Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(5): 164
https://doi.org/10.31083/j.rcm2305164

Editorial

A Brief Introduction to Management of LQTS

Richard G. Trohman[1,*]

[1]Section of Electrophysiology, Division of Cardiology, Department of Medicine, Rush University Medical Center, Chicago, IL 60612, USA
*Correspondence: rtrohman@rush.edu (Richard G. Trohman)

Academic Editor: Jerome L. Fleg
Submitted: 25 March 2022 Revised: 8 April 2022 Accepted: 11 April 2022 Published: 5 May 2022

In this special issue of *Reviews in Cardiovascular Medicine* we explore "The Management of Long QT Syndromes". In broad terms, there are two types of long QT syndromes (LQTS), congenital and acquired [1]. Torsades de Pointes (TdP), first described by Dessertenne in 1966 [2], may self-terminate or degenerate into fatal ventricular fibrillation. TdP may result from either cause of QT prolongation.

Congenital (heritable) long QT syndromes were first described in the 1950s and 1960s. Seventeen genes have been subsequently linked to LQTS [3]. The Clinical Genome Resource (ClinGen), has recent analyzed and reclassified a group of these genes to disputed or limited evidence, leaving seven genes with strong or definitive evidence of causality [3,4]. Dual genetic abnormalities may complicate management. In genotype negative families, a more complex polygenic architecture may be responsible for QT prolongation [3,5].

The most common subtypes of congenital LQTS are LQT1 (loss-of-function mutation in the gene [*KCNQ1*] that encodes the slow delayed rectifier current I_{Ks}), LQT2 (loss-of-function mutation in the gene [*KCNH2*] that encodes the rapid delayed rectifier current I_{Kr}) and LQT3 (gain-of-function variants in the gene [*SCN5A*], that encodes the fast inward cardiac sodium current I_{Na}). In general, management of congenital LQTS involves lifestyle adjustment, beta blockade, avoiding QT prolonging drugs, avoidance and/or prompt correction of electrolyte abnormalities (particularly hypokalemia), implantable cardioverter defibrillators (ICDs), and left cardiac sympathetic denervation (LCSD), particularly for individuals refractory to or intolerant of beta blockers, recipients of frequent ICD shocks, or as a bridge to ICD placement in young children [3,6].

Benefits of cardiac pacing in congenital LQTS are less studied and less well defined than its role in acquired LQTS. TdP may be bradycardia or tachycardia dependent in congenital LQTS [7]. There may be benefit for individuals with LQT2 where arrhythmias are almost always pause dependent. LQT3 is particularly associated with QTc prolongation at slow heart rates, suggesting pacing may be beneficial.

Enhanced understanding of the late inward sodium current's ($I_{Na\text{-}L}$) role in prolonging action potential duration and the QT interval (particularly at low heart rates) has provided evidence that additional pharmacological therapy such as mexiletine, flecainide, or ranolazine (blockers of the late inward sodium current) may be helpful for arrhythmia prevention in LQT3. Mexiletine has also been shown to decrease the corrected QT interval in LQT2 [3,8,9].

Acquired LQTS most frequently results from drug-induced QT prolongation. The most common drugs that that prolong QTc block the rapid component of the delayed rectifier potassium current I_{Kr} via hERG channel blockade [10,11]. In some instances, drugs that block I_{Kr} also enhance $I_{Na\text{-}L}$. The most comprehensive resource for drugs to be aware of [12], categorizes them as having: (1) Known TdP Risk; (2) Possible TdP Risk; (3) Conditional TdP Risk; and (4) Drugs to Avoid in Congenital Long QT. It is available at https://crediblemeds.org/druglist [12].

Risk factors for drug-induced TdP include female gender, heart failure/cardiomyopathy, diastolic dysfunction, myocardial ischemia/infarction, left ventricular hypertrophy, valvular heart disease, treatment with multiple QT prolonging drugs or agents that interfere with their metabolism, greater than average drug dosage, baseline QTc prolongation ($\geq$450 milliseconds), familial congenital LQTS, and prior drug-induced TdP. Liver or kidney dysfunction, bradycardia, and atrioventricular block also increase TdP risk [11,13,14].

Additional precipitants of acquired LQTS include electrolyte abnormalities (most commonly hypokalemia, hypomagnesemia, and less commonly hypocalcemia), hypothyroidism, and hypothermia. Cardioversion of a rapid supraventricular tachycardia (e.g., atrial fibrillation) after receiving a QT prolonging drug may result in QT prolongation. Recent evidence suggests a high prevalence of QTc interval prolongation in patients with anti-SSA/Ro antibodies, autoimmune and inflammatory diseases [14]. These factors may precipitate acquired LQTS or add to the risk of drug-induced LQTS.

All patients exposed to I_{Kr}-blocking agents do not develop QT prolongation. Exaggerated QT prolongation and arrhythmias are even less likely. In addition, not every patient with a *KCNH2* loss-of-function mutation displays QT interval prolongation. While it seems that subclinical congenital long QT syndrome mutations contribute to drug-induced TdP risk, the degree to which they explain the risk remains uncertain. This apparent clinical disconnect and the increasing recognition that normal repolarization is the result of a complex interaction among multiple components,

led (in the late 1990s) to the concept of "repolarization reserve". Repolarization is achieved via multiple channels (I_{Kr}, I_{Ks}, $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$, $I_{Na\text{-}L}$, I_{NCX}, etc.) and repolarization reserve suggests that a reduction in I_{Kr} might generate a huge effect in cells, or in patients, when other efficient repolarization mechanisms are lacking. In contrast, the same I_{Kr} reduction might result in little change in repolarization time when other mechanisms can readily accomplish normal repolarization [15–17].

It is widely believed that TdP initiating beats result from early afterdepolarization (EAD)-triggered focal activity from the subendocardial Purkinje network. EADs occur during late phase 2 or phase 3 when action potential duration is increased. The mechanism(s) responsible for perpetuating TdP remain controversial [10].

The initial therapy of choice for acute drug-induced TdP is intravenous magnesium sulfate. Immediate defibrillation is indicated if sustained, hemodynamically unstable polymorphic ventricular tachycardia or ventricular fibrillation develops.

Overdrive transvenous pacing is highly effective in shortening QTc and preventing arrhythmic recurrence. It is particularly useful when TdP is refractory to magnesium or when a pause or bradycardia precipitates TdP. Short-term pacing rates of 90 to 110 beats/minute are usually employed. When temporary pacing is unavailable or during preparation for transvenous catheter placement, isoproterenol titrated to a heart rate $\geq$90, is useful. Isoproterenol is contraindicated in patients with congenital LQTS or ischemic heart disease [11].

It is requisite that QT prolonging medications and drugs interfering with their metabolism be promptly discontinued and avoided (if possible) in the future. Electrolyte imbalances must be corrected (serum potassium should be maintained at a level of 4.5–5 mmol/L) [12].

In the setting of acquired long QT syndrome, TdP is almost invariably preceded by a pause followed by a markedly prolonged QT interval. TdP does not appear to occur when the effective pacing rate is $>$70 beats per minute. However, despite programmed rates $>$70 beats per minute TdP may appear in the presence of pause promoting programming or oversensing [18]. In a report on congenital LQTS, most pauses that led to TdP were indisputably longer than the preceding ventricular rate. The shortest precipitating pause was 760 ms (equivalent to 79 beats/minute) and the authors recommended a minimum pacing rate of 80 beats/minute [19].

While imperfect, management of acquired LQTS is more straightforward than management of congenital LQTS. In a recent review, expert commentary on the management of 4 cases of congenital LQTS revealed agreement on 10 points, disagreement on 3, and acknowledged gaps in knowledge about 8 points [20]. While this special issue of *Reviews in Cardiovascular Medicine* is unlikely to solve all disagreements or fill every knowledge gap, we hope to enhance readers understanding of LQTS and point future investigations in a direction that will improve our therapeutic armamentarium.

Author Contributions

RGT had full access to all the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. RGT—manuscript concept and design, acquisition of data, analysis and interpretation, draft of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical, and material support.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest. Richard G. Trohman is serving as one of the guest editor of this journal. We declare that Richard G. Trohman had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Jerome L. Fleg. Dr Trohman reported serving as an advisor to Boston Scientific/Guidant; receiving research grants from Boston Scientific/Guidant, Medtronic Inc, St Jude Medical (Abbott), Vitatron, and Wyeth-Ayerst/Wyeth Pharmaceuticals; serving as a consultant for Biosense Webster, Alta Thera Pharmaceuticals and Newron Pharmaceuticals P.s.A.; and receiving speakers fees or honoraria from Boston Scientific/Guidant CRM, Medtronic Inc, Alta Thera Pharmaceuticals, Daiichi Sankyo. and St Jude Medical (Abbott).

References

[1] Havakuk O, Viskin S. A tale of 2 Diseases: The History of Long-QT Syndrome and Brugada Syndrome. Journal of the American College of Cardiology. 2016; 67: 100–108.

[2] Dessertenne F. Ventricular tachycardia with 2 variable opposing foci. Archives des Maladies du Coeur et des Vaisseaux. 1966; 59: 263–272. (In French)

[3] Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. Heart. 2022; 108: 332–338.

[4] Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, *et al*. An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome. Circulation. 2020; 141: 418–428.

[5] Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, *et al*. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. Circulation. 2020; 142: 324–338.

[6] Cho Y. Left cardiac sympathetic denervation: an important treatment option for patients with hereditary ventricular arrhythmias. Journal of Arrhythmia. 2016; 32: 340–343.
[7] Viskin S. Cardiac Pacing in the Long QT Syndrome: review of available data and practical recommendations. Journal of Cardiovascular Electrophysiology. 2000; 11: 593–600.
[8] Bos JM, Crotti L, Rohatgi RK, Castelletti S, Dagradi F, Schwartz PJ, *et al*. Mexiletine Shortens the QT Interval in Patients with Potassium Channel-Mediated Type 2 Long QT Syndrome. Circulation: Arrhythmia and Electrophysiology. 2019; 12: e007280.
[9] Horváth B, Hézső T, Kiss D, Kistamás K, Magyar J, Nánási PP, *et al*. Late Sodium Current Inhibitors as Potential Antiarrhythmic Agents. Frontiers in Pharmacology. 2020; 11: 413.
[10] El-Sherif N, Turitto G, Boutjdir M. Acquired Long QT Syndrome and Electrophysiology of Torsade de Pointes. Arrhythmia & Electrophysiology Review. 2019; 8: 122–130.
[11] Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. American Heart Journal. 2007; 153: 891–899.
[12] Risk Categories for Drugs that Prolong QT & induce Torsades de Pointes (TdP). 2014. Available at: https://crediblemeds.org/druglist (Accessed: 6 March 2022).
[13] Khatib R, Sabir FRN, Omari C, Pepper C, Tayebjee MH. Managing drug-induced QT prolongation in clinical practice. Postgraduate Medical Journal. 2021; 97: 452–458.
[14] El-Sherif N, Turitto G, Boutjdir M. Acquired long QT syndrome and torsade de pointes. Pacing and Clinical Electrophysiology. 2018; 41: 414–421.
[15] Roden DM, Abraham RL. Refining repolarization reserve. Heart Rhythm. 2011; 8: 1756–1757.
[16] Roden DM. Taking the idio out of idiosyncratic—predicting torsades de pointes. Pacing and Clinical Electrophysiology. 1998; 21: 1029–1034.
[17] Roden DM, Johnson JA, Kimmel SE, Krauss RM, Medina MW, Shuldiner A, *et al*. Cardiovascular Pharmacogenomics. Circulation Research. 2011; 109: 807–820.
[18] Pinski SL, Eguia LE, Trohman RG. What is the Minimal Pacing Rate that Prevents Torsades de Pointes? Insights from Patients with Permanent Pacemakers. Pacing and Clinical Electrophysiology. 2002; 25: 1612–1615.
[19] Viskin S, Alla SR, Barron HV, Heller K, Saxon L, Kitzis I, Hare GF, Wong MJ, Lesh MD, Scheinman MM. Mode of onset of torsade de pointes in congenital long QT syndrome. Journal of the American College of Cardiology. 1996; 28: 1262–1268.
[20] Kaufman ES, Eckhardt LL, Ackerman MJ, Aziz PF, Behr ER, Cerrone M, *et al*. Management of Congenital Long-QT Syndrome: Commentary from the Experts. Circulation: Arrhythmia and Electrophysiology. 2021; 14: e009726.