# Arrhythmogenesis in Long QT Syndrome
## Mechanistic and Therapeutic Insight from an *in silico* Human Model

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## Introduction

QT prolongation is a major risk factor of sudden cardiac death in both congenital and acquired long QT syndrome (LQTS). Although the genetic or ionic causes of LQTS can vary widely, a key question remains whether they share a common mechanism of arrhythmia initiation.

In this study, 1D, 2D, and whole heart computational simulations were used to investigate the mechanisms of arrhythmogenesis in the different LQTS subtypes. Our results reveal a common underlying mode of arrhythmia initiation that is consistent with the specific clinical characteristics of different LQTS subtypes, which leads to new insights for a common therapeutic strategy.

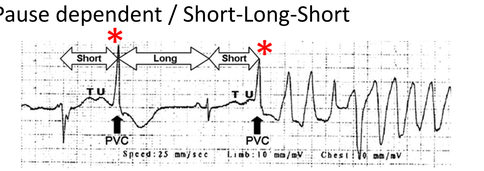
## Arrhythmogenesis in Long QT Syndromes

**Different genotypes**
**Different ion channels**

**LQT1 KCNQ1 (IKs)**
D242N
S225L
**LQT2 KCNH2 (IKr)**
R328C
P347S
**LQT3 SCN5A (INaL)**
ΔKPQ
I1768V

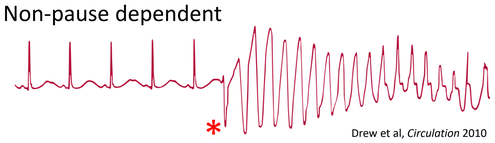
**Common Clinical Arrhythmia Initiation Patterns**

Pause dependent / Short-Long-Short



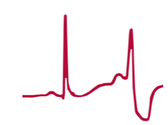

Morita, Wu, Zipes, *Lancet* 2008

Non-pause dependent



Drew et al, *Circulation* 2010

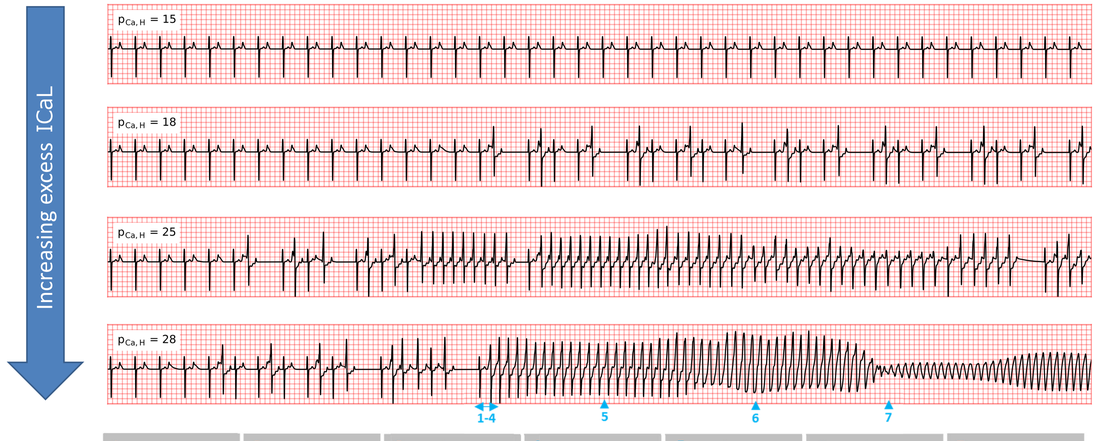
**R-on-T phenomenon**

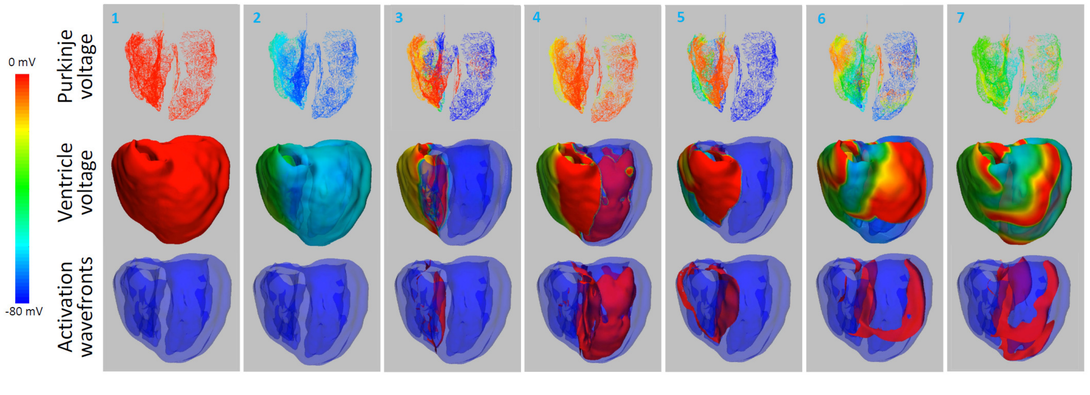


Arrhythmia initiates with an “R-on-T”

## Full spectrum of LQTS arrhythmias

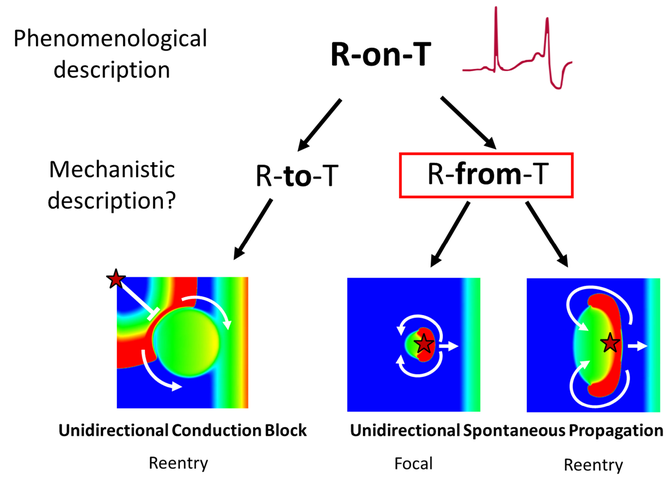
Computer simulations reproduce the full spectrum of LQTS arrhythmias with increasing excess ICaL current, including T-wave alterans, PVCs, focal trains, and reentrant arrhythmias.




The arrhythmias observed in our LQTS simulations demonstrate a new mode of initiation, where a PVC spontaneously emerges out of the repolarization gradient. These PVCs manifest as an “R-on-T” on ECG and then propagate unidirectionally, either resulting in focal trains or directly degenerating into reentrant arrhythmias. This mode of initiation was seen across the different LQTS subtypes, including LQT1, 2, and 3.

## Not all R-on-T are created equal!

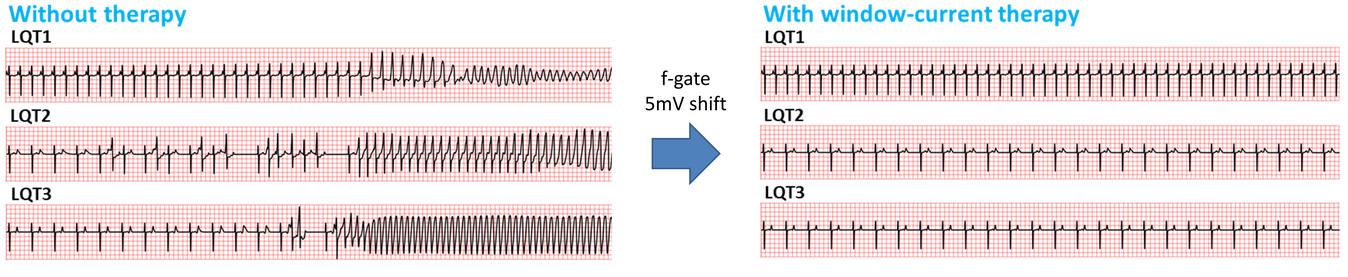



**“R-on-T”** is a phenomenological term to describe a ectopic R-wave superimposed on a T-wave. The mechanism we see in LQTS requires us to distinguish “R-on-T” into distinct “R-to-T” and “R-from-T” mechanisms.

**“R-to-T”** is the traditional arrhythmogenesis mechanism in which an external PVC runs into a vulnerable repolarizing region, causing unidirectional conduction block and reentry.

In **“R-from-T”** the PVC emerges directly from the repolarization gradient, with no external source. Depending on the geometry, this unidirectionally propagating PVC can either form a focal train or directly degenerate into reentry, without the need for any additional substrate. This is the mechanism we observe in LQTS.

## Common therapeutic target for different LQTS subtypes




As this mode of initiation critically depends on the increased excess ICaL current in the presence of Long QT, we can devise a common therapeutic target. As ICaL window current is known to be critical for the instability to form, we perform a small 5mV shift the ICaL calcium-dependent inactivation curve (f-gate). Despite the genotypic differences between the LQTS subtypes, this small change is able to single-handedly destroy the arrhythmias seen in LQT1, LQT2, and LQT3.