 genes, including those encoding myosin heavy and light chains, troponins, and actin, among others. Mutations in sarcomeric proteins lead to myocyte hypertrophy, myofibrillar disarray, and cardiac fibrosis. Medical treatment for symptomatic patients typically includes β-blockade, verapamil, and disopyramide, primarily to increase filling time and to counteract diastolic dysfunction. If patients are symptomatic or drug refractory and if intracavitary obstruction is significant, alcohol septal ablation or surgical septal myectomy may be considered to relieve obstruction.

Risk factors for SCD may include sudden death in first-degree relatives, malignant genotype, massive hypertrophy (>30 mm), complex ventricular ectopy on Holter monitoring, blunted blood pressure response on exercise testing, and unexplained syncope. Although it has been suggested that certain genotypes of HCM have a higher risk of sudden death, this has not been found to be a consistent independent predictor; environmental and somatic influences and the genetic milieu likely mitigate these effects.

EP Studies and Catheter Ablation
Programmed ventricular stimulation has generally not been useful in HCM risk stratification and is not generally recommended to assist in guiding treatment. Risk stratification is thus performed predominantly on noninvasive measures. Although none of these risk factors alone is predictive, those patients with ≥2 risk factors have an incidence of SCD of 3% to 6% compared with the 1% incidence for the general HCM population.

Cardiac Rhythm Management Devices for HCM
Implantable Cardioverter-Defibrillator
ICDs are thought to be efficacious in preventing sudden death in HCM because of a high incidence of appropriate and successful shocks in a high-risk population with implanted ICDs (Figure 4). Both the AHA/ACC/HRS and ESC guidelines for ICD implantation place HCM as a Class I indication in those patients with cardiac arrest and a Class II indication in those patients who are thought to be at high risk.

HCM patients may have increased defibrillation thresholds because of increased myocardial mass, particularly in conjunction with amiodarone therapy. Dual-coil leads, along with subcutaneous arrays or high-energy devices, may be necessary to achieve acceptable defibrillation threshold margins.

Dual-Chamber Pacemaker
Dual-chamber pacing was previously reported as efficacious for symptom reduction in patients with severe outflow tract obstruction. However, 3 randomized studies found pacing to have little or no benefit, in contrast to the initial observational reports. Current guidelines on pacing classify HCM as a Class Ib indication in medically refractory symptomatic patients with significant outflow tract reduction and a Class III indication in those who are asymptomatic, those who are...
medically controlled, or those without outflow tract obstruction.\textsuperscript{14}

**Familial AF**

AF is a common arrhythmia, affecting \( \approx 2.2 \) million people in the United States, with prevalence increasing with age.\textsuperscript{119} In the elderly, AF is frequently associated with hypertension or structural heart disease. A smaller proportion of AF occurs in the absence of heart disease, usually in a younger population.\textsuperscript{120} The mean age of those with idiopathic AF is 44 years, compared with 75 years for the general AF population. In one study, a positive family history was found in 5\%, but for lone AF, that increases to 15\%, which may represent the prevalence of familial AF.\textsuperscript{121} First described in 1943, familial AF has been linked to at least 4 potassium channel genes and 7 loci, with

---

**Figure 4.** HCM. A, This ECG from a patient with HCM illustrates severe left ventricular hypertrophy and Wolff-Parkinson-White pattern. B, ICD intracardiac electrogram with successful conversion using antitachycardia pacing for VT (top) and an appropriate shock-converting VF (bottom).
Figure 5. CPVT. A, Bidirectional ventricular ectopy induced during exercise testing in a CPVT patient. B, Chest x-ray from a small child with CPVT who underwent ICD implantation with a subcutaneous array system without a transvenous lead. C, Intracardiac electrograms with demonstration of secondary termination (bottom)—the defibrillation shock does not immediately convert the rhythm but does affect the rhythm enough to cause secondary conversion to sinus rhythm within a few seconds—and ICD storm (top)—a vicious cycle in which a shock for VF is followed by sinus rhythm and return of VF, likely exacerbated by the catecholamine surge associated with the ICD shock.
### Abridged Summary of Interventional EP Procedures for Inherited Arrhythmia Syndromes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Provocative Drug Testing</th>
<th>EP Study</th>
<th>Ablation</th>
<th>Cardiac Pacing</th>
<th>ICD</th>
<th>LCSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS</td>
<td>Catecholamine testing may improve diagnostic sensitivity</td>
<td>Not helpful</td>
<td>Not helpful</td>
<td>Recommended in patients with drug-refractory symptoms, bradycardia- or pause-dependent VT, LQT3</td>
<td>Recommended for secondary prevention in high-risk and other selected patients</td>
<td>Recommended in select patients with drug-refractory symptoms</td>
</tr>
<tr>
<td>SQTS</td>
<td>K+ channel blockers may normalize QT</td>
<td>Limited data</td>
<td>No data</td>
<td>No data</td>
<td>Recommended for secondary prevention in high-risk and other selected patients</td>
<td>No data</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Ajmaline, procainamide, or flecaïnide may unmask Brugada pattern</td>
<td>Controversial; poor but variable predictive value</td>
<td>Small studies with successful ablation of VT/VF trigger foci</td>
<td>Not helpful</td>
<td>Recommended for secondary prevention in high-risk and other selected patients; controversial in asymptomatic patients</td>
<td>Not helpful</td>
</tr>
<tr>
<td>ARVD/C</td>
<td>Not helpful</td>
<td>Negative EP study does not indicate low SCD risk; may identify highest-risk patients; can voltage map</td>
<td>May be helpful in reducing arrhythmia burden, but arrhythmias likely to recur in this progressive disease</td>
<td>Indicated when significant conduction system involvement is present</td>
<td>Recommended for secondary prevention in high-risk and other selected patients</td>
<td>Not helpful</td>
</tr>
<tr>
<td>HCM</td>
<td>Not helpful</td>
<td>Not helpful/controversial</td>
<td>Can treat accessory pathways; not helpful for VT</td>
<td>Controversial but not helpful in most patients for outflow tract obstruction reduction</td>
<td>Recommended for secondary prevention in high-risk and other selected patients; used as primary prevention in some patients</td>
<td>Not helpful</td>
</tr>
<tr>
<td>Familial AF</td>
<td>Not helpful</td>
<td>Not helpful</td>
<td>Improving success in ablation of AF</td>
<td>Single- and dual-site atrial pacing may reduce AF</td>
<td>May reduce overall burden of AF for patients resistant to standard therapies</td>
<td>Not helpful</td>
</tr>
<tr>
<td>CPVT</td>
<td>Catecholamine testing may improve diagnostic sensitivity; carries risk of arrhythmic storm</td>
<td>Not helpful</td>
<td>Not helpful</td>
<td>Not helpful</td>
<td>Indicated if β-blocker therapy does not suppress VT</td>
<td>No data</td>
</tr>
</tbody>
</table>

Interventions for Familial AF

Catheter and surgical ablation for AF is progressing rapidly. Success rates vary but are commonly exceeding 70% in selected patients. Ablation may be particularly effective in younger patients with paroxysmal rather than chronic AF.

Atrial pacing (single and dual site) can reduce the incidence of AF in patients with bradycardia. A randomized comparison of single- or dual-site right atrial pacing and dual-chamber pacing demonstrated the safety of dual-site atrial pacing and prolongation of time to recurrent AF. Atrial defibrillators (combined with ventricular defibrillation) can effectively restore sinus rhythm, but use has been limited by associated pain and early recurrence of AF after termination. None of these interventions have been tested specifically for familial AF.

New AHA/ACC/ESC 2006 guidelines for the management of AF include recommendations on methods of anticoagulation, rate versus rhythm control, and the role for catheter ablation or device therapy.

Catecholaminergic Polymorphic VT

Catecholaminergic polymorphic VT (CPVT) is a rare disease characterized by syncope or SCD resulting from ventricular arrhythmia during exercise or emotional stress. It was first described in 1975 as bidirectional VT and was elucidated by Leenhardt et al., who described 21 children with stress- or emotion-induced syncope, structurally normal hearts, and normal resting ECGs. Polymorphic VT could be induced with exercise or isoproterenol. β-Blocker therapy dramatically reduced syncope and SCD over a mean of 7 years of follow-up. Mutations in the cardiac ryanodine receptor (RyR2) gene were identified, suggesting that abnormal sarcoplasmic reticulum calcium release or calcium overload may be the etiologic trigger for polymorphic VT. Two other calcium-handling proteins, calsequestrin 2 (CASQ2) and Ankyrin B, have also been identified in CPVT. If untreated, the death rate is 30% to 50% by age 30 years. Male gender and the RyR2 genotype seem to carry higher risk.

Early work proposed β-blockade alone as adequate SCD protection, but nearly 30% required additional therapy, mainly ICDs.

Interventions for CPVT

EP Studies

Programmed stimulation is of limited utility in CPVT because the VT is rarely inducible. Isoproterenol infusion or exercise testing may elicit the characteristic bidirectional VT (Figure 5).

Cardiac Rhythm Management Devices

When tachycardia is not documented, loop recorder implantation may be useful. When β-blocker therapy is not
adequately suppressing VT, ICDs are recommended. In one study, 50% of CPVT patients with ICDs had appropriate discharges over a 2-year follow-up. Because of the catecholaminergic nature of this disease, the risk of arrhythmic storm is particularly high. Vigilant ICD programming and discussions to minimize medication noncompliance are vital because even an inappropriate shock can trigger electrical storm with multiple shocks (Figure 2C). Psychological counseling should be considered for patients receiving multiple shocks.36,144

Summary
Inherited arrhythmia syndromes have multiple treatment options, including medications, lifestyle modifications, catheter ablation, and implantable cardiac rhythm management devices (see the Table). Interventional EP procedures are advancing rapidly, allowing a reduction in arrhythmia burden, improved quality of life, and decreased risk of death.

Disclosures
Dr Berul has received grant support from Medtronic and Boston Scientific. Dr Stephenson reports no potential conflicts of interest.

References
32. Korte T, Koditz H, Niehaus M, Paul T, Tebbenjohans J. High incidence of appropriate and inappropriate ICD therapies in children and ado-


35. McPate MJ, Duncan RS, Witchel HJ, Hancox JC. Disopyramide is an effective inhibitor of mutant HERG K+ channels involved in variant 1 short QT syndrome. *J Mol Cell Cardiol*. 2006;41:563–566.


KEY WORDS: ablation □ arrhythmia □ death, sudden □ electrophysiology □ genetics □ long-QT syndrome □ pacemakers
Electrophysiological Interventions for Inherited Arrhythmia Syndromes
Elizabeth A. Stephenson and Charles I. Berul

Circulation. 2007;116:1062-1080
doi: 10.1161/CIRCULATIONAHA.106.655779

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/116/9/1062

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/