Sudden Cardiac Arrest Without Overt Heart Disease

Simon Modi, MBBS; Andrew D. Krahn, MD

The topic of sudden unexplained cardiac arrest without overt heart disease is a highly emotive and important subject with a rapidly advancing knowledge base. The correct identification of those conditions predisposing to cardiac arrest is paramount, and is part of the role of every practicing cardiologist. This review article is designed to give the practicing cardiologist an up-to-date insight into a subspecialized field of cardiac electrophysiology and cardiac genetics. It seeks to help to formulate diagnoses with advanced electrophysiological testing and genetic profiling and also with a reminder of basic clinical presentations and pathophysiological features of the conditions in question. This article seeks to encapsulate the field in general and at the same time to provide a select amount of useful detail, both contemporary and historical, and to provide references from a resource of excellent reviews in the literature. We hope that the reader will develop confidence in identifying rare causes of cardiac arrest and an insight into the sort of patients that should be referred to subspecialist clinics.

Structural or coronary heart disease is by far the most common cause of sudden cardiac arrest.1 Once overt heart disease has been excluded in the cardiac arrest survivor, the differential diagnosis includes manifest or latent primary electrical disease and latent structural causes (Tables 1 and 2). These conditions predispose the patient to recurrent ventricular arrhythmia and cardiac arrest without overt heart disease. The overriding immediate concern in these patients is recurrence of unheralded ventricular tachycardia or fibrillation. Every effort must be made to define the underlying pathophysiology in order to understand prognosis, direct therapy, and identify family members who may be at risk if the culprit is an inherited condition.

The conditions in question are largely those causing abnormalities in cardiac depolarization or repolarization, usually due to inherited, drug-, metabolic-, or electrolyte-induced ion channel dysfunction. They have loosely been termed the channelopathies or primary electric diseases. Often included in the category of cardiac arrest without overt heart disease are patients with subclinical structural diseases such as myocarditis, coronary spasm, arrhythmogenic right ventricular cardiomyopathy (ARVC), and sarcoidosis.2 Although these conditions may be readily diagnosed with overt evidence of a structural cause of cardiac arrest, structural abnormalities may be subtle or even undetectable with standard testing early in their course, requiring a high index of suspicion to discern.

Survivors of cardiac arrest without overt heart disease typically come under the care of an electrophysiologist because of the need for implantation of an implantable cardioverter-defibrillator (ICD). Care is ideally delivered by a team of individuals with expertise in genetics, electrophysiology, and cardiomyopathies, with input from imaging experts as well. This team deals with survivors of cardiac arrest, their family members when an inherited cause is identified, and the less fortunate families when sudden death occurs without overt heart disease and families are sent for screening.3–6 This is often referred to as cascade family screening.3–7 It should be recognized, however, that even when each of the known causes of cardiac arrest without overt heart disease has been systematically excluded with in-depth testing, nearly half of the causes of cardiac arrest in these patients will remain unexplained.2

Investigation of the Sudden Cardiac Arrest Survivor

Survivors of cardiac arrest require a comprehensive clinical review with an in-depth sequential testing strategy (Figure 1). This includes a detailed presenting history with witness statements as well as comprehensive family and drug histories. Family history should inquire not only about sudden death, but also about events such as drowning, fatal single-vehicle accidents, sudden infant death syndrome, and frequent miscarriages, all potential signs of an inherited predisposition to sudden death. Baseline electrolyte and metabolic testing should be undertaken to look for reversible causes of cardiac channel instability, along with markers of cardiac injury. These are infrequent explanatory mechanisms of cardiac arrest but may be substantial triggers in predisposed individuals. Further biochemical, immunologic, and serological testing should be undertaken if findings are suggestive of cardiac involvement of systemic disease, such as amyloid, sarcoid, autoimmune disease, and viremia.

Structural and electric testing should then be routinely performed. The term overt heart disease is open to a degree of subjectivity. For the vast majority of settings, it is defined as the absence of a clear structural or electric cause of cardiac arrest on coronary angiography, echocardiography, and resting ECG. Further imaging with cardiac magnetic resonance imaging...
Table 1. Causes of Sudden Cardiac Arrest

<table>
<thead>
<tr>
<th>Cardiac arrest with overt structural heart disease</th>
<th>Coronary disease</th>
<th>Cardiomyopathies</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ischemic heart disease</td>
<td>Ischemic cardiomyopathy</td>
<td>Wolff-Parkinson-White syndrome</td>
</tr>
<tr>
<td></td>
<td>Anomalous coronary circulation</td>
<td>Hypertrophic cardiomyopathy</td>
<td>Commtion cordis</td>
</tr>
<tr>
<td></td>
<td>Coronary spasm</td>
<td>Dilated cardiomyopathy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Infiltrative (eg, sarcoid, amyloid)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Takotsubo cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left ventricular noncompaction cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocarditis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corrected congenital cardiomyopathy</td>
<td></td>
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<tr>
<td>Cardiac arrest without overt heart disease</td>
<td>Primary electric</td>
<td>Metabolic imbalance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-QT syndromes</td>
<td>Hyperkalemia/Hypokalemia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Short-QT syndromes</td>
<td>Hypocalcemia</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Brugada syndromes</td>
<td>Hypomagnesemia</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td></td>
<td>Early repolarization syndromes</td>
<td>Acidosis</td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>Drug overdose</td>
<td>Drug overdose</td>
</tr>
<tr>
<td></td>
<td>Idiopathic ventricular fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metabolic imbalance</td>
<td>Concealed structural</td>
<td>Conerformed structural</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arhythmogenic right ventricular cardiomyopathy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Myocarditis</td>
<td>Myocarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary spasm</td>
<td>Coronary spasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoaidosis</td>
<td>Sarcoaidosis</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Noncardiac</td>
<td>Noncardiac</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute intracranial hemorrhage</td>
<td>Acute intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Massive pulmonary embolus</td>
<td>Massive pulmonary embolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epilepsy</td>
<td>Epilepsy</td>
</tr>
</tbody>
</table>

(MRI) and drug provocation should be included in the new standard approach to investigation of this population.2,8,9

Resting 12-lead ECGs and monitored telemetry strips should be reviewed both during the acute admission and historically (if available), with the clinician looking for evidence of repolarization abnormalities, coronary ischemia or spasm, preexcitation, or ventricular ectopy, all of which may play a significant etiologic role in cardiac arrest. Postresuscitation ECGs can often display changes in depolarization and repolarization, and patients undergoing postarrest hypothermic protocols in the intensive care setting are equally subjected to transient ECG changes, including Osborne J waves and transient QT prolongation. Many patients in the intensive care setting will receive either sympathomimetic infusions or drugs that affect repolarization that can provide clues to an underlying diagnosis. ECG findings in these metabolically deranged states should only be used as a guide to investigation or diagnosis once normal physiology returns rather than as a definitive diagnosis.

Coronary imaging, usually with coronary angiography, is required to exclude coronary artery disease, particularly in those patients with a history of chest pain or known risk factors. In the younger population, coronary angiography is principally used to rule out congenital coronary anomalies. Although coronary spasm may occur as a result of catheter positioning, this commonly occurs in the proximal portion of the major coronary vessels. Coronary spasm elsewhere in the vessel, particularly if imaging is undertaken during an acute presentation with ST elevation, is highly likely to be significant. If coronary atheroma is observed but is nonocclusive in nature, this should be noted because it may represent a possible substrate for coronary spasm. We typically advocate consideration of ergonovine or acetylcholine challenge in patients with suspicion of coronary spasm, acknowledging the associated recognized remote risk of myocardial infarction and ventricular arrhythmias.

Echocardiography is routinely recommended even when left ventriculography has been performed at cardiac catheterization. Specific attention should be paid to the presence of chamber hypertrophy, dilatation, and systolic function. Apparent left ventricular apical hypertrophy can be observed in patients with left ventricular noncompaction cardiomyopathy, and care must be taken to visualize endocardial borders and noncompaction channels, usually with contrast media. Changes in the right ventricle can be difficult to assess with echocardiography. Nevertheless, attempts should be made to look for thinning and aneurysm formation in the right ventricular free wall, apex, and outflow tract as well as chamber dilatation. Echocardiographic changes of myocarditis are notoriously subjective but should still be investigated.

Subsequent testing in the absence of clear pathology at this stage should include treadmill testing and a signal-averaged ECG. Treadmill testing serves as a provocation test for catecholaminergic polymorphic ventricular tachycardia (CPVT)2 as well as some idiopathic outflow tract ventricular tachycardias. It is also used to uncover subtle clues leading to a diagnosis of long-QT syndrome (LQTS), such as inadequate QT shortening, postural T-wave change, and exercise-related T-wave notching.10,11 The QT interval can be difficult to assess during exercise because of motion artifact, and bicycle testing is often substituted to provide clearer definition. An ECG performed immediately after the patient is in recovery often provides a useful surrogate to inspect peak exercise QT changes. Signal-averaged ECG testing is primarily used to look for evidence of late potentials, which is helpful in the screening of ischemic cardiomyopathy, subclinical arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome.

Drug provocation to unmask a primary electric cause of cardiac arrest plays a key role when the diagnosis remains unclear or to further risk stratify phenotypically suggestive patterns. Provocation testing protocols, including sympathomimetic or sodium channel–blocking drug infusions, are primarily used to unmask phenotypes of LQTS, Brugada syndrome, and CPVT. They are usually performed in a coronary

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Table 2. Summary of Conditions Causing Sudden Cardiac Arrest Without Overt Heart Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
<th>Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-QT syndromes</td>
<td>Abnormally long and/or morphologically abnormal QT/T wave (&gt;440 ms male, &gt;460 ms female)</td>
<td>History, ECGs, exercise, and adrenaline provocation and genetic testing</td>
<td>See long-QT syndrome (Table 3)</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Abnormal ST elevation in precordial leads</td>
<td>History, ECGs, and sodium channel blockers provocation testing</td>
<td>Genetic testing low yield</td>
</tr>
<tr>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>Normal resting ECG but exercise/adrenergic-induced ectopy and ventricular tachycardia (bidirectional or polymorphic)</td>
<td>History, exercise, and adrenaline provocation and genetic testing</td>
<td>Genetic testing may be useful</td>
</tr>
<tr>
<td>Early repolarization syndrome</td>
<td>ST elevation or J-point slurring in inferolateral leads</td>
<td>ECG</td>
<td>No reliable provocation test</td>
</tr>
<tr>
<td>Short-QT syndrome</td>
<td>Shortened QT interval with peaked T wave; consider if QTc &lt;360 ms</td>
<td>QT on ECG, peaked T wave</td>
<td>Usually QTc &lt;320 ms</td>
</tr>
<tr>
<td>Coronary spasm</td>
<td>Transient regional ST elevation and myocardial dysfunction with normal or near-normal epicardial coronary arteries</td>
<td>History and ECGs; small marker rise; provocation testing (ergonovine or acetylcholine)</td>
<td>Often mild coronary disease in smokers</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Features of right ventricular dilatation, thinning, fibrosis, and aneurysm formation, often not seen on echocardiogram; epsilon waves, right bundle branch block; may have ventricular tachycardia originating in the right ventricle</td>
<td>ECGs, imaging especially MRI, genetic testing, electroanatomic voltage map, biopsy in select cases</td>
<td>Often has structural change evident</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Recent viral illness or chronic systemic inflammatory condition; regional or global ventricular dysfunction together with small marker rise</td>
<td>ECGs, imaging especially MRI with gadolinium, biopsy where available</td>
<td>Often will show evidence of ventricular dysfunction</td>
</tr>
<tr>
<td>Sarcoioidis</td>
<td>Other signs of systemic sarcoidosis (eg, pulmonary, ocular)</td>
<td>Imaging especially MRI, biopsy where available (may be extracardiac if systemic involvement)</td>
<td>Commonly associated with systemic involvement</td>
</tr>
</tbody>
</table>

MRI indicates magnetic resonance imaging.

care unit, monitored investigation unit, or electrophysiology laboratory and can be safely performed as day case investigations. Their diagnostic yield varies between conditions and will be discussed in more detail later in this review.

Advanced imaging such as gated cardiac MRI or computed tomographic scanning should be considered unless a clear diagnosis has been obtained. The key purpose is to detect subclinical ARVC, sarcoidosis, myocardial injury from coronary spasm, and myocarditis. Detailed discussion of the optimal imaging sequences to detect these conditions is beyond the scope of this review.

When the diagnosis remains unclear at this juncture, further testing is exploratory and unlikely to offer a definitive result. Additional tests to be considered in elusive cases are electrophysiology studies with voltage mapping and cardiac biopsy. Genetic testing is indicated when an inherited phenotype (ARVC, Brugada, CPVT, or LQTS) is detected, both for diagnosis and to aid family screening. The role of blanket genetic screening in phenotypically ambiguous or negative patients is unclear but clearly remains a research tool at present.

This diagnostic strategy has been applied in a registry of patients with apparently unexplained cardiac arrest after exclusion of coronary artery disease, left ventricular dysfunction, and manifest LQTS or Brugada syndrome² (Figure 1).

This study assessed survivors of cardiac arrest defined as documented cardiovascular collapse with ventricular tachycardia or fibrillation requiring direct current cardioversion or defibrillation with an ejection fraction >50%. Patients were excluded if they had a coronary stenosis >50%, an abnormal resting QT interval (male QTc <460 ms, female QTc <480 ms), and diagnostic Brugada ST segments.² Patients were predominantly white, with 60% men and a mean age of 43 years. A clinical diagnosis was reached in 56% of patients, with an inherited cause found in 40% (Figure 2). The underlying diagnoses included a range of conditions that will be described in further detail below. This registry is limited by its exclusion of patients with manifest repolarization disorders such as LQTS or Brugada syndrome and its setting in a specialty referral network in Canada. Of importance, this strategy is predicated on access to costly advanced diagnostic tools such as MRI and genetic testing. The author’s perspective is that deployment of these resources is warranted, given the typical young patient with an otherwise excellent prognosis and the implications for family screening and further prevention of cardiac arrest and sudden death. This perspective is clearly contextual.

Therapy for the cardiac arrest survivor depends largely on the underlying diagnosis, typically combining condition-
specific medication with an ICD, which is discussed in more detail below.

**Relatives of the Sudden Cardiac Arrest Survivor**

The management of families is driven by the outcome of thorough evaluation of the index cardiac arrest survivor. The focus is on exclusion of known phenotypes/genotypes or, alternatively, the blind workup of a relative of an undiagnosed cardiac arrest. This may involve reevaluation of postmortem studies or accessing prior health records to look for historical ECGs from the deceased index case. Occasionally, it may be pertinent to obtain a postmortem genotype in cases of high clinical suspicion. This technique of molecular autopsy has been shown to provide genetic clues in up to 30% of both young adult and childhood sudden unexplained death in which the standard autopsy is negative. It has proven most helpful for genetic mutations in LQTS or CPVT. Many experts in the field would advocate this in their standard patient workup, especially in cases in which the infrastructure for testing exists. In situations in which the index case diagnosis is unclear, a tiered approach to screening is usually offered, including ECG, echocardiogram, exercise testing, signal-averaged ECGs, and Holter monitoring. Cardiac MRI, electrophysiology studies, and cardiac biopsy are reserved for diagnostic uncertainties. The depth to which screening should permeate through family lineage is often considered and is aided significantly with positive genotyping. In this often-asymptomatic group, discussion is commonly centered on education and therapy for new phenotypically or genotype-positively affected family members, together with consideration of drug and/or ICD therapy. Counseling, particularly in the setting of infant or young adult death, clearly plays an important role, with achievement of closure being significantly helped when a unifying diagnosis is reached.

**Causes of Sudden Cardiac Arrest Without Overt Heart Disease**

This review will now focus on the most common causes of cardiac arrest without overt heart disease, detailing important clues to diagnosis as well as reviewing recommended and novel diagnostic and therapeutic options.

**Long-QT Syndrome**

**Presentation and Diagnosis**

Our understanding of LQTS has been driven by extensive molecular and genetic research combined with outstanding natural history data from the International LQT Registry established by Schwartz and Moss in 1979. Initial descriptions of congenital LQTS with or without congenital deafness have grown into 12 individual subtypes (Table 3), with an estimated prevalence of 1:2000. More than 95% of cases represent abnormalities in the rectifier potassium channels (IKr, IKs) or inward sodium channels corresponding to LQT types 1 to 3. At some point, 30% to 50% of patients are symptomatic, typically presenting with syncope. The lifetime risk of cardiac arrest is in the order of 3% to 5%, with cardiac arrest as the initial manifestation in a small proportion of these patients. The hallmark arrhythmia is torsades de pointes (pause-dependent, oscillatory polymorphic ventricular tachycardia). Index events are noted to occur at any age, but often present in prepubescent males or postpubescent females with LQT1. Gene-specific triggers of symptoms have been reported and should be sought in the history, including swimming- or exercise-related events in LQT1, auditory or emotional triggers in LQT2, and resting- or sleep-related events in LQT3. The postpartum stage in females is also noted as a high-risk period. Arrhythmia in LQTS may also present as unexplained accidents or drowning (given its relation to swimming). Sudden infant death syndrome, and epilepsy.

Concerns should also be raised when syncope or cardiac arrest occurs in the setting of new medication. Current literature reports hundreds of drugs with definitive or potential effects on the QT interval, which are summarized at http://www.qtdrugs.org. In addition, QT prolongation in the ab-

**Figure 1.** Investigation cascade in the patient with cardiac arrest without overt heart disease. SAECG indicates signal-averaged ECG; CMR, cardiac magnetic resonance; CT, computed tomography; EP, electrophysiological; and RV, right ventricular.

**Figure 2.** Diagnostic yield of comprehensive testing in unexplained cardiac arrest patients without overt heart disease. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long-QT syndrome; and Repol, repolarization. Adapted from Krahn et al with permission of the publisher. Copyright © 2009, Lippincott Williams & Wilkins.
Table 3. The Long-QT Syndromes

<table>
<thead>
<tr>
<th>Long-QT Type</th>
<th>Genotype</th>
<th>Characteristic QT Morphology</th>
<th>Clinical Phenotype</th>
<th>Incidence, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KCNQ1</td>
<td>Broad based, symmetrical T wave</td>
<td>Adrenergic triggers (swimming, emotion, or exercise)</td>
<td>30–35</td>
<td>Most common but least severe; homozygotes have severe phenotype with congenital deafness (Jervell and Lange-Nielsen); β-blockers efficacious</td>
</tr>
<tr>
<td>2</td>
<td>KCNH2/HERG</td>
<td>Bifid T wave</td>
<td>Commonly drug induced; auditory stimuli</td>
<td>25–30</td>
<td>Second most common; β-blockers largely efficacious</td>
</tr>
<tr>
<td>3</td>
<td>SCN5A</td>
<td>Delayed-onset/ asymmetrical T wave</td>
<td>Rest/sleep</td>
<td>5–10</td>
<td>Little β-blocker effect; may respond to sodium channel blockers</td>
</tr>
<tr>
<td>4</td>
<td>ANK2</td>
<td>Exercise</td>
<td></td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KCNE1</td>
<td>Exercise and emotion</td>
<td></td>
<td>&lt;1</td>
<td>Homozygotes have severe phenotype with congenital deafness (Jervell and Lange-Nielsen)</td>
</tr>
<tr>
<td>6</td>
<td>KCNE2</td>
<td>Rest, drugs, or exercise</td>
<td></td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>KCNJ2</td>
<td>Prominent U waves with pseudo QT prolongation</td>
<td>Rest or exercise</td>
<td>&lt;1</td>
<td>Linked to Andersen-Tawil syndrome; periodic paralysis; skeletal muscle deformity, and hypokalemia</td>
</tr>
<tr>
<td>8</td>
<td>CACNA1C</td>
<td>Prominent and widely split T-U waves; prolonged terminal T-wave slope and minimal QT prolongation</td>
<td>Exercise</td>
<td>&lt;1</td>
<td>Timothy syndrome; congenital heart disease, autism; syndactyly, and immune deficiency; early-onset, malignant arrhythmic course; some response to calcium channel blockers</td>
</tr>
<tr>
<td>9</td>
<td>CAV3</td>
<td>Rest or sleep</td>
<td></td>
<td>&lt;1</td>
<td>Possible limb-girdle myodystrophy link</td>
</tr>
<tr>
<td>10</td>
<td>SCN4B</td>
<td>Exercise</td>
<td></td>
<td>&lt;0.1</td>
<td>Atrioventricular block</td>
</tr>
<tr>
<td>11</td>
<td>AKAP9</td>
<td>Exercise</td>
<td></td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>SNTA1</td>
<td>Bifid</td>
<td>Rest</td>
<td>&lt;0.1</td>
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</table>

Consequence of congenital LQTS is often evident in the patient with myocardial infarction or cerebral anoxia and during hypothermia protocols.28,29

The 12-lead ECG is the cornerstone of LQTS diagnosis. It is now generally recognized that the absolute QT interval should be measured from the start of the QRS to the end of the T wave, preferably in either lead II or V5, over an average of 3 to 5 cycles on standard 25-mm/s and 10-mm/mV calibration ECG paper. The duration of the normal versus pathological QT duration is open to interpretation. Corrected QT intervals >440 ms in men and >460 ms in women are widely considered prolonged, and at times a further 20-ms zone is considered borderline. Central to accurate QT interval measurement is defining the end of the T wave, particularly when the T wave is low amplitude or has a complex morphology. Interoperator error and variability are well reported,30 and therefore standardization of measurement techniques should be attempted. Techniques involve the creation of a threshold level of the T-wave amplitude or the use of the projected slope of the T wave.31 Our practice involves the use of the projected maximum slope to baseline intersection (Figure 3). It must be noted that mutations affecting the latter part of repolarization (I_{K_{s}}) can often change the trajectory of the terminal portion of the T wave, making this tangential method less accurate. The U wave should generally be ignored when the T-wave end is defined. Secondary deflections of equal or higher amplitude to the T wave are classified as a bifid T wave, not as a U wave, and should be incorporated into the QT measurement.10 QT correction for heart rate commonly involves the widely used Bazett’s formula (QTc=QT/√R-R [seconds]), which is less accurate at extremes of heart rate, although numerous alternative correction methods are reported.32 The ECG also allows assessment of morphological differences in the T wave. To date, type-specific T-wave morphology has been suggested in LQT1 to LQT333,34 (Figure 4).

QT prolongation is not always manifest on the resting ECG in LQTS, and there is often a disparate relationship between symptoms, genotype, and QT interval.35 The repolarization reserve hypothesis helps to explain this. This theory posits that cardiac repolarization is a multifactorial entity requiring the interplay of a number of factors for correct function. Thereby, if a single potassium channel is genetically defective, other factors may compensate to produce apparently normal repolarization. Further imbalance within the reserve, created, for example, by electrolyte- or drug-induced disturbance, will lead to phenotypic abnormalities of repolarization.36 It is this severance of genotype and phenotype that provocation testing helps to unite. Testing usually involves exercise protocols or infusion of sympathomimetic agents. With exercise protocols, the combination of posture- and exercise-related QT change, including failed QT shortening, has been shown to reliably predict the LQT1 genotype.37 Epinephrine (adrenaline) testing is now in widespread use, and both continuous infusion and bolus protocols have demonstrated high sensitivity and specificity for unmasking both concealed LQT1 and possibly LQT2.38 Other novel protocols have included intravenous erythromycin, facial immersion, and adenosine boluses.39–41

Prognosis and Therapy

Prognosis has improved significantly with early identification, family screening programs, and drug therapy. Sudden cardiac death is increasingly rare in the era of antiarrhythmic therapy and patient education.32 As noted, of the 3 common LQTS subtypes, LQT3 and LQT2 appear to confer a worse
cardiac arrest prognosis, which may be related to the highly efficacious use of adrenergic blockade in the LQT1 group.43 Therapy in LQTS centers on education, specifically \( \beta \)-blocker compliance,42 avoidance of triggers, and, at times, exercise restriction. Triggers may be exercise related (eg, swimming in LQT1), noise related (eg, alarm clocks in LQT2), or metabolic (eg, hypokalemia in LQT2),44 and are known to be related to an increase in subtype-specific cardiac events. Patients should also be educated about avoidance of QT-prolonging medications. \( \beta \)-Blockers are the mainstay of therapy in LQT1 and LQT2, and although they are classically believed to be less efficacious in LQT3, recent data suggest a reasonable effect of adrenergic blockade.45 The use of sodium channel blockers such as flecainide and mexiletine is also beneficial in LQT3.46,47 Rarely, more aggressive interventions such as sympathetic denervation surgery or implantable defibrillators are needed in high-risk cases, such as the cardiac arrest survivor, patients with persistent symptomatic VQTc intervals persistently >550 ms, or symptomatic patients with \( >1 \) genotype (compound heterozygotes).48,49 Although sympathetic denervation surgery has traditionally been used as an adjunct to defibrillator therapy, its safety and therapeutic success in the era of minimally invasive thoracoscopic surgery have raised its profile, and it should now be considered as a therapeutic option before ICD implantation in drug-refractory cases.50

Figure 3. Measurement of the QT interval. A, Use of the maximum slope technique to establish the end of the T wave in an ECG with normal T-wave morphology. B, Twelve-lead ECG of a young woman who suffered a cardiac arrest during a stressful situation. C, Magnified lead \( V_2 \) of the ECG in B. This shows a notched T wave. The patient was subsequently diagnosed with type 2 long-QT syndrome. For further discussion, see Reference 31.

Cardiac Arrest Without Overt Heart Disease

Brugada Syndrome

Presentation and Diagnosis

The Brugada syndrome, first identified by Martini et al in 1989,51 was subsequently described by the Brugada brothers in 1992 as an abnormal persistent ST elevation with right bundle-branch block pattern in a small cohort of cardiac arrest survivors with structurally normal hearts.52 The original ECG pattern, now known as type 1, was associated with polymorphic ventricular tachycardia or ventricular fibrillation usually during sleep, particularly in young men from Southeast Asia.53–55 Although initially believed to be a common cause of cardiac arrest without overt heart disease, recent data suggest a prevalence of no more than 5% in cases of sudden cardiac arrest without overt heart disease.2,56 Fever, autonomic factors, sodium channel–blocking drugs, and a full stomach are all reported to precipitate the characteristic ECG pattern and/or arrhythmia.57–60 The syndrome has also been linked with atrial fibrillation, supraventricular tachycardia, and bradyarrhythmias.61

The ECG is again the cornerstone of diagnosis. Three Brugada ECG patterns are recognized: a type 1 Brugada pattern is characterized by \( \geq 2 \) mV coved ST elevation with T-wave inversion in 2 contiguous precordial leads, usually \( V_1 \) through \( V_3 \), with standard ECG lead positions. Varying degrees of right bundle branch block are commonly seen.52–62 Type 2 and 3 patterns have a saddleback appearance, with a markedly less concerning natural history unless a type 1 ECG can be provoked with sodium channel–blocker infusion (see below). Temporal variation in ECG appearance is also noted. Body surface mapping has also identified the usefulness of high precordial leads in the identification of the Brugada pattern, although this modality has limited correlation with prognosis (Figure 5).63,64 Signal-averaged ECG testing for late potentials is believed to be helpful in screening for the
Brugada syndrome, particularly in high-risk patients. A novel method of bipolar precordial lead recordings also promises to be a potentially useful adjunct in ST-elevation identification, although it is not currently in widespread use.

Provocation testing with sodium channel–blocking agents such as ajmaline, flecainide, and procainamide is now widely used to unmask the Brugada pattern. Inducibility of ventricular arrhythmias at electrophysiological testing has no established role in the cardiac arrest survivor, who should undergo ICD implantation.

To date, >293 mutations linked with Brugada syndrome are documented. The dominant pathology was believed to involve defects in the cardiac sodium channel encoded by the SCN5A gene, with loss-of-function mutations noted, distinguishing this sodium channelopathy from the LQT3 mutation (gain of function). However, genetic mutations are identified in only 21% of patients with the Brugada syndrome phenotype. Some of these mutations have also been described in family members with no resting or provokable evidence of the Brugada ECG. Recently, there is growing awareness that genes encoding calcium channels have been implicated in the Brugada syndrome with an associated short-QT interval. Recent work in this area suggests, however, that the calcium channel variant is less prone to ventricular arrhythmia than its sodium channel counterpart. Therefore, explaining the syndrome with a sole genetic and physiological defect has proven difficult. Current opinion suggests that the Brugada phenotype may well represent a confluence of etiologies, including abnormal fetal development of the right ventricular outflow tract. As such, the role of genetic testing in Brugada syndrome is largely to facilitate family screening.

Prognosis and Therapy
Recent registry data from the largest series of Brugada patients published from 4 Northern European countries have shown a relatively good prognosis in anything other than symptomatic, spontaneous type 1 patients. Here, a 7.7% annual event rate was noted in cardiac arrest survivors, with a much lower 1.9% and 0.5% annual event rate in syncopal and asymptomatic patients, respectively. Similarly, meta-
analyses of risk stratification tools suggest a 3-year event rate of 10% overall, with spontaneous type 1 ECGs in symptomatic males increasing the relative risk of events. ICD therapy is therefore strongly recommended in spontaneous type 1 Brugada patients of male sex who continue to be symptomatic. Avoidance of sodium channel–blocking drugs (http://www.brugadadrugs.org) and prompt fever control are important. There is no medical therapy of proven benefit in Brugada syndrome, although quinidine has been reported to be of use in limited studies.73

Catecholaminergic Polymorphic Ventricular Tachycardia

Presentation and Diagnosis

CPVT is a rare and malignant condition, typically presenting in late childhood and early adolescence with exertional syncope or cardiac arrest.2,74 Its true prevalence is unknown, but it has been reported in 13% of cardiac arrests without heart disease.2,75 Syncope or cardiac arrest is induced by stressful events or exertion, which can include sporting events, on-stage presentations, arguments, and examinations, which are common in the presenting age range. Frequent exertional syncope or palpitations are common, although initial presentation can be with cardiac arrest.76 Misdiagnosis as childhood epilepsy is not uncommon.24,76 Arrhythmias occur in the absence of QT prolongation. The underlying mechanism is attributed to intracellular calcium overload because of failed reuptake of calcium into the sarcoplasmic reticulum, typically related to mutations in the RyR2 gene, leading to calcium leak at the level of the ryanodine receptor.77

The ECG in CPVT is usually normal, although recent investigations have suggested prominence of tall U waves and secondary T waves (T2) as markers of delayed afterdepolarizations, believed to be the trigger for arrhythmias in calcium overload states.78,79 Resting bradycardia has been linked to the CPVT genotype and should not dissuade the clinician from initiation of β-blocker therapy (see below).80 QT prolongation is not seen, and is suggestive of an alternate pathology. Stress testing with exercise or infusion of β-agonists (epinephrine, isoproterenol) is the key to obtaining a diagnosis.9,81 Increasing frequency of ventricular ectopy or the development of polymorphic ventricular tachycardia and/or bidirectional ventricular tachycardia with increasing adrenergic stimulus is highly suggestive of CPVT (Figure 6). Although less recognized, the authors have seen a number of cases of cardiac arrest in early and mid adulthood with adrenaline- and exercise-induced polymorphic ventricular ectopy. In the absence of other clear etiologies, this may represent a late-onset form of CPVT.2

Up to 60% of patients with CPVT display mutations in 1 of 2 genes.82 Mutations in the cardiac ryanodine receptor gene (RyR2) are by far the most common, which is inherited in an autosomal dominant pattern in up to 50% of cases.77 Much less frequently, mutations in the cardiac calsequestrin gene (CASQ2) present with an autosomal recessive form of CPVT.82 The presence of a genotype-positive form of CPVT, particularly RyR2, confers an earlier onset of the disease and a more aggressive form, helping to tailor therapeutic strategy.76

Prognosis and Therapy

Untreated CPVT carries a poor prognosis, with sudden death in up to one third of affected individuals by the age of 30 years.83 Efficacy of therapy with β-blockers is debatable. In a recently reported long-term study, β-blockers reduced events by approximately one half, with 8-year event rates falling to 27%.84 However, earlier studies have reported a near complete resolution of symptoms on antiadrenergic therapy, with events only occurring because of medication noncompli-
The event rates on \( \beta \)-blockers reported by Hayashi et al\(^{84} \) are further compounded by at least one third of affected patients admitting to omitting their medication on the day of the event. \( \beta \)-Blockers therefore remain the mainstay of therapy. Resistance to therapy requires consideration of other therapies, including cardiac sympathectomy, flecainide, or, finally, ICD implantation, especially when medication compliance is assured and symptoms persist.\(^{50,85,86} \) Unfortunately, ICD therapy may be ineffective because of the adrenergic effect that commonly accompanies appropriate or inappropriate shock therapy, leading to early arrhythmia recurrence. The use of left cardiac sympathectomy should be strongly advocated, particularly in the era of minimally invasive surgery.\(^{50,87} \)

### Early Repolarization Syndrome

**Presentation and Diagnosis**

Early repolarization syndrome (ERS) was first reported in the 1930s,\(^{88} \) and has long been believed to be a normal ECG variant and benign entity, which is also termed *juvenile ST pattern*. Recent work has questioned this, with ERS being identified in 31% of patients with apparent idiopathic ventricular fibrillation.\(^{89} \) In recent data from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER), the estimated prevalence of ERS in cardiac arrest without structural heart disease was 8%.\(^{2} \) A 30-year follow-up in a large Finnish cohort study has estimated the relative risk of ERS for arrhythmic death to be greater than that of QT prolongation and left ventricular hypertrophy.\(^{90} \) As such, ERS stands to become an important entity in our understanding of cardiac arrest and idiopathic ventricular fibrillation. ERS has been noted to be more prevalent in young men, athletes, and black patients, with the prevalence of ERS in a normal population believed to be up to 5%.\(^{90-92} \) This makes interpretation of the significance of ERS a challenge.

The mechanism of ERS is incompletely understood, and debate exists regarding whether ECG changes represent late depolarizations or early repolarizations. ECG improvement with isoproterenol and typical absence of late potentials on signal-averaged ECG make it unlikely to be a depolarization abnormality.\(^{89} \) One theory suggests that regional phase 1 potential differences due to localized early repolarization cause region-to-region current flow and ST-segment shift; however, proof is lacking for this and the mechanism of arrhythmia induction.\(^{93} \)

The diagnosis relies solely on the ECG. ST-segment elevation with notching or slurring (J wave, Osborn wave) of the QRS-ST junction (J point) of at least 0.1 mV from the baseline in the inferior and/or lateral leads has been used to describe ERS in most recent studies\(^{89,90} \) (Figure 7). Anterior precordial leads (V\(_{1} \) through V\(_{3} \)) are generally excluded to avoid confusion with ARVC or Brugada syndrome, although ERS in the inferolateral leads appears to be more prevalent in Brugada syndrome patients.\(^{94} \) Some authors have suggested 0.05- to 0.2-mV J-point elevation cutoffs, with the degree of J-point elevation appearing to confer a worse prognosis.\(^{93} \) Temporal as well as beat-to-beat variation in J-point elevation is common.\(^{89} \) ECG interpretation should be in conjunction with the knowledge of other tests to exclude other causes of ST-elevation syndromes such as coronary occlusion, ventricular aneurysm, and pericarditis. There are currently no provocation tests to induce or amplify ST changes in ERS or to provoke arrhythmias. No genetic basis for ERS has been identified, although promising links under investigation are in

![Figure 7. ECG in a 32-year-old Asian man with unheralded cardiac arrest. There is inferolateral early repolarization with ST elevation and QRS notching. See text for discussion.](http://circ.ahajournals.org/)

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\(^{74,80} \) The event rates on \( \beta \)-blockers reported by Hayashi et al\(^{84} \) are further compounded by at least one third of affected patients admitting to omitting their medication on the day of the event. \( \beta \)-Blockers therefore remain the mainstay of therapy. Resistance to therapy requires consideration of other therapies, including cardiac sympathectomy, flecainide, or, finally, ICD implantation, especially when medication compliance is assured and symptoms persist.\(^{50,85,86} \) Unfortunately, ICD therapy may be ineffective because of the adrenergic effect that commonly accompanies appropriate or inappropriate shock therapy, leading to early arrhythmia recurrence. The use of left cardiac sympathectomy should be strongly advocated, particularly in the era of minimally invasive surgery.\(^{50,87} \)
the KCNJ8 gene\textsuperscript{65} and mutations in the L-type calcium channel (CACNA1C, CACNB2, and CACNA2D1).\textsuperscript{96}

**Prognosis and Therapy**

The high prevalence of ERS in the general population makes its interpretation difficult. Case-control studies demonstrate compelling evidence of association but do not prove causality.\textsuperscript{95,97} Little is known of the manner in which to risk stratify patients with ERS other than careful symptom-rythm correlation in the syncopal patient and the use of ICDs for secondary prevention. Antiarrhythmic therapeutic options for recurrent arrhythmia are largely unhelpful, other than quinidine for chronic therapy and isoproterenol for acute arrhythmia storms.\textsuperscript{89,98}

**Short-QT Syndrome**

**Presentation and Diagnosis**

The recognition that QT shortening was linked to cardiac arrest was first published in 1993,\textsuperscript{99} followed by rare reports of short-QT syndrome (SQTS) families presenting with atrial and ventricular fibrillation.\textsuperscript{100} Shortening of the refractory periods of the atrium and ventricle predisposes the patient to fibrillation. The finding of marked QT shortening (but not necessarily the SQTS) is rare, with a prevalence of 0.02\% (<320 ms) and 0\% (<300 ms) in a healthy, young, male population of >40,000 conscripts.\textsuperscript{101} As a cause of cardiac arrest, it appears extremely rare.\textsuperscript{2} Presentation age is varied, between 4 and 80 years old (median 30 years), with approximately one third presenting with cardiac arrest, one third with syncope, and one third with palpitations. Atrial fibrillation in the young and sudden infant death syndrome may also alert the clinician.\textsuperscript{102} The underlying pathophysiology is related to gain-of-function mutations in the inward rectifier potassium channels, shortening the action potential duration. This is the converse of mutations seen in LQT1, LQT2, and LQT7. There are 5 reported SQTS subtypes to date.

The 12-lead ECG is characteristically abnormal. A corrected QT interval of <360 ms represents a short-QT interval based on 2 standard deviations in a normal population but obviously does not necessarily denote the SQTS. Early reports detailed significantly shorter intervals in their SQTS patients, with values ranging from 360 ms to <300 ms.\textsuperscript{100,103,104} There is currently no consensus with respect to an absolute cutoff value; however, the diagnosis of SQTS should be considered in any symptomatic patient with QTc <360 ms and in asymptomatic patients with QTc <330 ms. Tall or peaked T waves are common, and a depressed PR interval is sometimes seen. Shorter J point to T peak with longer T peak to T end times appear to predict a higher-risk SQTS group.\textsuperscript{105} Temporal variations in QT interval are also noted. The QT interval has limited heart rate variation, and widely used QT/heart rate correction methods can overestimate the QT interval in SQTS; as such, Holter-based QT assessment has been advocated.\textsuperscript{106} No current provocation tests are in use to unmask latent SQT, although hyperkalemia, hypercalcaemia, hyperthermia, acidosis, catecholamines, and drugs such as digitalis are known to shorten the normal QT interval.

Electrophysiology testing is not sensitive for risk stratification, but can help to strengthen diagnoses by documentation of extremely short ventricular and atrial effective refractory periods, sometimes reaching 120 ms in the atrium and 130 ms in the ventricle.\textsuperscript{100,102} Mutations in 5 different genes lead to the 5 subtypes SQT1 through SQT5. Gain-of-function inward rectifier K\textsuperscript+ channel mutations make up SQT1 through SQT3, and loss-of-function L-type calcium channel mutations comprise the remaining SQT4 and SQT5. Most patients with the SQTS, however, do not display a known genotype.\textsuperscript{102} Despite limited numbers, certain phenotypic features of each genotype are being recognized, such as the markedly symmetrical T waves in KCNH2- and KCNQ1-induced SQT1 and SQT2, the resistance to class III antiarrhythmics in KCNH2 SQT1,\textsuperscript{107} and the association with the Brugada pattern in the CACNA1b- and CACNB2c-associated SQT4 and SQT5.\textsuperscript{69}

**Prognosis and Therapy**

Prognostic data are limited, and, where present in the general population, short-QT intervals in themselves do not appear to predict adverse outcome.\textsuperscript{108} The true SQTS, however, represents a short-QT interval with associated symptoms, often with a QT interval of <300 ms, and confers a predicted 50\% chance of cardiac arrest by the age of 40 years.\textsuperscript{102} ICD implantation is currently the only therapy proven to reduce cardiac arrest, although high rates of inappropriate therapy due to peaked T-wave oversensing are reported. The seemingly obvious therapeutic approach of initiating QT-prolonging drugs has not produced effective results, unfortunately. Thus far, only quinidine has been shown to affect QT intervals and electrophysiology testing outcome.\textsuperscript{109}

**Concealed Structural Cardiac Causes of Cardiac Arrest**

Certain structural diseases that have well-recognized arrhythmogenic substrates can present as cardiac arrest without overt heart disease if they occur in a subclinical or concealed state. The extent to which the patient is investigated for structural disease will obviously predict the prevalence of these conditions within this cohort. Arrhythmogenic right ventricular cardiomyopathy and myocarditis are clear examples of this. Establishing or excluding these diagnoses in the cardiac arrest survivor is of paramount importance because their presence establishes or excludes the need for family screening, and specific therapies often stem from each diagnosis.

**Arrhythmogenic Right Ventricular Cardiomyopathy**

A full review of ARVC is beyond the scope of this review. With respect to considerations in the cardiac arrest survivor without overt structural disease, ARVC was detected in 7 of the first 100 patients with apparently unexplained cardiac arrest enrolled in the CASPER.\textsuperscript{3} MRI testing has replaced echocardiography as the gold standard noninvasive imaging modality in this disease (Figure 8). Additional testing, as described above, may demonstrate findings that meet the recently updated ARVC Task Force criteria for the diagnosis.\textsuperscript{110} Electroanatomic voltage mapping of the right ventricle...
in the electrophysiology laboratory is a discretionary tool that may be considered to detect evidence of subclinical ARVC. Genetic testing in high-probability cases has a diagnostic yield of 40% to 50%; thus, a positive test is useful, but a negative test is not. The genes underlying ARVC are characterized by considerable natural variability, making a variant of unknown significance a common outcome of genetic testing, further emphasizing the need for careful phenotyping.

**Myocarditis**

Myocarditis may present primarily with arrhythmia without overt evidence of left ventricular dysfunction. There may be biochemical or serological markers, but unless fulminant, myocarditis does not usually produce significant ventricular dilatation or systolic impairment on echocardiography. The appearance of regional, subepicardial, delayed gadolinium enhancement on MRI, however, provides a highly sensitive tool for the detection of myocarditis that would have been deemed absent with other imaging modalities (Figure 9). Recognition of these findings leads to a clinical challenge if other diagnoses have been excluded. Although it is a transient process that is potentially reversible, ICD implantation appears warranted, although long-term risk is intuitively low.

**Coronary Spasm**

Coronary spasm is a well-reported cause of cardiac arrest. It occurs commonly in the absence of severe coronary disease and can present with or without anginal pain. Transient ST elevation is the hallmark of the disease, making it difficult to diagnose unless monitored. Minor coronary disease in the absence of other causes of cardiac arrest might suggest the diagnosis, particularly in a male smoker. Provocation testing with ergonovine or acetylcholine, extended cardiac monitoring, or the use of continuous ST analysis software in implantable defibrillators may reveal the diagnosis, as was discussed above (Figure 10).

**Idiopathic Ventricular Fibrillation**

The diagnosis of idiopathic ventricular fibrillation is made when no other cause is found. The Canadian CASPER has demonstrated that despite systematic screening tests, approximately half of cardiac arrest patients without overt heart

![Figure 8](image1.png)

**Figure 8.** Top, Cardiac magnetic resonance image. T1-weighted double inversion recovery image demonstrates intramyocardial fat in the right ventricular free wall (left) with matched cine image in systole demonstrating regional akinesia (right). Bottom, CARTO voltage/scar map of right ventricle demonstrating typical basal low-voltage scar burden seen in arrhythmogenic right ventricular cardiomyopathy.

![Figure 9](image2.png)

**Figure 9.** Cardiac magnetic resonance imaging of myocarditis. T2-weighted short-axis image demonstrates increased tissue water signal in lateral wall segments (left). Matched delayed enhancement post gadolinium image demonstrates epicardial-based myocardial necrosis, both consistent with acute myocarditis (right). Regional inflammation is commonly seen in early disease.
primary electric diseases. Even so, a significant proportion of these remain undiagnosed. Until our understanding of these causes leads to definitive disease-specific treatment, protection with an ICD is warranted in all but exceptional cases. Ongoing studies are needed in both genetic and electrophysiological fields to further expand our understanding in this area, ideally leading to optimal therapeutic and prevention strategies.

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