Cardiac Channelopathies

11

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Introduction

Primary inherited arrhythmia syndromes or "channelopathies" are a set of disorders in which one or more of the cardiac ion channels functions abnormally. Mutations in genes encoding critical ion channels, most commonly sodium, calcium, and potassium channels, are the cause of the cardiac pathology. This has various implications on cardiac conduction including resultant Long or Short QT Syndrome, Brugada Syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), all of which are considered channelopathies.

Channelopathies may be identified after an individual cardiac arrest, family history of sudden cardiac death (SCD), or clinical suspicion based on evaluation after a syncopal event. Patients with channelopathies generally have structurally normal hearts. The more recent widespread use of genetic testing has allowed providers to better identify patients at risk and initiate treatment. This may, in turn, lower the overall risk to the patient and immediate family members.

The Guidelines for Sudden Cardiac Death and Arrhythmia Evaluation recommend genetic testing as a part of diagnosis, depending on specific channelopathy suspected. Genetic testing is not only important to obtain a specific diagnosis with high clinical suspicion, but to risk stratify, guide therapy, and provide screening for relatives. Recently, it has been more common to use multigene or whole exome sequencing using a blood or buccal swab. These tests have high sensitivity, can identify multiple gene mutations simultaneously, and can identify "modifier" genes which affect expression or intensity of expression in the patient. Interpretation is complicated and testing should only be completed by providers versed in counseling on the implications of the results. There are often "variants of unknown significance" identified. These are genetic variants but the specific location on the gene is not specifically associated with a disease.

Long QT Syndrome

The first identified and most common channelopathy is the Long QT Syndrome (LQTS). This syndrome occurs when the QT interval on the EKG is prolonged due to either a congenital mutation or acquired due to medications, electrolyte abnormalities, metabolic disorders, ischemia, or intracranial pathology. The most common QT-prolonging medications are listed on the Crediblemeds.org website. Important offending medications to know would be specific antiemetics, PPIs, SSRIs, antipsychotics, and some antibi-

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otics/antifungals. Many frequently used medications including Zofran, Benadryl, Pepcid, Protonix, Celexa, Paxil, Imodium, Zithromax, and antiarrhythmics are on the list. The most commonly associated electrolyte abnormalities associated with QT prolongation are hypokalemia, hypomagnesemia, and hypocalcemia.

The QT interval is the total electrical sum of ventricular depolarization and repolarization. It is measured from the beginning of the QRS complex to the end of the T wave on a 12-lead EKG. A normal QT interval is <440 ms in a male or <460 ms in a female. It should shorten with higher heart rates and lengthen with slower heart rates. The corrected QT interval (QTc) is calculated by measuring the intervals on EKG and using a formula to correct for the heart rate. There are various correction formulas that can be used including Bazett, Framingham, Hodges, and Fredericia to adjust for heart rate. The Bazett (most common) formula for the corrected QT (QTc) interval is QT/ $\sqrt{}$ R-R (see below) and should be directly measured rather than relying on the computer read, which is often inaccurate. The QT interval should be measured in leads V5 or II. The limb lead with the sharpest end of the T wave can also be used. The R-R interval should be measured immediately preceding the beat where QT was measured. In atrial fibrillation, the average of 5 consecutive QT intervals should be measured and then averaged, due to the potential irregularity of the R-R interval (Figs. 11.1 and 11.2).

When the QT prolongs, it predisposes the patient to R-on-T phenomenon which is where a PVC occurs during a vulnerable period of repolarization of the ventricule (during the T wave). This triggers polymorphic ventricular tachycardia, or Torsades de Pointes (TdP). Torsades can be preceded by a long-short R-R interval or bradycardia causing "pause-dependent" ventricular tachycardia (VT).

The prevalence of the genetic type of LQTS occurs in about 1/2000 individuals. The risk of death in untreated LQTS is 21% in the year after a first syncopal event but decreases to ~1% over 15 years if treated [7]. SCD can be the initial presentation of this syndrome. Arrhythmias are more common in younger patients and can occur around menses or childbirth.

The congenital form of LQTS can be caused by multiple gene mutations with 13 types now identified. Approximately 15–20% of patients with a prolonged QT are gene positive and less than 5–10% are de novo mutations. The most common types are Long QT I, II, and III. Romano-

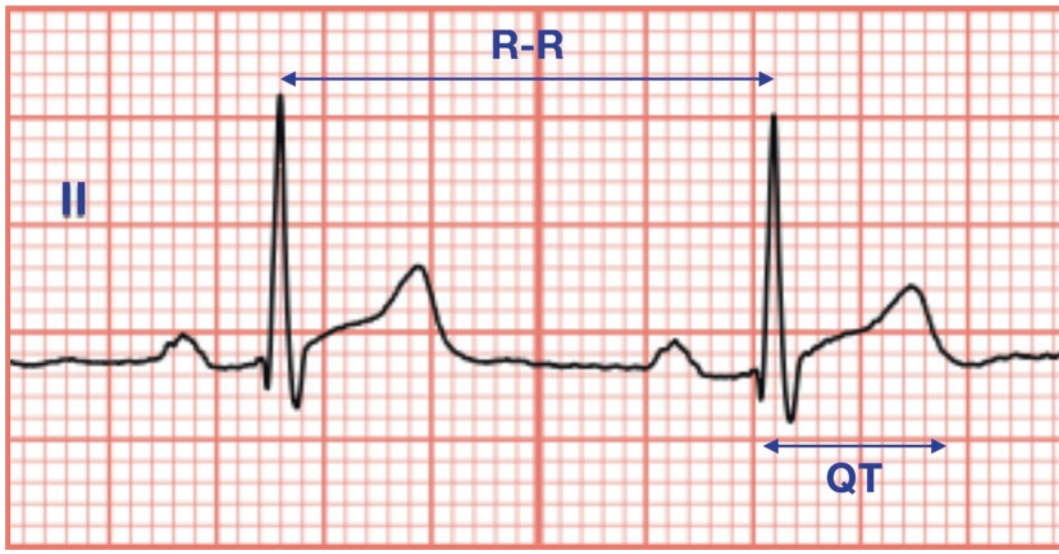

Fig. 11.1 Measure QT and previous R-R. Then calculate QTc with formula: measured QT/$\sqrt{}$R-R

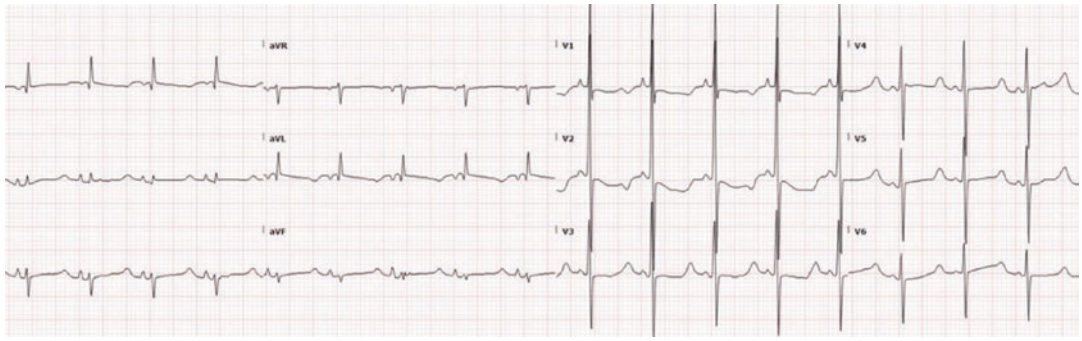

Fig. 11.2 Long QT interval on EKG

Ward syndrome is the autosomal-dominant form and Jervell-Lange Nielson syndrome is autosomal recessive and associated with congenital deafness. LQTS1 is associated with a gene mutation in KCNQ1 and described as an event occurring during exertion, especially during swimming. LQTSII has a gene mutation in KCNH2 and is classically associated with ventricular arrhythmia triggered by a startle or by emotional stress. LQTS3 is a defect in SCN5A and is associated classically with ventricular arrhythmia and cardiac arrest during sleep.

Treatment of all types of Long QT Syndrome includes a reduction in adrenergic tone and prevention of ventricular arrhythmias. Beta blockers are indicated in all diagnosed patients, with nadolol being the preferred agent and propranolol as the second-line agent due to therapeutic characteristics including being non-cardioselective. Beta blockers are most effective in patients with LQTS1 as it blocks the epinephrine released during exertion. Mexiletine, flecainide, or ranolazine may also be added for LQTS3 patients. Implantable cardioverter defibrillators (ICDs) are recommended in patients with resuscitated SCD, syncope, ventricular arrhythmia, or other high-risk features such as significantly prolonged QT or significant family history. Left cervicothoracic stellectomy/gangliectomy (sympathetic denervation) is also an option for non-responders to therapy or if therapy cannot be tolerated. This procedure is accomplished with a video-assisted thoracoscopic technique (VATS procedure) where the left stellate ganglion and a few left thoracic ganglion are removed, blocking sympathetic signals to the heart.

Short QT Syndrome

This condition is due to an accelerated repolarization phase of cardiac conduction. Short QT is defined as a QTc ≤340 ms or ≤360 ms with a pathogenic gene mutation or family history. Associated genes are inherited in an autosomal-dominant fashion in KCNH2, KCNQ1, and KCNJ2. EKG may also show peaked T waves. This is an uncommon disorder but is associated with 40% of patients having a cardiac arrest by age 40. Other arrhythmias are common, especially atrial fibrillation, and diagnosis may be elicited by a stress test or electrophysiology study. No risk factors for SCD have been identified other than syncope. Treatment consists of ICD implantation, hydroquinidine, or other antiarrhythmics depending on specific gene mutation (Fig. 11.3).

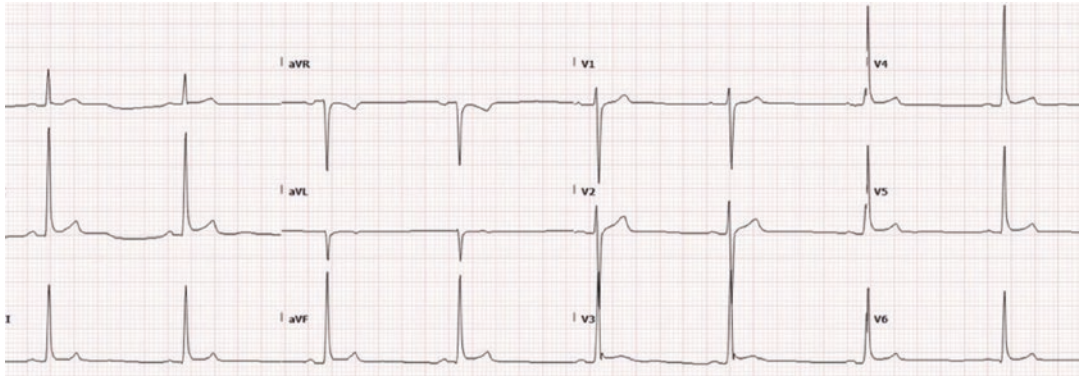

Fig. 11.3 Short QT interval on EKG

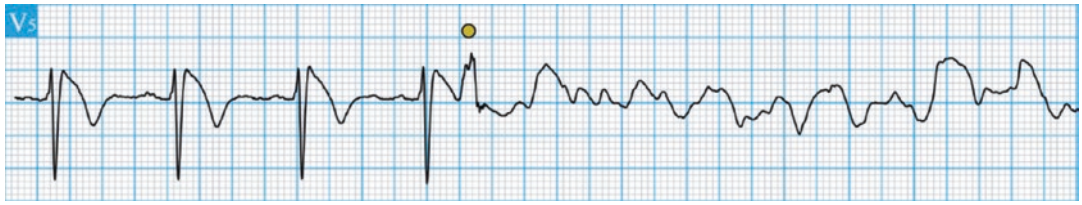

Fig. 11.4 Brugada pattern with PVC falling on a T wave, initiating polymorphic VT

Brugada Syndrome

Brugada syndrome (BrS) is a disorder characterized by right precordial ST elevation on EKG with or without right bundle branch block, predisposing to SCD. SCD risk is due to polymorphic VT degenerating to ventricular fibrillation (VF) (*see* Fig. 11.4). It usually presents in males in the 3rd or 4th decade of life as syncope or SCD. The prevalence is about 1/5–10,000, more commonly in Southeast Asia (where it is known as the Widow Ghost who comes in the night to carry off the souls of their young males). Diagnosis can be made based on symptoms and emergence of Type I pattern in leads V1 or V2 (Fig. 11.5). The sensitivity may be increased with these leads moved to the second intercostal space. The pattern may emerge during fever or with provocative testing. There are three patterns associated with Brugada syndrome, Type I, II, and

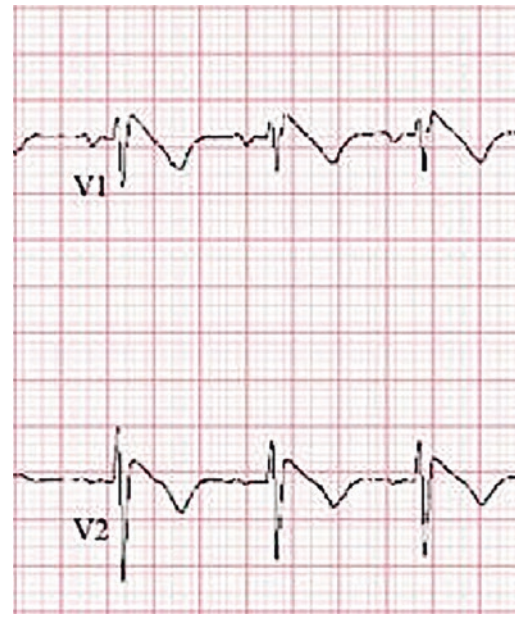

Fig. 11.5 Type I Brugada pattern Type 1

III. Diagnosis can only be made in the setting of Type I pattern but Type II and III may manifest Type I pattern in the setting of fevers or provocative testing. Type I pattern is associated with increased risk of SCA (see below).

The most common gene mutation is in SCN5A with genetics being positive in only about 25% of patients. Brugada syndrome is inherited in an autosomal-dominant fashion. Management consists of avoiding certain drugs (BrugadaDrugs.org) and aggressively treating fever. ICDs are reserved for high-risk patients (syncope or SCD). While often used, beta blockers are of more limited efficacy in patients with Brugada syndrome. Quinidine has been shown to be effective in prevention of recurrent ventricular arrhythmias in patients with this syndrome. More recently, catheter ablation has shown favorable outcomes as well, targeting abnormal tissue on the epicardial RVOT surface that has been implicated as the initiating substrate for ventricular arrhythmia in these patients.

CPVT

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a condition of adrenergically mediated ventricular arrhythmia that causes syncope, cardiac arrest, or SCD with a structurally normal heart. Exertion or emotional stress precedes the event and baseline EKG is normal or shows resting bradycardia. Patient may have Premature Ventricular Contractions (PVCs), bidirectional VT (Fig. 11.6), or TdP during exercise test (Fig. 11.7). This condition can coexist with LQTS, BrS, or hypertrophic cardiomyopathy. Mean age of symptom onset is 8 years old but the potential for a first syncopal event may not occur until adulthood. The more common gene defect is an autosomal-dominant mutation in RYR2 but less commonly CPVT may be due to a recessive mutation in CASQ2. Genetics are positive in 65% of CPVT patients and 30% of patients have SCD as their first presentation. Treatment consists of a beta blocker. Flecainide has also shown to be effective in patients with symptoms despite beta blocker therapy. ICD implantation is indicated in patients with recurrent ventricular arrhythmia (VA) despite beta blocker therapy although they must be used with caution as ICDs shocks can increase adrenergic tone which can further promote VA in these patients. Specific risks versus benefits must be weighed due to possible VT storm with ICD shocks. Left cardiac sympathetic denervation is also a potential added therapy.

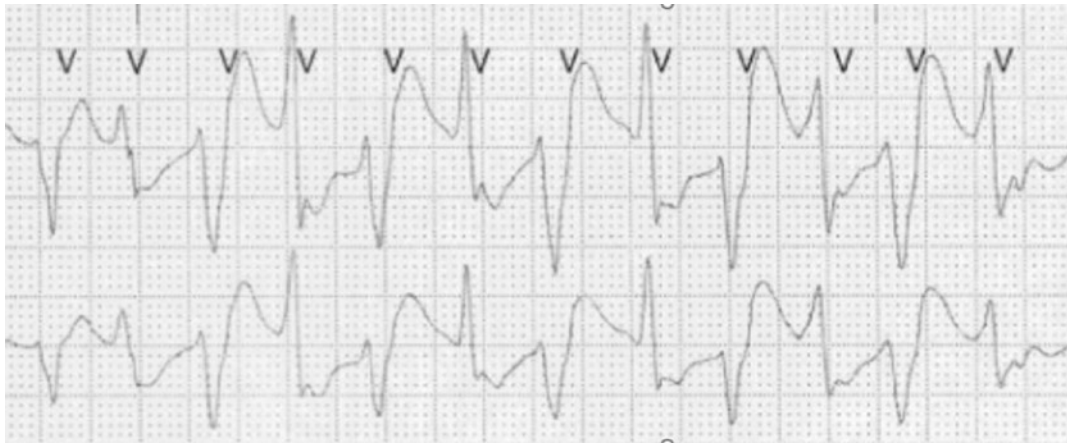

Fig. 11.6 Bidirectional VT in a patient with CPVT

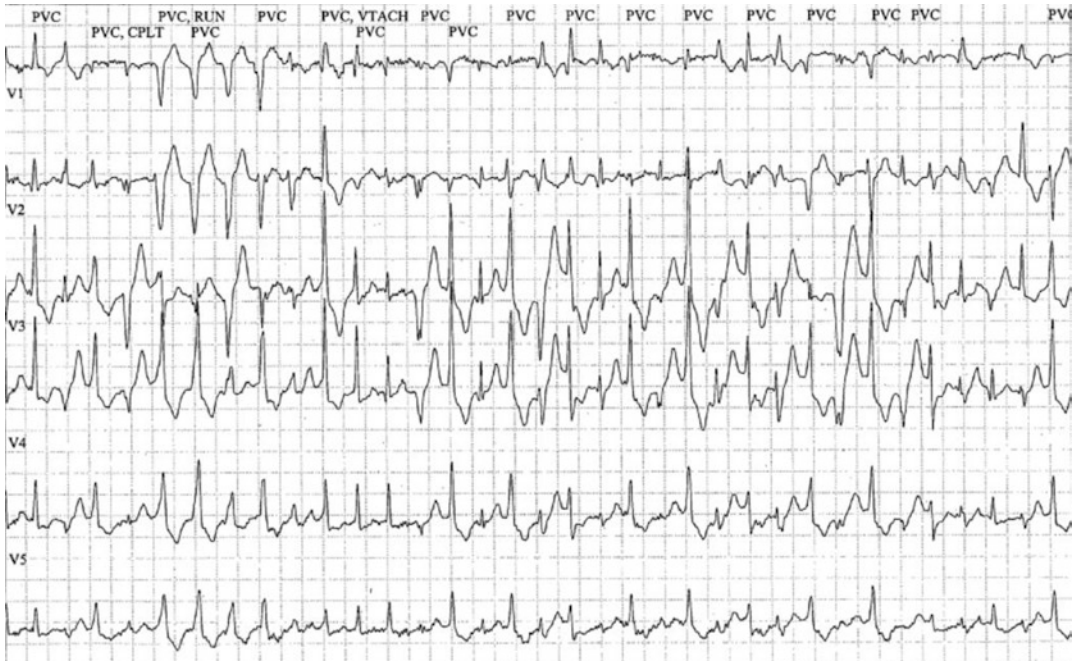

Fig. 11.7 Rhythm on a stress test of a patient with CPVT

Pearls

- QTc = QT/$\sqrt{}$R-R.
- LQTS1 = KCNQ1 gene mutation, events with exertion.
- LQTS2 = KCNH2 gene mutation, events with startle.
- LQTS3 = SCN5A gene mutation, events with sleep.
- Beta blockers for all Long QT-Nadolol or Propranolol are best.
- Brugada-Type 1 pattern in V1, V2-3rd or 4th decade of life, more in males.
- CPVT-VT with adrenaline-RYR2 or CASQ2.

Further Reading

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