# Isoproterenol suppresses recurrent torsades de pointes in a patient with long QT syndrome type 2

Keith Suarez, MD,* Ryan Mack, MD,* Evan L. Hardegree, MD,* Christopher Chiles, MD,* Javier E. Banchs, MD, FHRS,* Mario D. Gonzalez, MD, FHRS†

*From the *Division of Cardiology, Department of Medicine, Baylor Scott & White Health, Scott & White Memorial Hospital, Temple, Texas, and †Penn State Heart & Vascular Institute, Penn State Hershey Health, Hershey, Pennsylvania.*

## Introduction

Congenital long QT syndrome (LQTS) remains a major cause of sudden cardiac death in young adults.[1] Beta-blockers remain the mainstay pharmacologic intervention.[2] Lack of appropriate shortening of the action potential with emotions or exercise favors the occurrence of early afterdepolarization (EAD). Beta-blockers ameliorate the inflow of calcium into the cell during phase 2 of the action potential, reducing the occurrence of EAD. Mexiletine, ranolazine, and flecainide can be antiarrhythmic in some patients with long QT syndrome type 3. Nonresponders may require the implantation of a defibrillator. In patients with drug- or bradycardia-induced LQTS, temporary cardiac pacing and intravenous isoproterenol infusion have been used successfully to raise the heart rate and shorten the QT interval as a temporizing measure.[3] In contrast, adrenergic stimulation is usually avoided in patients with congenital LQTS owing to concern of inducing EADs that can trigger torsades de pointes (TdP).[4,5] This has led to the assumption that treatment with isoproterenol in this scenario would be counterproductive, although in the literature we did not find any study testing this hypothesis in humans. Beta-blockers and transvenous pacing are usually recommended as the initial therapy. We present the case of a female patient with drug-refractory congenital LQTS type 2 (LQT2) that responded quickly to an isoproterenol infusion.

## Case report

A 19-year-old woman with family history of LQT2 was admitted after an aborted episode of sudden cardiac death. She had delivered a healthy child 2 weeks earlier, and was awakened suddenly from sleep gasping for air prior to becoming unresponsive. Cardiopulmonary resuscitation was started immediately by her family and then continued by emergency medical personnel upon arrival.

Her initial rhythm was documented to be ventricular fibrillation, which was subsequently treated with external defibrillation. Resuscitation continued for approximately 20 minutes prior to return of spontaneous circulation. She was intubated, started on therapeutic hypothermia, and given a 1-time empiric dose of intravenous amiodarone during the initial resuscitation efforts.

Her initial electrocardiogram revealed a prolonged corrected QT (QTc) interval of 790 ms (Figure 1). Her initial laboratory values revealed potassium and magnesium levels of 3.5 mEq/L and 1.9 mg/dL, respectively. The patient had not been on QT-prolonging drugs and her toxicology screen was negative. Following completion of the hypothermia protocol and rewarming 48 hours later, she developed recurrent episodes of sustained TdP, requiring more than 20 defibrillations (Figure 2). Her electrical storm sustained despite the use of repeated doses of up to 3 mg intravenous propranolol followed by a propranolol infusion, sedation with propofol, and replacement of potassium and magnesium, keeping levels above 4.0 and 2.0 mEq/L, respectively. Owing to the lack of response and the critical condition of the patient, isoproterenol was administered intravenously (1–2 μg/min titrated to maintain a heart rate above 100 beats/min) prior to attempting transvenous pacing. Shortly after initiation of treatment, TdP was suppressed and no further recurrence was seen while on the infusion. Transvenous pacing was not required. Weaning off the isoproterenol was attempted on hospital day 3, resulting in reinitiation of TdP. The infusion was restarted, again eliminating further episodes of ventricular tachyarrhythmia. A transthoracic echocardiogram showed no structural abnormalities. In order to maintain suppression of TdP in the long term and at the same time to allow a taper of the isoproterenol, the patient received a dual-chamber implantable cardioverter-defibrillator and the atrial pacing lower rate limit was programmed at 80 beats/min. Owing to her family history of LQT2, genetic testing was performed looking specifically for the same mutation

**KEYWORDS** Electrical storm; Isoproterenol; Long QT syndrome; Postpartum; Prolonged QT; Sudden cardiac death
(Heart Rhythm Case Reports 2018;4:576–579)

**Address reprint requests and correspondence:** Dr Javier E. Banchs, Scott & White Memorial Hospital, 2401 S Street, MS-33-ST156, Temple, TX 76508. E-mail address: Javier.Banchs@bswhealth.org.



https://doi.org/10.1016/j.hrcr.2018.08.013

## KEY TEACHING POINTS

- Out-of-hospital cardiac arrest can be the initial presentation of congenital long QT syndrome.
- Patients with long QT syndrome type 2 presenting with torsades de pointes may respond favorably to intravenous isoproterenol, as shown in this case.
- Genetic counseling and testing is an important tool in the evaluation of family members of patients with congenital long QT syndrome.

that her cousin had. Presence of the latter was confirmed as a nonsense mutation in the *KCNH2* gene caused by a G2781A nucleotide change and leading to a W927X amino acid alteration. This mutation along with her clinical presentation was consistent with a diagnosis of congenital LQT2. The patient was discharged home in stable condition with no neurologic sequelae. She was started on oral nadolol 40 mg twice a day for further prevention of TdP. On review of older records, she had an electrocardiogram performed 4 years prior with a QTc interval of 470 ms (Figure 3). At the present time she is healthy, followed regularly in cardiology and device clinic, with no recurrence of syncope or shocks from her defibrillator. The patient underwent genetic counseling and her children and extended family were referred to genetic counseling and testing as appropriate.

## Discussion

The pathogenesis of LQT2 involves a loss-of-function mutation in the KCNH2-encoded human ether-a-go-go-related gene that contributes to the attenuation of the rapidly activating delayed rectifier potassium channel (IKr) during phase 3 of the action potential.[5] Loss of function of IKr can result in prolongation of the action potential and further activation of the L-type Ca2+ channels, an inward depolarization current. The activation of this channel occurs during the repolarization phase, resulting in EADs and further prolongation of the QT interval.[6] Specific myocardial cells that are most sensitive to changes in the IKr channel in the midventricular myocardium (M cells) create a "zone of functional refractoriness," and then an EAD may induce reentry, which can provoke TdP.[7,8]

Isoproterenol has been given successfully in TdP secondary to acquired QT prolongation, and is particularly helpful when bradycardia or prolonged pauses are present.[9,10] Adrenergic stimulation increases IKs (slow component of delayed rectifier K+ current) expression through activation of the protein kinase A, which should shorten the QTc under normal circumstances.[8] Isoproterenol has been avoided in all congenital LQTS owing to concern of an increase in EADs and therefore the probability of developing TdP.[9–11] However, in LQT2, which has defective function of IKr, activation of IKs may accelerate repolarization, compensating for the reduced IKr and reducing the inflow of calcium that can trigger EADs.

It should be remembered that administration of catecholamines has different effects than intrinsic activation of the sympathetic nervous system. This was demonstrated by a study in canine hearts in which intravenous infusion of catecholamines induced a greater reduction of the temporal dispersion of recovery than that observed during stimulation of intrinsic sympathetic inputs to the ventricles.[12] Furthermore, single-cell patch-clamp studies in myocytes and optical mapping of whole hearts from transgenic LQT2 rabbits suggests that the mechanism of EADs may be different under an adrenergic surge versus high sympathetic tone.[13] This finding is also supported by the changes in the QTc interval

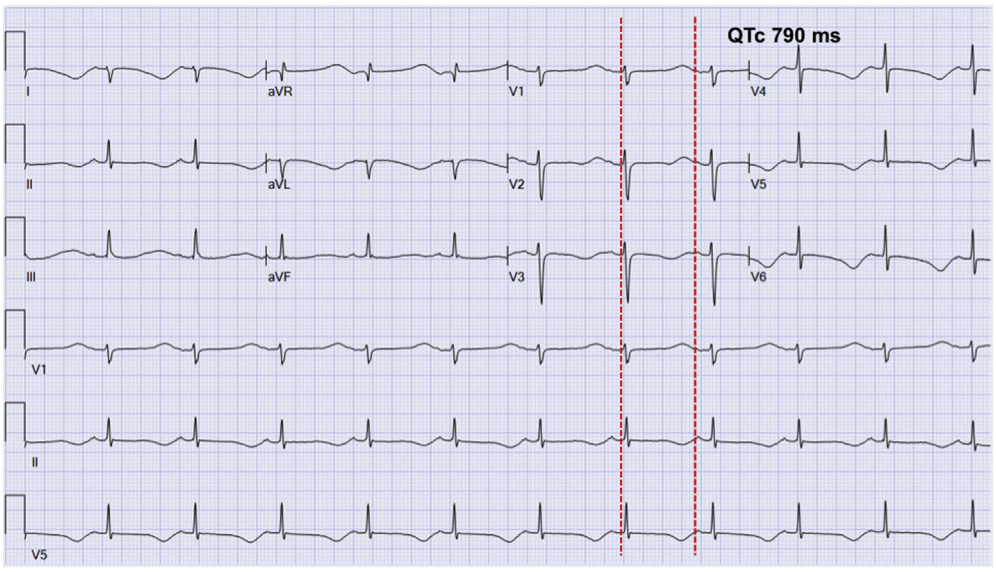


**Figure 1** Twelve-lead electrocardiogram in the intensive care unit after resuscitation and a single empiric dose of intravenous amiodarone administered in the emergency department. Corrected QT interval (QTc) measures 790 ms.

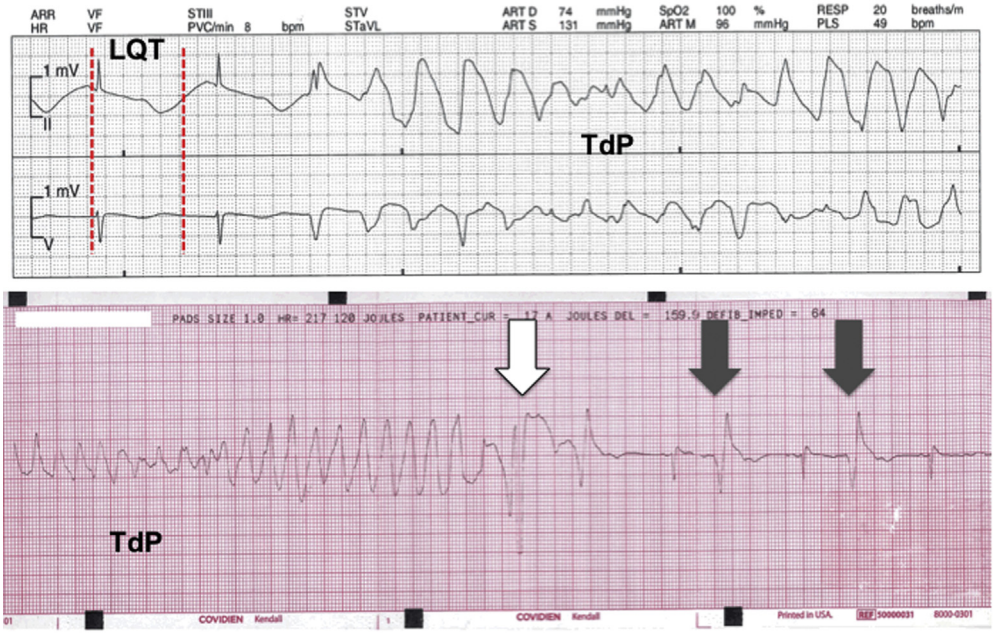


**Figure 2** Top panel shows electrocardiographic tracings from the telemetry monitor showing prolonged QT (LQT) and initiation of torsades de pointes (TdP) polymorphic ventricular tachycardia. Bottom panel corresponds to the electrocardiographic registration of 1 of multiple external defibrillations (*white arrow*) prior to initiation of intravenous isoproterenol. *Gray arrows* show premature ventricular contractions at the end of the QT interval that correspond to early afterdepolarizations.

seen in patients with LQT2 during an epinephrine infusion challenge, where at peak effect it lengthens and at steady state it approaches baseline measurements.[14] In contrast to LQT2, the prolongation of the QTc interval seen after giving epinephrine in patients with long QT syndrome type 1 is sustained beyond the peak effect, which raises the concern on whether the use of isoproterenol in this situation may be harmful. This finding has been reproduced in the lab on canine hearts with the use of the IKs channel inhibitor chromanol 293B.[15]

These observations are consistent with an antiarrhythmic effect of isoproterenol infusion specifically in patients with congenital LQT2. This disparate action of intrinsic autonomic activation versus isoproterenol administration may explain the apparent paradoxical antiarrhythmic action of isoproterenol in LQT2, like in the present case, with arrhythmic events triggered by arousal. Additional cases or a multicenter registry is needed to further confirm the safety and efficacy of isoproterenol in congenital LQT2.

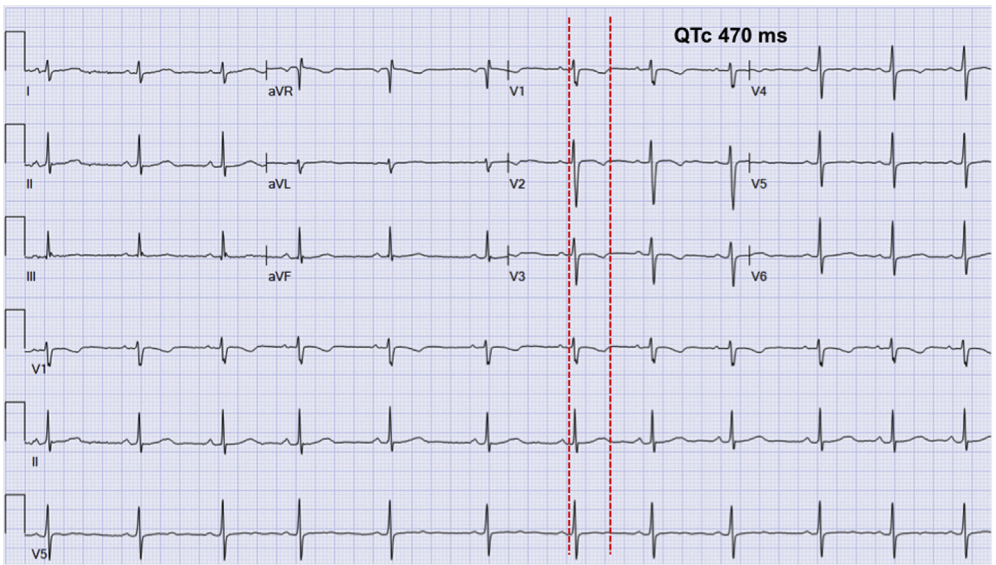


**Figure 3** Twelve-lead electrocardiogram 4 years prior to presentation. Corrected QT interval (QTc) measures 470 ms.

## Conclusion

We present a young woman with LQT2 and an electrical storm due to recurrent TdP that was refractory to beta-blockers, requiring multiple defibrillations and finally controlled with isoproterenol. This observation suggests that isoproterenol may be used as a temporizing measure in congenital long QT syndrome type 2.

## References


1. Kusumoto FM, Bailey KR, Chaouki AS, Deshmukh AJ, Gautam S, Kim RJ, Kramer DB, Lambrakos LK, Nasser NH, Sorajja D. Systematic review for the 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72:1653–1676.
2. Abu-Zeitone A, Peterson DR, Polonsky B, McNitt S, Moss AJ. Efficacy of different Beta-blockers in the treatment of long QT syndrome. J Am Coll Cardiol 2014;64:1352–1358.
3. Thomas SH, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. Br J Clin Pharmacol 2016;8:420–427.
4. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. J Am Coll Cardiol 2000;35:778–786.
5. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome. Gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
6. Wu J, Naiki N, Ding WG, Ohno S, Kato K, Zang WJ, Delisle BP, Matsuura H, Horie M. A molecular mechanism for adrenergic-induced long QT syndrome. J Am Coll Cardiol 2014;63:819–827.
7. Huang X, Kim TY, Koren G, Choi BR, Qu Z. Spontaneous initiation of premature ventricular complexes and arrhythmias in type 2 long QT syndrome. Am J Physiol Heart Circ Physiol 2016;311:1470–1484.
8. Shimizu W. Effects of sympathetic stimulation on various repolarization indices in the congenital long QT syndrome. Ann Noninvasive Electrocardiol 2002;7:332–342.
9. Khan IA. Clinical and therapeutic aspects of congenital and acquired long QT syndrome. Am J Med 2002;112:58–66.
10. Shimizu W, Ohe T, Kurita T, Takaki H, Aihara N, Kamakura S, Matsuhisa M, Shimomura K. Early afterdepolarizations induced by isoproterenol in patients with congenital long QT syndrome. Circulation 1991;84(5):1915–1923.
11. Shimizu W, Ohe T, Kurita T, Shimomura K. Differential response of QTU interval to exercise, isoproterenol, and atrial pacing in patients with congenital long QT syndrome. Pacing Clin Electophysiol 1991;14:1966–1970.
12. Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. Circ Res 1964;14:44–60.
13. Liu GX, Choi BR, Ziv O, Liv W, de Lange E, Qu Z, Koren G. Differential conditions for early after-depolarizations and triggered activity in cardiomyocytes derived from transgenic LQT1 and LQT2 rabbits. J Physiol 2012;590:1171–1180.
14. Shimizu W, Aiba T, Antzelevitch C. Specific therapy based on the genotype and cellular mechanism in inherited cardiac arrhythmias. Long QT syndrome and Brugada syndrome. Curr Pharm Des 2005;11:1561–1572.
15. Burashnikov A, Antzelevitch C. Block of I(Ks) does not induce early afterdepolarization activity but promotes beta-adrenergic agonist-induced delayed afterdepolarization activity. J Cardiovasc Electrophysiol 2000;11:458–465.