Electrocardiographic Characteristics of Ventricular Arrhythmia in Inherited Channelopathies

Nilubon Methachittiphan, MD[a],
Peerawut Deeprasertkul, MD[a], Mark S. Link, MD[b,*]

KEYWORDS

• Long-QT syndrome • Short-QT syndrome • Brugada syndrome
• Catecholaminergic polymorphic ventricular tachycardia • Ventricular fibrillation

KEY POINTS

- Ventricular arrhythmias in idiopathic VT often present as monomorphic VT, and the overall prognosis is usually benign. Ventricular arrhythmias in channelopathies usually are polymorphic VT and ventricular fibrillation, and the prognosis is more variable.
- Since ventricular arrhythmias in some type of channelopathies can often be fatal, recognizing their ECG patterns is important.
- Some types of channelopathies require further testing such as exercise stress test, EP study, and genetic testing, which will help with risk stratification and prevention of sudden cardiac death by defibrillators in high risk patients.

INTRODUCTION

Ventricular arrhythmias occurring in a structurally normal heart generally account for between 5% and 15% of all patients presenting with ventricular arrhythmias.[1] These arrhythmias can be divided into idiopathic ventricular arrhythmia, in which there is no known ion mutation or genetic component, and inherited ion channelopathies, in which gene mutations causing ion-channel dysfunction play an important role in the mechanism of ventricular tachycardia (VT).[2,3] Arrhythmias may also be characterized as monomorphic or polymorphic (**Fig. 1**). Ventricular arrhythmias in idiopathic VT often present as monomorphic VT, and the overall prognosis is usually benign. However, ventricular arrhythmias in channelopathies usually are polymorphic VT and ventricular fibrillation (VF), and the prognosis is more variable.

Sudden cardiac arrests (SCA) in patients with structurally normal hearts are usually confined to those with channelopathies, although rarely SCA may be secondary to idiopathic VT or Wolff-Parkinson-White (WPW) syndrome. In the last 15 years, the results of mutation screening (molecular autopsy) in sudden unexplained death syndrome or sudden infant death syndrome have been reported in several studies. Although the yield of molecular autopsy reported by different studies is highly variable, ranging from 4% to 30%, a positive genetic test may allow the extension of genotyping to family members of those affected to reduce additional deaths in the family.[1]

The authors have nothing to disclose.

[a] Department of Medicine, University of Texas Medical Branch, 301 University Boulevard 5.106 John Sealy Annex, Galveston, Texas 77555-0553, USA; [b] Department of Medicine, Tufts Medical Center, 800 Washington Street, Box # 197, Boston, MA 02111, USA
* Corresponding author.
E-mail address: mlink@tuftsmedicalcenter.org

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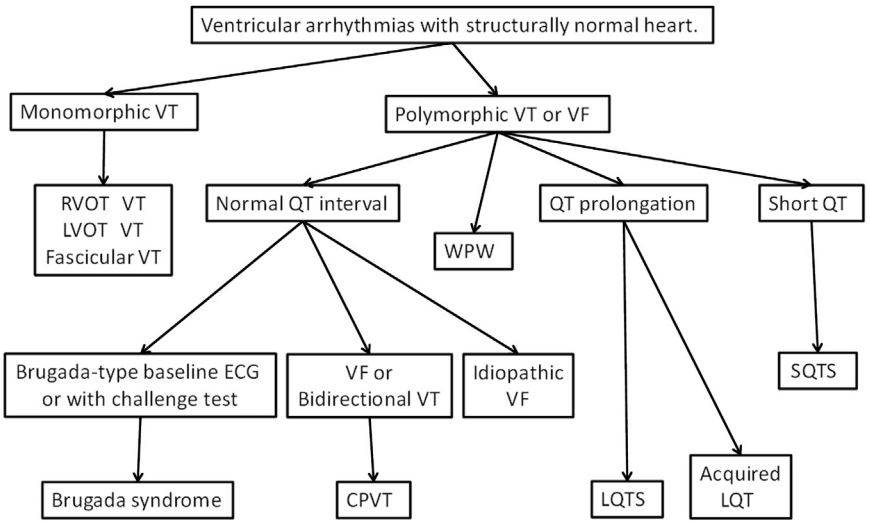

Fig. 1. Proposed clinical approach to ventricular tachycardia with a structurally normal heart. CPVT, catecholaminergic polymorphic ventricular tachycardia; LQT, long QT; LQTS, long-QT syndrome; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; SQTS, short-QT syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

LONG-QT SYNDROME

Background

Long-QT syndrome (LQTS) is caused by cardiac ion-channel abnormalities involved in repolarization. Patients with this syndrome have an increased risk for SCA. LQTS was first described in 1957 by Jervell and Lange-Nielsen.[4] This syndrome was found in children with deafness, recurrent syncope, SCA, and QT prolongation. Homozygous mutation in recessive manifestation in the *KCNQ1* gene was found to be responsible for this disorder. Subsequently, Romano and colleagues[5] and Ward and colleagues reported another congenital long QT (LQT), which had an autosomal dominance pattern of inheritance. To date 13 types of LQT have been described, and more will certainly be discovered with time.

Genetics and Pathogenesis

More than 300 gene mutations have been found to be related to LQT in 13 different genes.[6] However, most patients (75%) are those with LQT1, LQT2, and LQT3.[7,8] Repolarization abnormalities in LQT can be due to a decrease in repolarizing potassium currents or inappropriate late entry of sodium currents into cardiac myocytes.[9] In LQT1, a *KCNQ1* defect is responsible for slowly acting repolarizing potassium currents (I_{Ks}), whereas in LQT2 rapidly repolarizing potassium channel (I_{Kr}) defective genes (*KCNH2*) are found. Mutations in these potassium channels account for delayed repolarization.[10] In LQT3, a prolonged QT interval is caused by mutations of sodium channel protein (*SCN5A*), leading to persistent inward sodium currents. Mutations in this gene cause failure of the sodium channel to close after ventricular depolarization.[10]

Electrocardiographic Characteristics

An LQT diagnosis is traditionally described as greater than 460 milliseconds in women and greater than 450 milliseconds in men.[11] However, there is an overlap in QTc for those with LQTS and those without the syndrome. The 95th-percentile values of normal distribution of QT intervals are the same as the QTc, so 2.5% of individuals without LQTS will have a prolonged QTc. In addition, approximately 10% to 30% of LQT cases may have normal QTc at rest.[12] The QT interval can be altered by heart rate, age, gender, electrolyte disturbances, and medications. Thus, electrocardiograms (ECGs) with prolonged QT interval do not necessarily indicate that affected individuals have LQTS. The positive predictive value for diagnosis of LQTS with this cutoff (>460 milliseconds in women and >450 milliseconds in men) is less than 1%. However, the longer the QTc, the more likely an individual has the diagnosis of LQTS. At a QTc of 500 milliseconds, nearly all will have LQTS.[13]

Accurate measurement of QT interval is essential for the diagnosis of LQTS; errors in measurements by physicians and the dynamic nature of QT intervals account for the misdiagnosis of LQTS, and are often observed.[14] The QT interval should be obtained manually from 3 to 5 cardiac cycles, and should be made in leads II, V5, and