Sudden Cardiac Arrest From Primary Electrical Diseases
Provoking Concealed Arrhythmogenic Syndromes

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Cardiac arrest most commonly occurs as a consequence of acute myocardial ischemia or develops with identifiable substrate such as scar because of previous myocardial infarction, cardiomyopathy, or hypertrophy.1,2 Despite extensive noninvasive and invasive evaluation, cardiac arrest remains unexplained without evidence of structural heart disease in ≈10% of individuals surviving sudden cardiac arrest.1,2 Autopsy data confirm that a similar minority of victims of sudden death have no identifiable cardiac abnormality at postmortem evaluation.1 It is now recognized that inherited electrophysiological abnormalities, termed primary electrical diseases, are the common underlying cause of these unexplained cardiac arrests. Such tragic events disproportionately affect people <40 years old.1,2 These conditions include Wolff-Parkinson White syndrome, long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT).3–9 The remaining patients without such distinct electrophysiological abnormalities are generally categorized as having idiopathic ventricular fibrillation.1–3 It is evident that implementing appropriate screening and therapeutic strategies is dependent on accurate identification of those affected. The diagnosis of these conditions remains a vexing challenge for clinicians because the conditions commonly are not identifiable with standard clinical evaluation. In this respect, they are considered concealed arrhythmogenic syndromes, which manifest only intermittently or with specific provocative maneuvers.

Although Brugada syndrome can present with the characteristic right bundle-branch block and persistent ST-segment elevation, latent or intermittent forms of the condition commonly make the diagnosis difficult.4,5 The ECG can be modulated by changes in autonomic balance, body temperature, glucose levels, and the administration of drugs.4,5 The subtle ST-segment shifts can be difficult to diagnose even with provocative measures. β-Adrenergic stimulation commonly normalizes the ECG. It is now appreciated that loss of the action potential dome in the right ventricular epicardium leads to the development of closely coupled extrasystoles via phase 2 reentry that precipitate ventricular fibrillation.4–5 Antiarrhythmic drugs do not prevent sudden death in symptomatic or asymptomatic individuals, making the implantable cardioverter defibrillator the only proven effective therapy.3–5

CPVT is diagnosed clinically by the development of characteristic arrhythmias with bidirectional ventricular tachycardia with emotional stress or physical activity.6–11 The resting ECG is generally normal. Arrhythmias usually are not induced by programmed stimulation.6–11 CPVT can be transmitted as either an autosomal dominant or a recessive trait with mutations of the cardiac ryanodine receptor (RyR2) or calsequestrin.6–11 Risk stratification based on genetic or clinical profiling is not currently possible. This lack of knowledge limits specific therapeutic strategies. Although β-blockers appear effective, patients presenting with cardiac arrest or having ventricular arrhythmias while taking this therapy should have implantable cardioverter defibrillator therapy.6–11

Identification of the molecular determinants of many inherited arrhythmogenic conditions has allowed important insights into several aspects of these primary electrical disorders.3,12 The genetic basis, pathogenesis, and genotype-phenotype correlation of diseases such at Brugada syndrome, CPVT, and idiopathic ventricular fibrillation are characterized by a high degree of genetic heterogeneity.3,12 The excitement for the emerging knowledge on genotype/phenotype correlations and development of gene-specific diagnosis, risk stratification, and treatment of patients has been tempered by the unexpected complexity that has emerged with regard to these arrhythmogenic syndromes.3,12 Variable penetrance and expressivity result in carriers of some mutations manifesting no clinical phenotype or phenotypes that are not characteristic of a monogenic arrhythmogenic syndrome. Screening family members of a genotyped proband with a primary electrical disease often reveals that many carriers of the genetic mutation appear to be unaffected based on clinical evaluation.3,12 In cases of Brugada syndrome and CPVT with the diagnosis established on clinical criteria, genetic screening is positive in a minority of cases.3,12 It has become evident that a multiplicity of mechanisms may cause inherited forms of cardiac arrhythmias that predispose to cardiac arrest.3,12 Defects in the same gene may manifest with different clinical phenotypes.3,12 Thus, the actual clinical utility of genetic testing for establishing the diagnosis of concealed or manifest arrhythmogenic syndromes remains limited.

Because of these considerations, the diagnosis of primary electrical diseases based on clinical criteria assumes even more importance. In this issue of Circulation, Krahn and colleagues report the results of a noninvasive challenge using procainamide and epinephrine to provoke abnormalities in index cases of survivors of unexplained sudden cardiac arrest and their
family members. After excluding structural heart disease and coronary artery disease by transthoracic echocardiography and coronary angiography, all patients and consenting relatives underwent additional testing with a standard protocol. This protocol included electrocardiographic monitoring, a signal-averaged ECG, exercise testing, cardiac MRI, epinephrine, and procainamide challenge. Programmed ventricular stimulation was used selectively. All probands with resuscitated cardiac arrest were treated with an implantable defibrillator with selective use of β-blockers. Family members with a clinical phenotype suggesting CPVT were treated with β-blockers and offered therapy with an implantable defibrillator. This protocol resulted in a final diagnosis of CPVT in 10 patients (56%), Brugada syndrome in 2 (11%), and idiopathic ventricular fibrillation in 6 (36%). Of 55 family members evaluated, 9 additional affected members were detected from 2 families, including 8 CPVT patients and 1 with Brugada syndrome. The predominance of CPVT in this series of unexplained cardiac arrest patients contrasts with findings of it being less common in previous studies, raising the possibility that it was underdiagnosed previously. Importantly, the present study suggests that epinephrine infusion may be more effective than exercise testing. Exercise testing provoked arrhythmias in only half of those who responded to epinephrine. The authors conclude that a thorough noninvasive protocol with subsequent provocative testing with procainamide and epinephrine may unmask concealed arrhythmogenic syndromes in two thirds of cases.

Although the absence of a control population to establish the true sensitivity and specificity of this approach is a limitation, previous studies indicate that epinephrine infusions do not provoke ventricular arrhythmias in healthy controls. The predictive accuracy of procainamide infusion for the diagnosis of Brugada syndrome remains to be determined. Other limitations of the study include the relatively small population of patients, the absence of comprehensive screening of all family members, and the lack of programmed stimulation on all patients. Despite these deficiencies, the study suggests that this protocol with epinephrine and procainamide infusion has clinical utility in establishing a diagnosis in cases of unexplained cardiac arrest. Given the safety of this approach and the incremental diagnostic yield, these measures should now be considered a standard part of the comprehensive evaluation of patients resuscitated cardiac arrest without evident structural heart disease or a manifest arrhythmogenic syndrome. The absence of a true clinical or genetic gold standard that allows definitive diagnosis of these arrhythmogenic syndromes should be kept in mind when assessing the significance of these findings.

In the future, refined clinical and genetic testing may assume more importance in the diagnosis of manifest or concealed primary electrical diseases. MRI, positron emission tomography, or innovative measures of cardiac electrical function may define latent structural or functional abnormalities and thereby allow identification of individuals before symptomatic arrhythmias emerge. More accurate diagnosis would allow implementation of lifestyle modification and preventive therapy. Because effective therapies are available, the early identification, risk stratification, and treatment of susceptible patients should reduce the frequency of these unexplained cardiac arrests. In the meantime, the clinician must rely on the best available clinical criteria to diagnose primary electrical diseases predisposing to unexplained cardiac arrest. In this respect, the clinical assessment in the report of Krahn et al provides a safe and useful approach to the diagnosis of patients who have been resuscitated from or who are at risk for sudden cardiac arrest. In the future, more robust genotype-phenotype correlations will likely add to our ability to precisely identify and treat individuals with concealed arrhythmogenic syndromes. Until then, these provocative clinical measures should be considered part of the routine evaluation of affected patients and family members to unmask the concealed arrhythmogenic syndromes causing unexplained cardiac arrest.

**References**


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