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## Recurrent Torsades with Refractory QT Prolongation in a 54-Year-Old Man

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

**Patient:** Male, 54  
**Final Diagnosis:** Recurrent torsades de pointes  
**Symptoms:** Sudden cardiac death  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Cardiology

**Objective:** Congenital defects/diseases

**Background:** QT prolongation is a common, easily overlooked clinical problem with potentially dire consequences. Drug-induced and congenital forms are not mutually exclusive, but are treated differently. Here, we present a case of cryptogenic underlying congenital long QT syndrome (cLQTS) successfully treated with isoproterenol, a drug contraindicated in most congenital forms of this condition.

**Case Report:** We present the case of a 54-year-old man who experienced severe QT prolongation after drug administration followed by recurrent episodes of torsade de pointes (TdP) with subsequent ventricular fibrillation (VF) arrest unresponsive to typical therapy. After failing electrolyte repletion, magnesium, amiodarone, and lidocaine, the patient was started on an isoproterenol drip to achieve a heart rate of at least 90 beats per minute (bpm). Isoproterenol resulted in an immediate near-normalization of his QT interval and cessation of his recurrent TdP. The patient was subsequently found to have a mutation of undetermined significance in the KCNQ1 gene, which is implicated in long QT syndrome type 1 (LQT1). Although isoproterenol is contraindicated in LQT1, our patient had an astonishingly therapeutic benefit.

**Conclusions:** After reviewing the electrophysiology of the delayed rectifier potassium current as it relates to long QT syndrome, we propose a mechanism by which our patient's specific mutation may have allowed him to derive benefit from isoproterenol treatment. We believe that there are patients with variants of LQT1 who can be safely treated with isoproterenol.

**MeSH Keywords:** Death, Sudden, Cardiac • Isoproterenol • KCNQ1 Potassium Channel • Long QT Syndrome • Torsades de Pointes

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/912326>



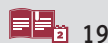
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## Background

QT interval prolongation is a commonly encountered clinical problem that can be life-threatening. Acquired long QT syndrome (LQTS) is caused by medications or electrolyte disturbances, and therapy consists of medication discontinuation and correcting the underlying pathology. Here, we present a case of treatment-resistant QTc prolongation with recurrent episodes of torsades de pointes treated with isoproterenol in a patient subsequently found to have a genetic polymorphism in the KCNQ1 gene associated with congenital long QT syndrome type 1 (LQT1).

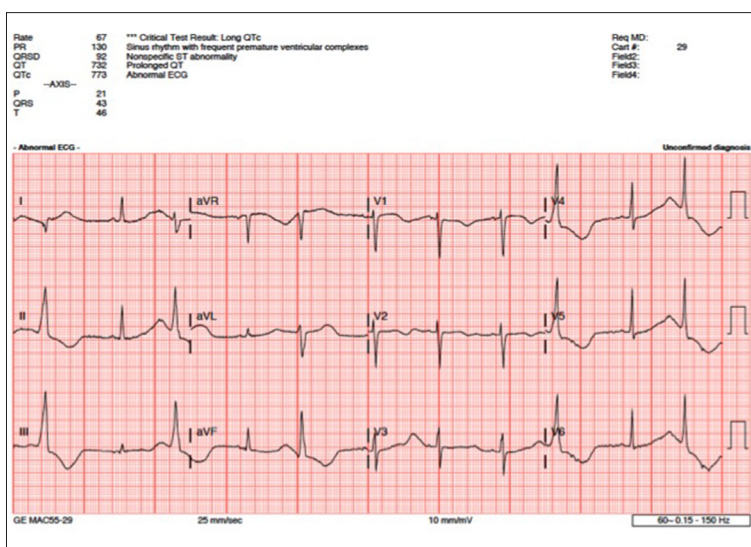
## Case Report

A 54-year-old white man with past medical history significant for hypertension, hyperlipidemia, chronic kidney disease, and type 2 diabetes mellitus was transferred to our institution's Intensive Care Unit (ICU) after suffering an episode of ventricular fibrillation (VF) arrest, which occurred at a neighboring community hospital, where he had been admitted for treatment of alcohol-induced pancreatitis. He had been receiving intravenous fluids, ondansetron, and opioid analgesics for 2 days prior to suffering a witnessed VF arrest. Advanced cardiac life support (ACLS) was initiated and return of spontaneous circulation (ROSC) was obtained with a single defibrillation. The patient immediately returned to his baseline mental status. Post-arrest evaluation showed no electrolyte abnormalities, signs of active myocardial ischemia, or hypoxia, and a previous echocardiogram did not show evidence of structural heart disease. His electrocardiogram (EKG), however, revealed prolongation of his corrected QT interval (QTc) and broad, late-peaking T waves. He had no family history of QT prolongation, arrhythmias, or sudden cardiac death.

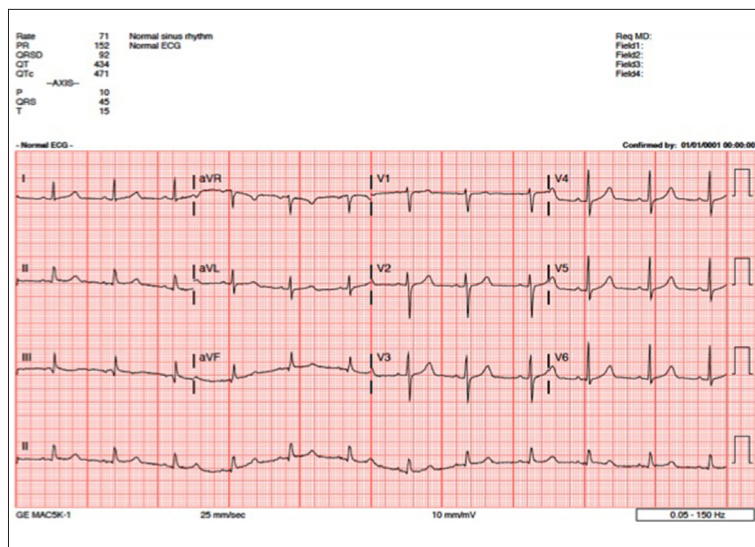
The patient was started on an amiodarone drip at the referring hospital and subsequently transferred to our facility for further management. Initial EKG upon arrival showed QTc prolongation at 773 ms and frequent premature ventricular contractions (PVCs) (Figure 1). Approximately 30 min after arrival, the patient suffered another VF arrest, terminated by defibrillation. Telemetry revealed a preceding episode of torsades de pointes (TdP). His opioid analgesics and amiodarone drip were discontinued at that time and the patient's potassium level was restored to the upper limit of normal. Despite initial improvement in his QTc, he developed recurrent TdP culminating in VF arrest. After ROSC, magnesium and lidocaine drips were initiated, resulting in lengthening of his QTc to 816 ms. Finally, isoproterenol was started with a goal HR of 90 bpm. With this therapy, his QTc quickly improved to 490 ms, and he had no further TdP. The patient underwent cardiac catheterization, which was without significant atherosclerotic disease, and placement of an implantable cardioverter defibrillator (ICD). Genetic testing identified a mutation of unknown significance in the KCNQ1 gene, which is associated with LQT1. A review of several previous EKGs obtained 8 years prior to this event revealed mild QT prolongation (<500 ms) with normal T wave morphology (Figure 2). The patient was discharged on beta-blocker therapy with metoprolol. On subsequent follow-up, the patient's QTc continued to be mildly prolonged (450–480 ms).

## Discussion

Here, we present the case of a patient with previously unrecognized congenital LQT1, treated with isoproterenol. Interestingly, beta agonists are contraindicated in LQT1 as increased sympathetic tone precipitates arrhythmias in this specific subtype of LQTS. In this report we describe the definition and mechanism of QT prolongation, discuss the electrophysiology of the



**Figure 1.** EKG upon ICU admission, showing severely prolonged QT interval with frequent PVCs.



**Figure 2.** Baseline EKG showing QTc prolongation with largely normal T wave morphology.

slow component of the delayed rectifier potassium current ( $I_{Ks}$ ), encoded by the *KCNQ1* gene in mediating myocardial repolarization, and discuss a putative mechanism by which our patient's particular mutation caused him to have a strong therapeutic benefit with isoproterenol.

Although there are differences of opinion on what constitutes QTc prolongation, it is most frequently defined as QTc >430 ms in men and >450 ms in women [1]. In the majority of cases, QT prolongation is acquired, often due to prescribed medications, including many antiarrhythmics, antipsychotics, and some antibiotics [1–3]. In contrast, congenital long QT Syndrome (cLQTS) occurs due to functionally significant mutations in one of 5 genes located on chromosomes 3, 7, 11, and 21. Each associated gene encodes an ion channel or component thereof. In most cases the produced ion channels mediate currents active during the repolarization phase (phase 3) of the myocardial action potential [3]. Congenital and acquired LQTS, however, are not mutually exclusive. In fact, Roden et al. [4] estimate that 5–10% of patients with drug-induced LQTS do carry potentially predisposing mutations in one of these 5 genes [4–6]. Although numerous mutations have been described in each of these gene *loci*, the clinical significance of many are unknown.

As in most cases of cLQTS, the molecular pathology that contributed to our patient's susceptibility to QT prolongation was attributable to a protein channel that mediated myocardial repolarization. Specifically, his genetic testing revealed a missense mutation in codon 12 of the *KCNQ1* gene, which resulted in the substitution of glutamic acid for a moderately conserved lysine residue located in the cytoplasmic C-terminal region of the resulting protein [7]. This particular mutation is estimated to be present in 0.002% of the population and has been implicated in cases of cLQTS [3]. *KCNQ1*, the most commonly mutated gene in cLQTS, encodes the pore-forming subunits of a

potassium channel responsible for mediating the slow component of the delayed rectifier potassium current [8,9]. The delayed rectifier potassium current is the most prominent current active during myocardial repolarization, and is composed of fast ( $I_{Kr}$ ) and slow ( $I_{Ks}$ ) components, which are mediated by different potassium channel protein complexes. Potassium efflux through these channels allows for rapid repolarization of the cell membrane during phase 3 of the myocardial action potential [2,10,11]. Clinically significant mutations in proteins mediating either component of the delayed rectifier potassium current cause various forms of cLQTS.

In contrast to cLQTS, which can be caused by mutations disrupting the function of several different ion currents, drug-induced LQTS (diLQTS) is nearly always due to blockade of  $I_{Kr}$ , the largest and most important component of the delayed rectifier potassium current [2,10,11]. The contribution of  $I_{Ks}$  to maintaining action potential duration (APD) is increased in situations where drug-induced  $I_{Kr}$  blockade exists. When the channel mediating  $I_{Ks}$  is likewise mutated and unable to augment potassium efflux, APD and QT interval prolongation occur [2,4,9]. This concept has been verified experimentally by Jost et al. [12], who showed that the degree of APD prolongation in human myocytes with chemically-induced  $I_{Kr}$  blockade is mitigated by increasing potassium efflux through  $I_{Ks}$  [2,12]. Roden and Yang [9] have championed the term repolarization reserve to describe this observed interdependence of repolarizing currents, which serves to maintain APD within physiologic limits [9,13]. The concept of repolarization reserve nicely explains the dramatic increase in our patient's QTc after exposure to QT-prolonging medications. In his case, drug challenge with resulting blockade of  $I_{Kr}$  unveiled a predisposition towards QT prolongation, which is explained by an inability to augment potassium efflux through a congenitally defective channel mediating  $I_{Ks}$ .

In many patients with LQT1, adrenergic stimulation in the form of increased physical or emotional stress precipitates episodes of QT prolongation and TdP. This has been experimentally verified by numerous investigators who have demonstrated increased QT interval prolongation, increased transmural dispersion of repolarization, and increased arrhythmogenicity in cases of  $I_{Ks}$  dysfunction with subsequent isoproterenol challenge [3,14,15]. In fact, Jost [12] and others report that beta adrenergic stimulation is required to produce TdP in cases of  $I_{Ks}$  blockade [3,12,15]. Why then did our patient experience such a dramatic improvement in his QTc with administration of isoproterenol? Proposing an answer to this question will require a brief look at the many electrophysiologic actions of this drug. Isoproterenol is a non-selective beta agonist that can be used in cases of recurrent torsades, especially where transvenous or transcutaneous pacing is not available, or as a bridge to such therapy [2,16–18]. Mechanistically, isoproterenol increases the activity of multiple ion currents, including calcium-activated  $I_{Ks}$ , calcium-activated chloride current ( $I_{Cl(Ca)}$ ), and the sodium calcium exchange current ( $I_{Na-Ca}$ ) [3,16,19]. In patients with dilQTS, isoproterenol decreases the QT interval by preferentially increasing potassium efflux through  $I_{Ks}$  [3]. Its deleterious effects in congenital LQT1 are ostensibly due to a net increase in sodium influx secondary to preferential augmentation of the sodium calcium exchange current in the presence of a mutated  $I_{Ks}$ -mediating channel [3]. In our patient's case, we postulate that isoproterenol "rescued" the defective channel, preferentially increasing potassium efflux through it. It is likely that our patient's mutation of undetermined significance in

KCNQ1 resulted in a channel that failed to fulfill its role in mitigating QTc prolongation with  $I_{Kr}$  blockade; however, the defective channel remained exquisitely sensitive to augmentation of  $I_{Ks}$  with isoproterenol. This suggests that some patients with clinically silent mutations in KNCQ1 have an intermediate phenotype in which isoproterenol administration produces a particularly therapeutic effect.

## Conclusions

In conclusion, our patient had a mutation in a protein channel responsible for mediating  $I_{Ks}$ , which made him particularly susceptible to QT prolongation with subsequent QT-prolonging drug challenge. Treatment with isoproterenol resulted in abrupt near-normalization of his corrected QT interval despite his underlying mutation. Further investigation is required to determine if there are subsets of clinically asymptomatic carriers of mutated LQT1-associated genes who can safely be treated with isoproterenol in instances of severe QT prolongation or TdP. At present, however, isoproterenol remains contraindicated in patients suspected of having cLQTS [3].

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