Sudden cardiac death (SCD) is predominantly related to coronary artery disease and its sequelae, cardiomyopathy, and congenital or valvular heart disease. No structural abnormalities are detectable in 5–8% of SCDs. Identified ion channelopathies such as Brugada syndrome, long-QT syndrome (LQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) contribute to this incidence. The diagnosis requires a high level of suspicion because of a resting ECG that is often borderline, intermittently normal, or frankly normal. Genetic testing does not provide a simple solution to this issue, as it is often neither sensitive nor specific even when the phenotype points to a specific entity and may yield results that are difficult to interpret (ie, variants of unknown significance). Pharmacological and/or exercise testing by manipulation/stressing the cardiac action potential can accentuate the desired abnormality or provoke a characteristic arrhythmia response. A systematic approach to clinical testing that includes drug provocation results in unmasking of the cause of apparently unexplained aborted SCD in >50% of patients and is very helpful in directing genetic testing of the index case and family to diagnose genetically mediated arrhythmia syndromes. This review will seek to highlight the clinical utility of provocative testing and describe how to perform and interpret provocative testing for the diagnosis of Brugada syndrome, LQTS, and CPVT.

Performing Provocative Testing
Pharmacological challenge should be performed in an area that has comprehensive monitoring and resuscitation equipment (including an external cardioverter-defibrillator). Testing should be performed with continuous monitoring of the patient by adequately trained/experienced personnel in an area equipped with advance resuscitation equipment (including external defibrillator) and personnel trained in advance resuscitation and an expert physician promptly available. Given the potential risk for hemodynamically compromising ventricular arrhythmias during exercise stress testing (particularly when exercise stress testing for CPVT), we advise the presence of physically capable personnel to prevent the patient from falling, should hemodynamic collapse occur.

Continuous monitoring of the ECG should be undertaken, and 12-lead ECGs should be recorded at 1- to 10-minute intervals, depending on the rate and nature of the drug infused. Frequent blood pressure monitoring should be performed. After drug administration, the ECG should be monitored for another 30 minutes or until it normalizes. Physicians and staff should be familiar and knowledgeable regarding the pharmacodynamics and pharmacokinetics of the agents used (Tables 1 and 2).

Provocative testing may not always produce the classic ECG response, given the varied test accuracies. Therefore, the absence of a classic response or the presence of borderline changes should not supplant clinical evidence (that includes genetic testing). Even a clearly normal or abnormal provocative test result must be carefully reviewed within the clinical context. Therefore, provocative testing should be viewed as another part of the diagnostic workup and in the context of the pretest probability, not as a binary positive or negative test. When provocative testing yields borderline changes or the absence of a classic response despite high clinical suspicion (high pretest probability), an alternative provocative test may be useful (eg, exercise stress testing plus catecholamine infusion for LQTS/CPVT, an alternative sodium channel blocker used to test for Brugada syndrome).

Long-QT Syndrome
Up to 50% of patients with LQTS display a nondiagnostic resting QTc (<460 ms), and overlap of the resting QTc intervals between healthy persons and patients with LQTS makes the diagnosis challenging. Genetic testing may be definitive but can often show a variant of unknown significance and only detects a mutation in approximately 75% of patients with LQTS. Clinical criteria such as the Schwartz criteria identified a high probability of LQTS (score >4) with a sensitivity of only 19% and specificity of 99%. The Keating criteria had 36% sensitivity and 99% specificity. This highlights the need for provocative testing to enhance diagnostic accuracy.

The QT interval is defined as the interval from the beginning of the QRS complex to the end of the T wave. The authors favor the maximum slope technique wherein the end of the T wave is
marked by the intersection point of the tangent line representing the maximal downward or upward slope of a positive or negative T wave, respectively, and the isoelectric baseline (Figure 1). Despite its imperfections, the Bazett formula (QT divided by the square root of the R-R interval) remains widely used to correct for heart rate. QT and QTc measurement during atrial fibrillation should be averaged over 10 consecutive beats. Significant sinus arrhythmia may also complicate assessment of QTc intervals because of relatively larger changes in the R-R intervals compared with lesser corresponding changes in the QT interval. QT and QTc intervals may be averaged over 10 consecutive beats in an attempt to correct for this. The longest QT intervals are generally measured in the precordial leads. The standard leads to measure the QT are V5 and lead II. U waves should not be included in the measurement.

Mechanism of LQTS

Eighty-five percent to 95% of all LQTS are due to LQT1, LQT2, and LQT3. A decreased outward potassium current mediated by a loss of function mutation in the slowly (IKs) and rapidly (IKr) activating delayed rectifier potassium channel leads to LQT1 and LQT2, respectively. This leads to failure of adrenergic stimulation to shorten the action potential duration and hence the QT interval. The IKr channels represent a smaller fraction of potassium channels responsible for repolarization compared with IKs channels. Furthermore, IKr is activated rapidly in low adrenergic circumstances and IKs gradually at higher adrenergic states. Because of the intact IKs channels in LQT3 (INa defect), no QT lengthening is characteristically observed with adrenergic stimulation (Figure 2B).

Provocative Testing in LQTS

Evaluation of the QT response to the brisk tachycardia induced by standing provides important information that aids in the diagnosis of LQTS. Despite similar heart rate acceleration in response to brisk standing in patients (n=68) and control subjects (n=82), on average, the QT interval of control subjects shortened by 21±19 ms, whereas the QT interval of LQTS patients increased by 4±34 ms (P<0.001). Additionally, the QTc interval increased by 50±30 ms in the control group and by 89±47 ms in the LQTS group (P<0.001). Receiver-operating characteristic curves showed that the test added diagnostic value and the response was particularly impaired in patients with LQT2.

Exercise stress testing has also been used for differentiating LQT1, LQT2, and unaffected individuals. End-of-recovery QTc

<table>
<thead>
<tr>
<th>Channelopathy</th>
<th>Drug Infusion Doses for Provocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugada syndrome</td>
<td>Flecainide 2 mg/kg (maximum, 150 mg) over 10 min</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Ajmaline 1 mg/kg over 10 min</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Procainamide 10 mg/kg over 20–30 min</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Pilsicainide 1 mg/kg over 10 min</td>
</tr>
<tr>
<td>LQTS and CPVT</td>
<td>Epinephrine Infusion started at 0.05 μg/kg per min and increased every 5 min to 0.1 and 0.2 μg/kg per min for 5 min at each dose</td>
</tr>
<tr>
<td>LQTS</td>
<td>Adenosine Rapid bolus adenosine injected at 6 mg incremental doses (maximum single dose of 24 mg) until atrioventricular block or sinus pauses lasting 3 s occurs</td>
</tr>
</tbody>
</table>

LQTS indicates long-QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

Table 2. Procainamide and Epinephrine Infusion Protocols

<table>
<thead>
<tr>
<th>Progress</th>
<th>Test</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>ECG/Vitals</td>
<td>Start procainamide 1 g over 30 min</td>
</tr>
<tr>
<td>10 min</td>
<td>ECG/Vitals</td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>ECG/Vitals</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>ECG/Vitals</td>
<td>Stop procainamide</td>
</tr>
<tr>
<td>40 min</td>
<td>ECG/Vitals</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>ECG/Vitals</td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>ECG/Vitals</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>ECG/Vitals</td>
<td>Start epinephrine 0.05 μg/kg per min</td>
</tr>
<tr>
<td>0:05 min</td>
<td>ECG/Vitals</td>
<td>Increase to 0.10 μg/kg per min</td>
</tr>
<tr>
<td>0:10 min</td>
<td>ECG/Vitals</td>
<td>Increase to 0.20 μg/kg per min</td>
</tr>
<tr>
<td>0:15 min</td>
<td>ECG/Vitals</td>
<td>Stop epinephrine</td>
</tr>
<tr>
<td>0:25 min</td>
<td>ECG/Vitals</td>
<td>10 min after epinephrine</td>
</tr>
<tr>
<td>0:35 min</td>
<td>ECG/Vitals</td>
<td>20 min after epinephrine</td>
</tr>
<tr>
<td>0:45 min</td>
<td>ECG/Vitals</td>
<td>30 min after epinephrine</td>
</tr>
</tbody>
</table>

*ECG should include high precordial leads.
may have clinical use in distinguishing patients with LQTS from healthy individuals—a QTc >445 ms at the end of recovery (4 minutes after cessation of exercise) had a sensitivity of 92% and specificity of 88% at identifying LQT1 and LQT2 individuals. Furthermore, early-recovery QTc may be used to distinguish LQT1 from LQT2 patients: early recovery QTc <460 ms had a sensitivity of 79% and specificity of 92% at identifying LQT2 patients (from LQT1). Increased QT hysteresis may be a unique feature of LQT2 syndrome. QT hysteresis is calculated as the QT interval difference between exercise and 1 to 2 minutes into recovery at similar heart rates (within 10 bpm) at heart rates of approximately 100 bpm. In LQT2 patients, the QT fails to shorten at intermediate heart rates in early exercise. However, recruitment of I_{Ks} at higher heart rates is associated with appropriate QT shortening, which persists into the recovery phase. This consequently leads to an exaggerated QT difference between exercise and recovery, which manifests as increased QT hysteresis. QT hysteresis of >25 ms has a sensitivity and specificity of 73% and 68%, respectively, at identifying patients with LQT2 over LQT1.

Figure 2. Proposed algorithmic approach to investigating for long-QT syndrome (LQTS; A) and schematic depiction of heart rate zones (B) when abnormal QTc intervals are most likely observed during provocative testing for LQTS. LQT1 indicates late exercise and recovery; LQT2, early exercise and recovery; and LQT3, rest.

Two major protocols have evolved for epinephrine infusion: the bolus and brief infusion (Shimizu protocol) and the gradually escalating dose protocol (Mayo protocol). Both are well tolerated, with a low incidence of adverse events. Gradually increasing doses of epinephrine (0.05, 0.1, 0.2, and 0.3 μg/kg per minute) can distinguish healthy control subjects from patients with concealed LQT1. In one study of 147 genotyped patients, the median change in QT interval during low-dose epinephrine infusion was −23 ms in the gene negative group, +78 ms in LQT1, −4 ms in LQT2, and −58 ms in LQT3. The paradoxical QT response was observed in 92% of patients with LQT1 compared with 18% of gene-negative, 13% LQT2, and 0% LQT3 patients. Overall, the paradoxical QT response had a sensitivity of 92.5%, specificity of 86%, positive predictive value of 76%, and negative predictive value of 96% for LQT1 status. Patients receiving β-blocker therapy at the time of testing are likely to have lower diagnostic accuracy.

Graded infusions of epinephrine in normal subjects can be associated with QTc prolongation. Up to 79% of normal subjects may show an abnormally prolonged QTc interval at 1 or more infusion levels of epinephrine. This may lead to an inappropriate diagnosis of LQTS. However, an absolute QT prolongation by more than 20–30 ms is not typically seen at any dose level of epinephrine. A positive test is defined if a paradoxical QT/QTc response is identified (Figure 1). Studies have proposed an increase in the absolute QT by 30 ms (at 0.05 μg/kg per minute epinephrine), an increase in absolute QT by 35 ms or QTc prolongation by
30 ms\textsuperscript{14} (at 0.10 \( \mu \)g/kg per minute epinephrine), or an increase in QTc by 65 ms\textsuperscript{15} or to a value above 600 ms\textsuperscript{1} during epinephrine infusion (up to 0.4 \( \mu \)g/kg per minute) as useful criteria for diagnosing LQTS (Figure 2). The authors favor the Mayo definition of an absolute QT prolongation of \( \geq 30 \) ms at 0.10 \( \mu \)g/kg per minute epinephrine but take into account the other parameters, particularly if there is a dramatic change at 0.20 \( \mu \)g/kg per minute epinephrine or a strong clinical suspicion of LQTS. QT measurement during adrenaline infusion can be challenging to interpret in the context of dynamic T-wave morphology changes, particularly when prominent U waves are present, the T wave is flattened or when notching of the T wave occurs. Assessing the ECG in all 12 leads may assist in defining the QT interval.

Adenosine-induced, sudden bradycardia and subsequent tachycardia have also been investigated to identify QT changes of diagnostic value in patients with LQTS. Adenosine challenge resulted in dissimilar response in LQT patients (n=18) and control subjects (n=20) in one study.\textsuperscript{16} A QT of \( \geq 410 \) ms at maximal bradycardia had a sensitivity of 0.94 and a specificity of 0.9 to detect LQTS. A QTc of \( \geq 490 \) ms at maximal bradycardia had a sensitivity of 0.94 and a specificity of 0.85 to detect LQTS. The small number of genotyped patients in this study series precludes reaching reliable conclusions regarding the utility of adenosine testing, but it is promising.

Data on the utility of Holter monitoring for the diagnosis and prognosis of LQTS are unclear. Some studies have reported the minimal diagnostic and prognostic utility of Holter monitoring in evaluating LQTS.\textsuperscript{17,18} However, studies have also reported the value of Holter monitoring in diagnosing LQTS, and in particular the utility of diurnal repolarization dynamics.\textsuperscript{19} Holter monitoring may be more useful in LQT2 and LQTS3 due to the more pronounced QT prolongation observed compared with LQTS1 at slow heart rates in these patients (particularly at night).\textsuperscript{20}

Provocative testing can be useful in patients with a suspected diagnosis of LQT1/LQT2 who have not been genotyped, in patients who have been genotyped with a diagnosis of LQT1/LQT2—if the patient’s resting ECG is unremarkable—or if the LQT1/LQT2-associated mutation is novel. The test is not recommended for patients with type 3 LQTS (Figure 2). The test can also be of diagnostic value in other LQTS that involve the \( I_{Ks} \) and \( I_{Kr} \) channels and other channels that are sensitive to sympathetic stimulation (eg, \( I_{Kr} \) channel in LQT7), although the rarity of these mutations make systematic study challenging.

During provocations, epinephrine infusion should be stopped if systolic blood pressure rises above 200 mm Hg, there is an increase in premature ventricular contractions or nonsustained ventricular tachycardia or polymorphic VT occurs, T-wave alternans develops, or the patient becomes intolerant to the test. Intravenous \( \beta \)-blocker therapy can be used to suppress ventricular arrhythmia and should be available for resuscitative efforts in the event of sustained ventricular arrhythmias.

**Catecholaminergic Polymorphic Ventricular Tachycardia**

CPVT is characterized by adrenergically induced ventricular arrhythmias associated with syncope and SCD. The resting ECG is usually normal, and the QT interval is usually normal or borderline, making diagnosis difficult. The diagnosis is based on exercise/catecholamine-induced polymorphic or bidirectional VT in the absence of structural heart disease or a prolonged QT interval.\textsuperscript{21}

**Mechanism of CPVT**

In CPVT, a gain-of-function mutation of the ryanodine receptor leads to a premature release of calcium from the sarcoplasmic reticulum.\textsuperscript{22} Cardiac calsequestrin mutations can also contribute to abnormal regulation of cellular calcium.\textsuperscript{23} Abnormal calcium handling can lead to arrhythmias mediated by delayed afterdepolarizations.\textsuperscript{24}

Arrhythmia is induced by sympathetic stimulation by exercise or by epinephrine infusion. Ventricular ectopy, bidirectional VT, and polymorphic VT may occur in a progressively predictable order with increasing heart rate. Continuation of provocative testing may lead to syncope. The tachyarrhythmias disappear with discontinuation of testing. Intravenous \( \beta \)-blocker therapy can be used to suppress ventricular arrhythmias in CPVT after provocative testing.

**Provocative Testing in CPVT**

A positive test is defined when complex ventricular ectopy, bidirectional VT, and/or polymorphic VT occurs (Figure 1). CPVT should not be diagnosed if simple isolated monomorphic ectopy is induced. However, CPVT patients often have outflow tract ectopy at the onset of induced arrhythmia at a relatively predictable heart rate threshold.\textsuperscript{25} Polymorphic or bidirectional VT is provoked with exercise in 63% and epinephrine in 82% of patients with CPVT.\textsuperscript{26} Therefore, a normal provocative test does not exclude the diagnosis. In a large series of CPVT patients (n=101), exercise testing was negative in 12 (of 17) asymptomatic family members with a positive CPVT genotype.\textsuperscript{26} In another study involving 30 mutation carriers, exercise stress testing induced ventricular arrhythmias in only 23.\textsuperscript{27} Holter monitoring may also be useful in active patients for the evaluation of CPVT by bringing out the progressive arrhythmia with exercise.\textsuperscript{21} However, compared with noninvasive monitoring alone, provocation testing significantly improves the diagnostic yield (by approximately 4-fold).\textsuperscript{25}

Suppression of exercise-induced ventricular arrhythmias with \( \beta \)-blocker therapy does not necessarily translate into long-term effectiveness of therapy.\textsuperscript{27} Furthermore, the absence of effort-induced symptoms and/or ventricular arrhythmia on stress testing may be observed in more than one-third of pathogenic RyR2 mutation carriers who still remain at future risk for SCD.\textsuperscript{26,28} However, repeated exercise tests on therapy have been used to titrate \( \beta \)-blocker, verapamil, and flecainide dosage.\textsuperscript{26,30}

**Brugada Syndrome**

The prevalence of fluctuations between diagnostic and nondiagnostic ECGs in patients with Brugada syndrome is high.\textsuperscript{31} In a study of 176 Brugada syndrome patients in whom repetitive baseline ECGs were recorded, only 90 patients had at least 1 positive baseline ECG for a type 1 pattern.\textsuperscript{32} The typical ECG features can be unmasked with sodium channel blockers. Automatic tone can also modulate the ECG phenotype: isoproterenol attenuates and acetylcholine accentuates the ECG changes in
affected patients. In a series of 334 patients, 30% could only be diagnosed with pharmacological challenge. The sensitivity of provocative pharmacological testing may vary, depending on the sodium channel blocker used, ECG lead position, the type and severity of the mutation, baseline autonomic tone, and genetic polymorphisms. Standard genetic testing is not universally feasible and has a low sensitivity (Table 1).

It is important to distinguish patients who are asymptomatic with a Brugada pattern ECG from Brugada syndrome, in which a type 1 ECG pattern is associated with symptoms. In one study, the cardiac event rate per year was 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients.

The type 1 Brugada ECG pattern is characterized by a complete or incomplete right bundle-branch block pattern with a coved morphology ST-segment elevation of at least 2 mm in the right precordial leads (V1–V3) followed by a negative T wave. The type 2 ST-segment elevation has a saddleback appearance with a high takeoff ST-segment elevation of >2 mm, a trough displaying >1-mm ST-elevation followed by a positive or biphasic T. Type 3 has an ST-segment morphology that is either saddleback or coved with an ST-segment elevation of <1 mm. Type 2 and type 3 ECGs are not diagnostic of the Brugada syndrome. Patients with a Brugada type 1 pattern on ECG diagnosed with leads placed 2 intercostal spaces above the standard position may have a similar prognosis to that of individuals with a type 1 ECG recorded from the standard position (Figures 1 and 3). When undertaking provocative testing with a sodium channel blocker, the infusion should be terminated when a type-1 ECG develops, premature ventricular beats or other arrhythmias develop, or the QRS widens to >130% of baseline. QRS prolongation ≥130% occurs in 50% of all tests. In 40% of positive tests, it occurs before diagnostic ECG changes. Always terminating the test when QRS prolongs ≥130% could possibly result in loss of important diagnostic information. Isoproterenol (by inhibiting Ito) can be effective in normalizing the ECG changes and to treat ventricular tachyarrhythmia.

Large cohort studies indicate the low incidence of arrhythmic events in asymptomatic patients with either the spontaneous or

Figure 3. Proposed algorithmic approach to investigating for Brugada syndrome (A) and high precordial lead placement (B).
drug-induced type 1 ECG compared with symptomatic subjects. Therefore, drug testing to unmask the type 1 ECG in asymptomatic patients with a non-type 1 ECG does not appear to have additional value for risk stratification. However, the authors favor considering this to provide practical lifestyle advice to patients with respect to treatment of fever, avoidance of provocative drugs (www.brugadadrugs.org), and reporting of syncope and seizures.

However, a drug-induced type 1 ECG is useful in asymptomatic patients showing only the non-type 1 ECG for diagnosis, prognosis, screening, and therapy. Additionally, screening of asymptomatic family members can be undertaken with drug testing for diagnosis and counseling. Drug challenge generally is not performed in asymptomatic patients displaying the type 1 ECG at baseline because the additional diagnostic value is considered to be limited, the added prognostic value is not clear, and the test has a very small risk of provoking arrhythmic events.

Mechanism of Brugada Syndrome
The arrhythmogenic substrate in Brugada syndrome is believed to relate to an increase in heterogeneity of the action potential duration in cells residing in epicardial compared with endocardial layers of the right ventricle. The reduction in the inward sodium current (I_{Na}) allows the transient outward (I_{o}) current to repolarize the cell in phase 1 beyond the voltage range in which L-type Ca^{2+} channels are active. Inactivity of the Ca^{2+} channel (along with the I_{o} repolarization current) results in loss of the action potential plateau, predominantly in the subepicardial cells. Conduction of the action potential from sites at which it is maintained (subendocardial) to sites at which it is abbreviated (subepicardial) is believed to cause local reexcitation. This situation may lead to closely coupled extrasystoles, thus triggering ventricular arrhythmias.

Provocative Testing in Brugada Syndrome
Varied potencies of inhibition of I_{o} and I_{Na} by various sodium channel blockers contribute to the varied effectiveness in unmasking Brugada syndrome. For example, flecainide and ajmaline reduce the depolarizing I_{Na} current. However, these agents also inhibit the repolarizing I_{o} current, which counters the I_{Na} inhibition. In addition to reducing the peak amplitude of I_{o}, ajmaline and flecainide also accelerate the decay of the I_{o} current. Class IA antiarrhythmic agents display a more rapid dissociation from the sodium channel. This may underlie their lesser potency compared with class IC agents in unmasking the ECG pattern. However in contrast to ajmaline and flecainide, procainamide produces no block of I_{o} at clinically relevant drug concentrations. A modest-sized study comparing the effect of intravenous flecainide versus ajmaline reported disparate responses, with a failure of flecainide in 7 of 22 cases (32% versus 0% with ajmaline). In another study, pharmacological challenge with flecainide or ajmaline was unable to unmask most silent gene carriers, with a positive predictive value of only 35%. Thus, sensitivity and specificity for pharmacological provocation remains under dispute in the absence of a large systematic study that exposes patients to serial drug testing with varied agents. Nonetheless, there is inference that ajmaline and flecainide are more sensitive than procainamide. Many countries do not have access to all 3 drugs in intravenous form.

Overall, the sensitivity of provocative tests in patients with an SCN5A mutation (which represents only 20% of all Brugada syndrome patients) is estimated to be 71–80%. The available study by Brugada et al on the sensitivity in non-SCN5A Brugada syndrome patients applies to patients with documented but transitory type 1 ECGs resuscitated from SCD; in this study, the sodium channel blocker test was found to be 100% sensitive.

Conclusions
Provocative drug and/or stress testing can unmask the diagnosis of Brugada syndrome, LQTS, and CPVT when the ECG is not diagnostic. It is particularly useful when an inherited arrhythmia is suspected in the context of syncope or cardiac arrest, or in family screening, assisting in arriving at an elusive diagnosis and in directing genetic testing of the index case and family.

Disclosures
None.

References
How to Perform and Interpret Provocative Testing for the Diagnosis of Brugada Syndrome, Long-QT Syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia

Manoj N. Obeyesekere, George J. Klein, Simon Modi, Peter Leong-Sit, Lorne J. Gula, Raymond Yee, Allan C. Skanes and Andrew D. Krahn

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