In Silico Investigation of Cardiac Arrhythmia Susceptibility in Long QT Phenotype

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- Anthony Owusu- Mensah obtained a master of science degree in Electronics Engineering from Norfolk State University (NSU), USA in 2019.
- He is currently studying at Old Dominion University (ODU) for a PhD in Biomedical Engineering under the supervision of Dr. Michel Audette (ODU) and Dr. Makarand Deo (NSU).
- His interest lies in developing working numerical single cell biophysical cardiac myocyte models and integrating these models into 3D anatomically realistic models to study mechanisms of arrhythmia initiation and maintenance.

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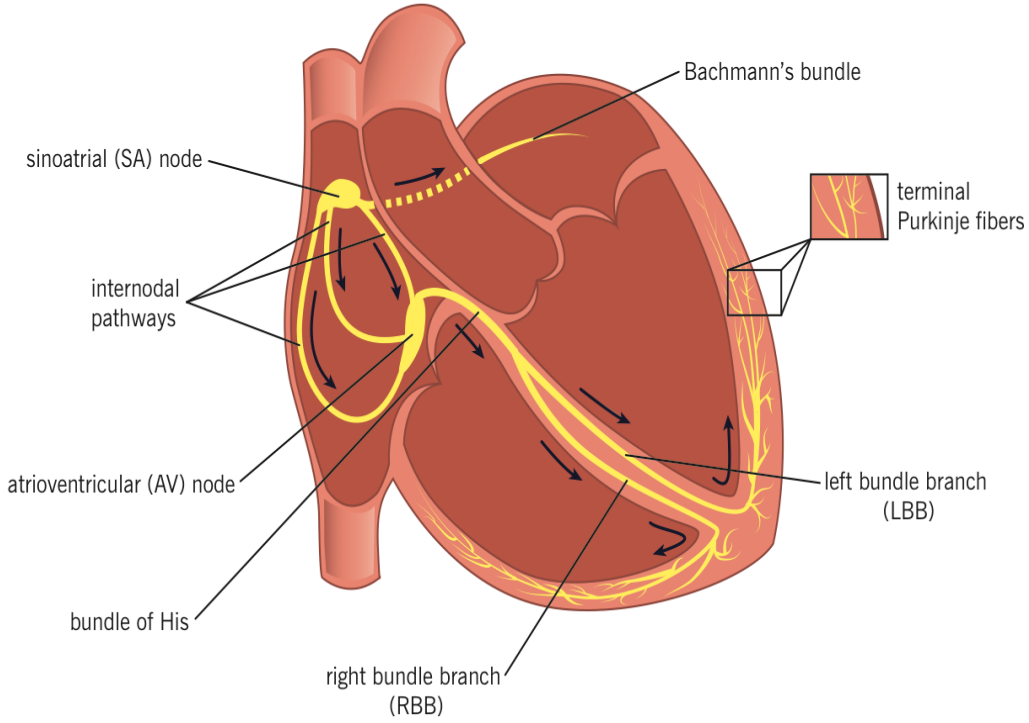
Aim and contributions of paper

- In our paper we aimed at:
  - Utilizing anatomically and electrophysiologically realistic numerical simulations to elucidate the mechanisms of arrhythmia initiation in the presence of blockade in rapid component of delayed rectifier potassium current, I_{Kr}.
- Contributions are as follows:
  - A realistic anatomical model was used to gain insight in LQT2.
  - The effects of I_{Kr} blockade on AP morphology are more severe in cardiac Purkinje cells than that in ventricular myocytes.
  - The loss of I_{Kr} function increases the spatial dispersion of repolarization and refractoriness resulting into increased vulnerability to reentry and ventricular tachycardia.
  - The His-Purkinje system plays an active role during maintenance of tachycardia.

Electrophysiology of the heart (Sinus Rhythm)

- The heart consist of 4 chambers – (2 Upper chambers- Right atrium (RA) & Left atrium (LA) and 2 lower chambers – Right Ventricle (RV) & Left Ventricle (LV).
- SA node is spontaneous – Initiates rhythmic pulses(in the form of action potentials) without any neural stimulation.
- Each pulse from SA propagates through AV node before it gets to the ventricles.
- Propagation delay through the AV node allows adequate time for atrial contraction and ventricular filling.
- From AV node electrical impulses propagates through the His-Purkinje system (PS) to the ventricles. This results in ventricular contraction.
- Any disruption to this rhythm is termed arrhythmia.

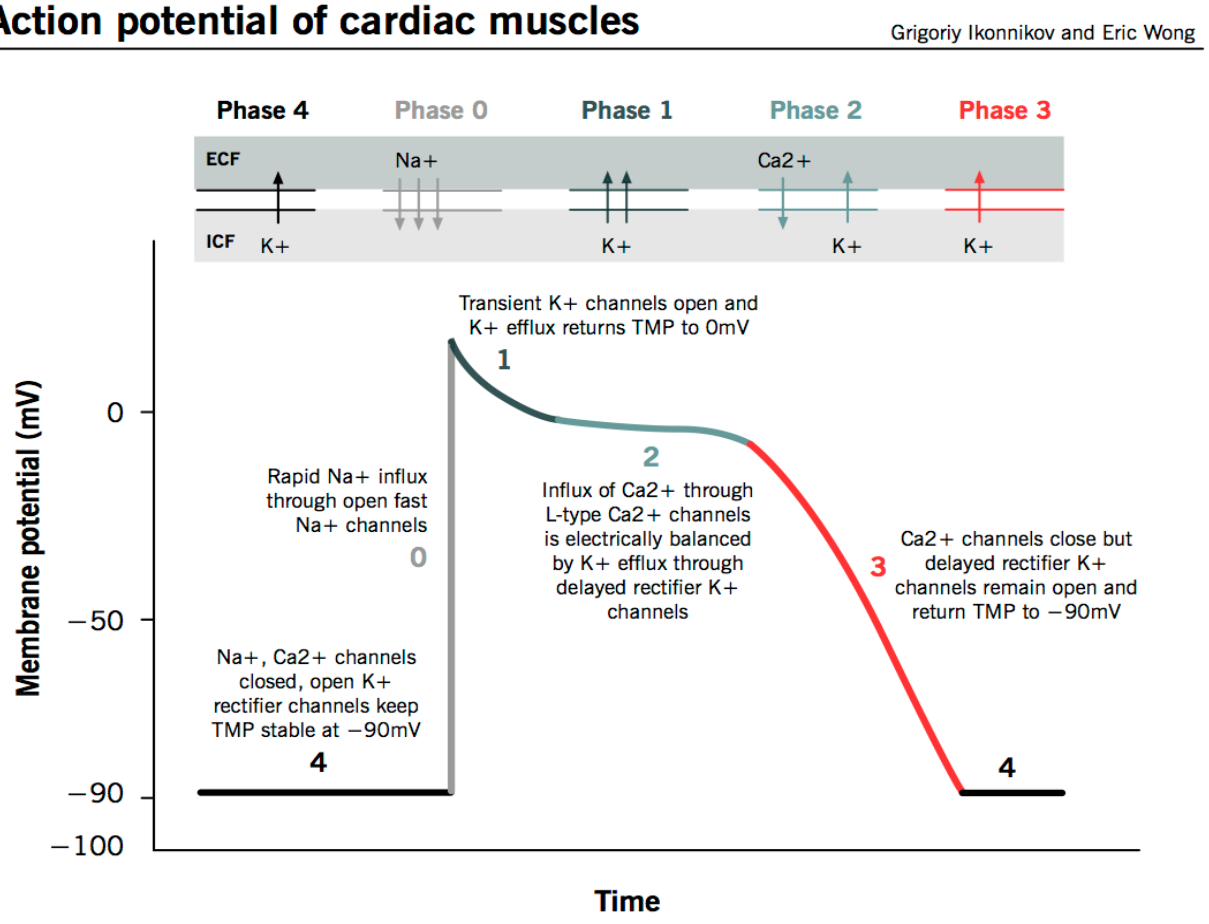


Electrical Conduction System of Heart

Ikonnikov and Yelle, McMaster Pathophysiology Review.

Cardiac Action Potential (AP)

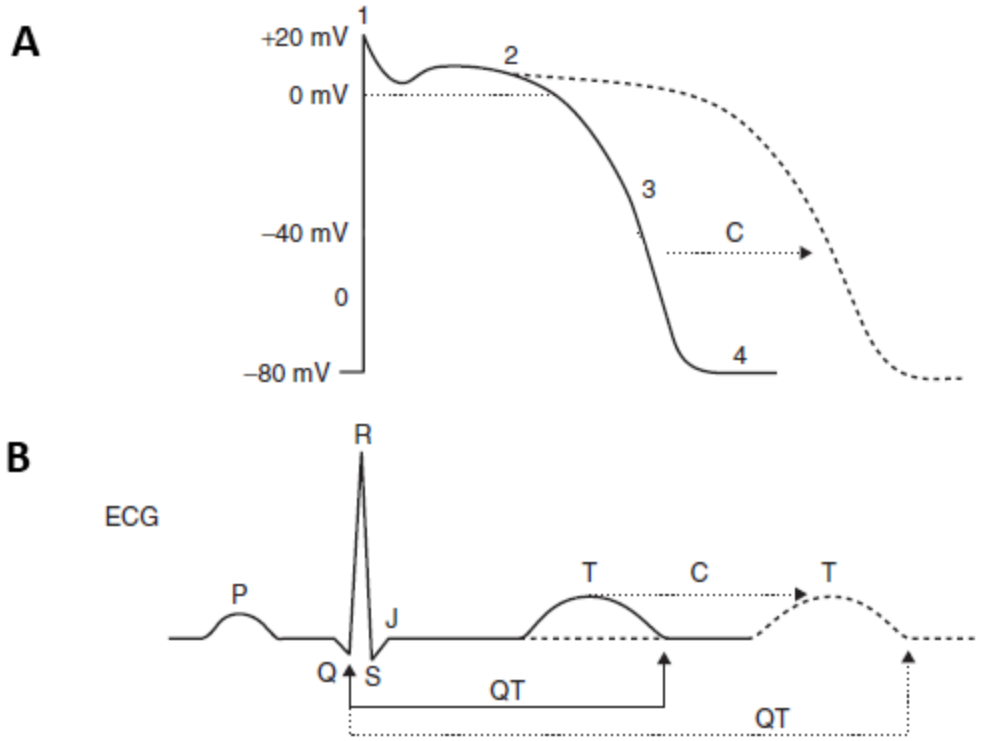
- AP is the electrical potential of an excitable cell.
- All or nothing events, regenerative, propagating and results when a threshold voltage is reached.
- Phases of action potential (AP)
  - 0 Upstroke
  - 1 Early repolarization
  - 2 Plateau
  - 3 Final repolarization
  - 4 resting



Ikonnikov and Yelle, McMaster Pathophysiology Review.

Long QT Syndrome (LQTS)

- Acquired or congenital cardiac disorder- manifest as QT prolongation on an ECG.
- Associated with life-threatening ventricular arrhythmias and sudden cardiac death.
- Common LQTS types – LQT1 (decrease in I_{Ks}), LQT2 (decrease in I_{Kr}) and LQT3 (increase in I_{Na}).
- *hERG* gene encodes I_{Kr} current.
- Ion channel mutation in *HERG* leading to LQTS causes complete or partial blockade of I_{Kr} current.
- Myriad of drugs (E-4031, dofetilide etc.) block I_{Kr} leading to drugs-induced LQTS.
- Arrhythmia due to LQT2 phenotype well documented – Mechanism however is not clearly understood.

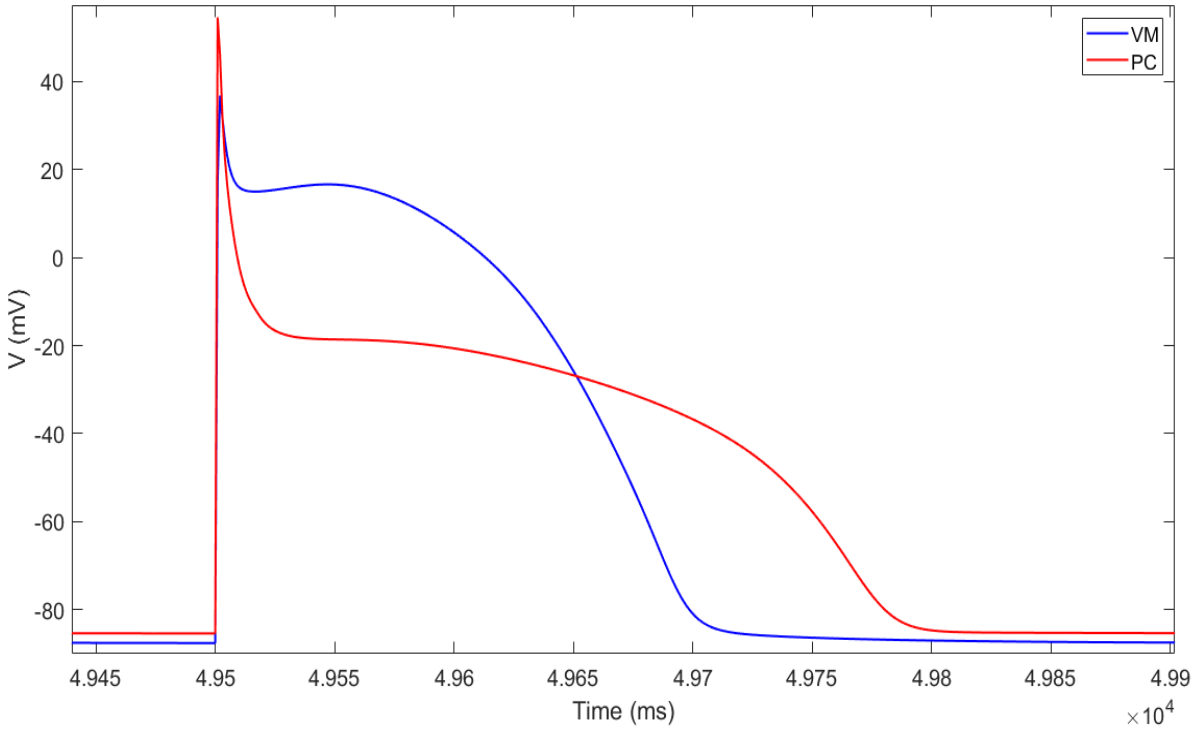


Ventricular AP prolongation (**A**) results in QT prolongation (**B**).

Crumb et al., Current protocols in pharmacology, 2003.

Single Cell Biophysical Modeling

- Single cell simulations were performed in Bench – an openCARP utility [1].
- Simulations were performed using a rabbit ventricular myocyte (VM) [2] and Purkinje cell (PC) [3] ionic models.
- I_{Kr} was blocked from 0% (Control) to 100% (Complete blockade).
- Both models were paced at a BCL of 500 ms for 50s to attain steady state.
- Effect of I_{Kr} blockade on AP durations at 50% (APD_{50}) and 90% (APD_{90}) repolarization was studied for both models.



Ventricular AP (blue) and Purkinje AP (red) from single cell simulation

1. https://opencarp.org/documentation/user-manual.
2. Mahajan et al., Biophys. J., 2008.
3. Aslanidi et al., Biophys. J., 2010.

3D Anatomical Modeling

- The 3D simulations were performed using a rabbit ventricular anatomical tetrahedral finite element mesh integrated with a PS.
  - 547,680 myocardial nodes
  - 862,515 nodes including surrounding bath and cavities
- The PS was a branching network of 1D cubic Hermite elements.
  - PS nodes were separated by gap junctions modeled as fixed resistors.
  - Purkinje Myocardial junctions modeled as fixed resistors.

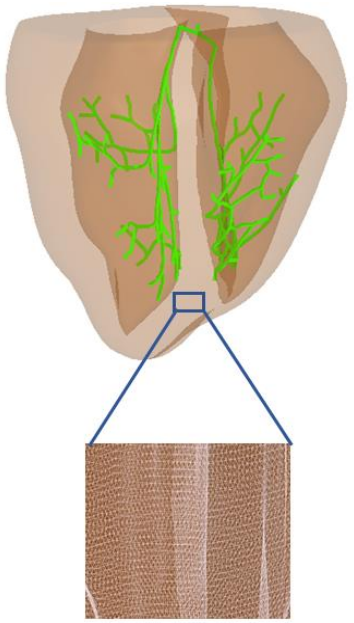
Governing Bidomain Equations

$$\nabla.(\bar{\sigma}_i + \bar{\sigma}_e)\nabla\Phi_e = -\nabla.\bar{\sigma}_i\nabla V_m - I_e \quad (1)$$

$$\nabla.\bar{\sigma}_i\nabla V_m = -\nabla.\bar{\sigma}_i\nabla\Phi_e + \beta I_m \quad (2)$$

$$I_m = C_m\frac{\partial V_m}{\partial t} + I_{ion}(V_m, \nu) - I_{trans} \quad (3)$$

I_m - Transmembrane current
$\bar{\sigma}_i, \bar{\sigma}_e$- Intra and extracellular conductivities.
Φ_i, Φ_e - Intra and extracellular potentials.
β - surface-to-volume ratio of the cardiac cells.
I_{trans} -Transmembrane current density stimulus as delivered by the intracellular electrode.
I_e - Extracellular stimulus current density, C_m - Membrane capacitance per unit area.
V_m - Transmembrane voltage
I_{ion} - Current density flowing ionic channels
ν – Variables influencing membrane voltage

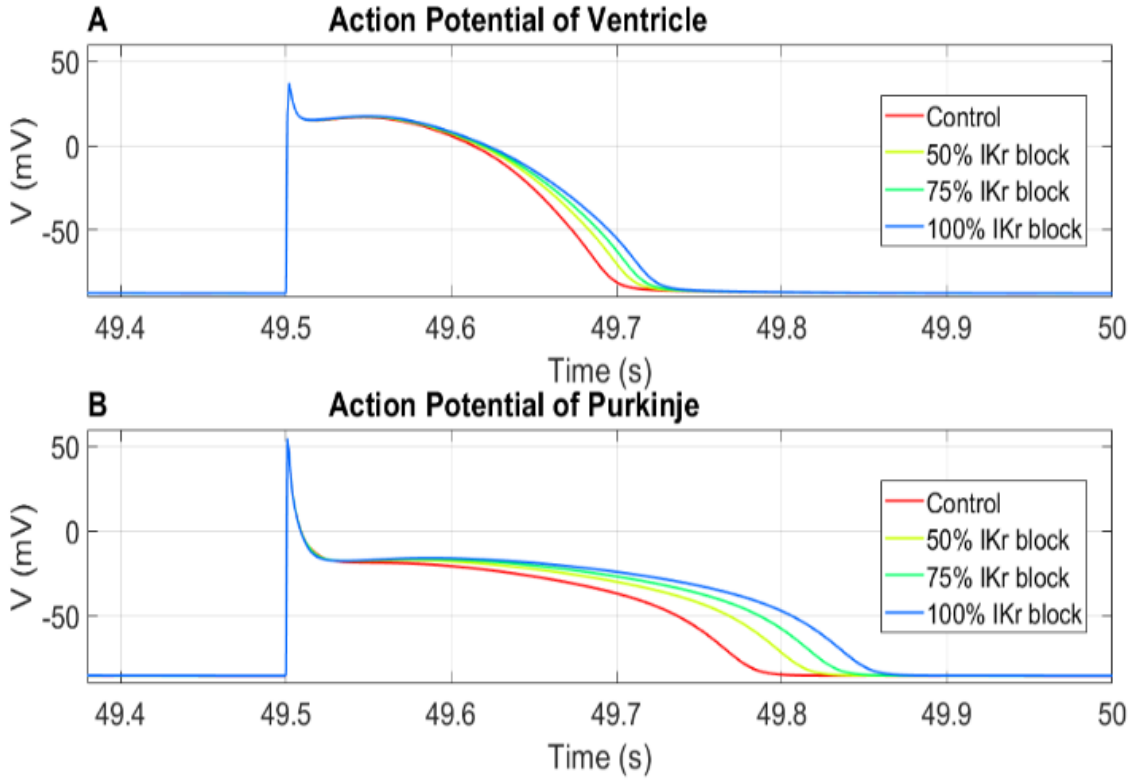


3D computational mesh of rabbit ventricles integrated with a PS (green color) used in our study. The inset shows the mesh discretization.

Reentry Induction Protocol

- Reentry was induced using S1-S2 protocol for both Control and 100% I_{Kr} blockade.
- Myocardial conductivity was reduced by 50% to lengthen reentrant path.
- Both models were paced at 500 ms BCL for 5s to simulate sinus rhythm (S1).
- Ectopic stimulus (S2) was then delivered to a quarter region of the RV.
- S1-S2 interval was varied between 200 ms – 300 ms in 10 ms steps to determine a window of vulnerability to reentry.
- S1-S2 duration was varied in steps of 1-5 ms within the window of vulnerability to allow fine control of the timing at which reentry occurs.
- Reentry activations sustained beyond 500 ms were classified as tachycardia.

Single Cell Biophysical Modeling Results

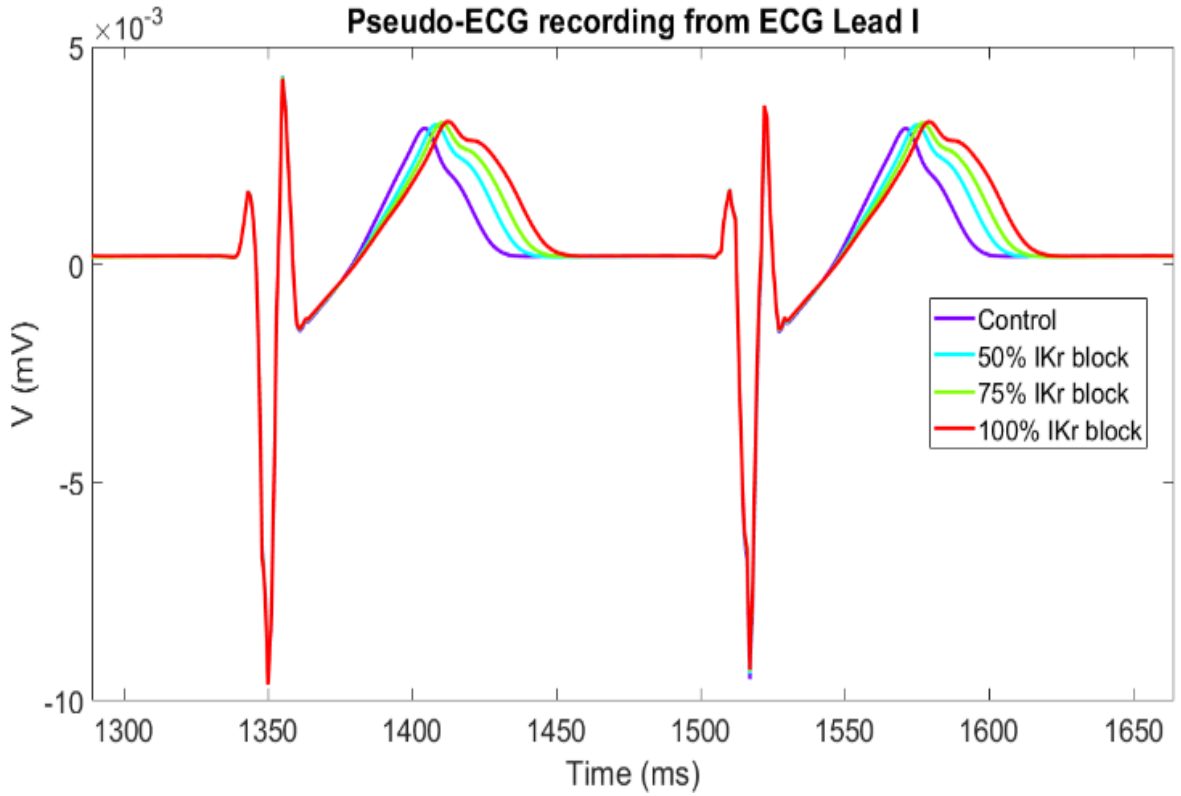


I_{Kr} block	VM		PC	
	APD_{90} (ms)	% Prolongation	APD_{90} (ms)	% Prolongation
0% (Control)	192	0	267	0
50%	203	6	299	12
75%	209	9	317	19
100%	216	13	336	26

- PCs have inherently longer AP duration and prominent notching than VMs.
- I_{Kr} blockade prolonged AP duration in both cell types.
- Effect of I_{Kr} blockade was severe in PCs than VMs (26% vs 13% prolongation for 100% I_{Kr} blockade).

Pseudo-ECG from 3D Anatomical Modeling

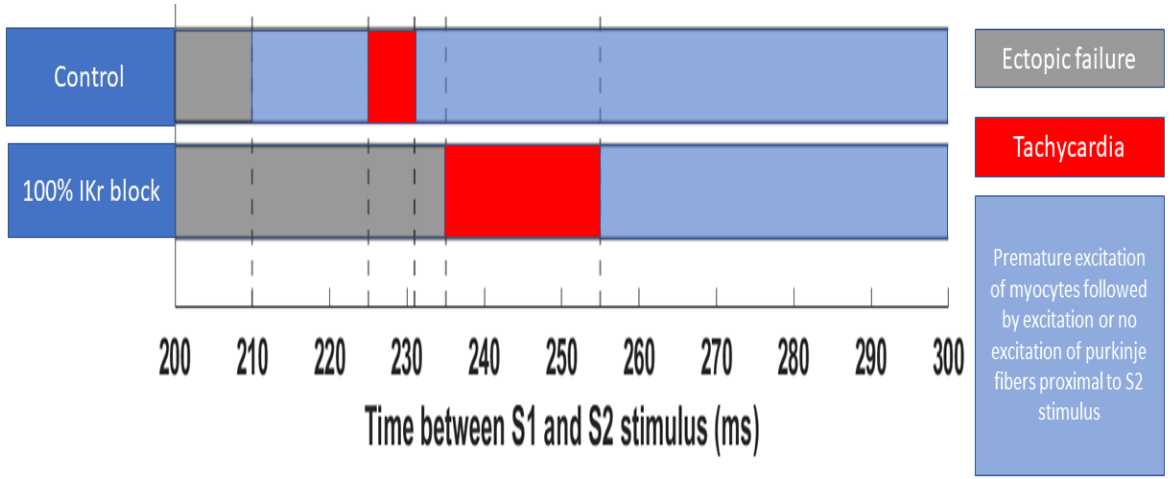
- Pseudo-ECGs were obtained by extrapolating extracellular potentials to approximate limb locations for leads I,II and III .
- Blockade of I_{Kr} produced QT prolongation. QT duration increased as I_{Kr} conductance was reduced(26% prolongation for 100% I_{Kr} block).
- Notch prominence in T-wave increased as I_{Kr} blockade increased.
- QT prolongation in the model was in agreement with experimental and clinical findings.

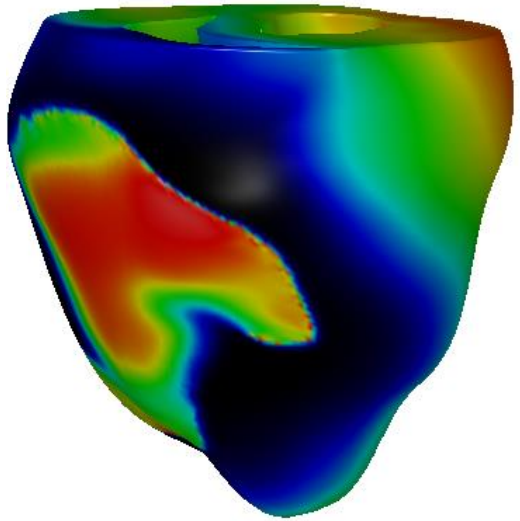


Lead I Pseudo-ECG recording for Control, 50%, 75%, and 100% I_{Kr} block during sinus rhythm.

Window of Vulnerability to Reentry

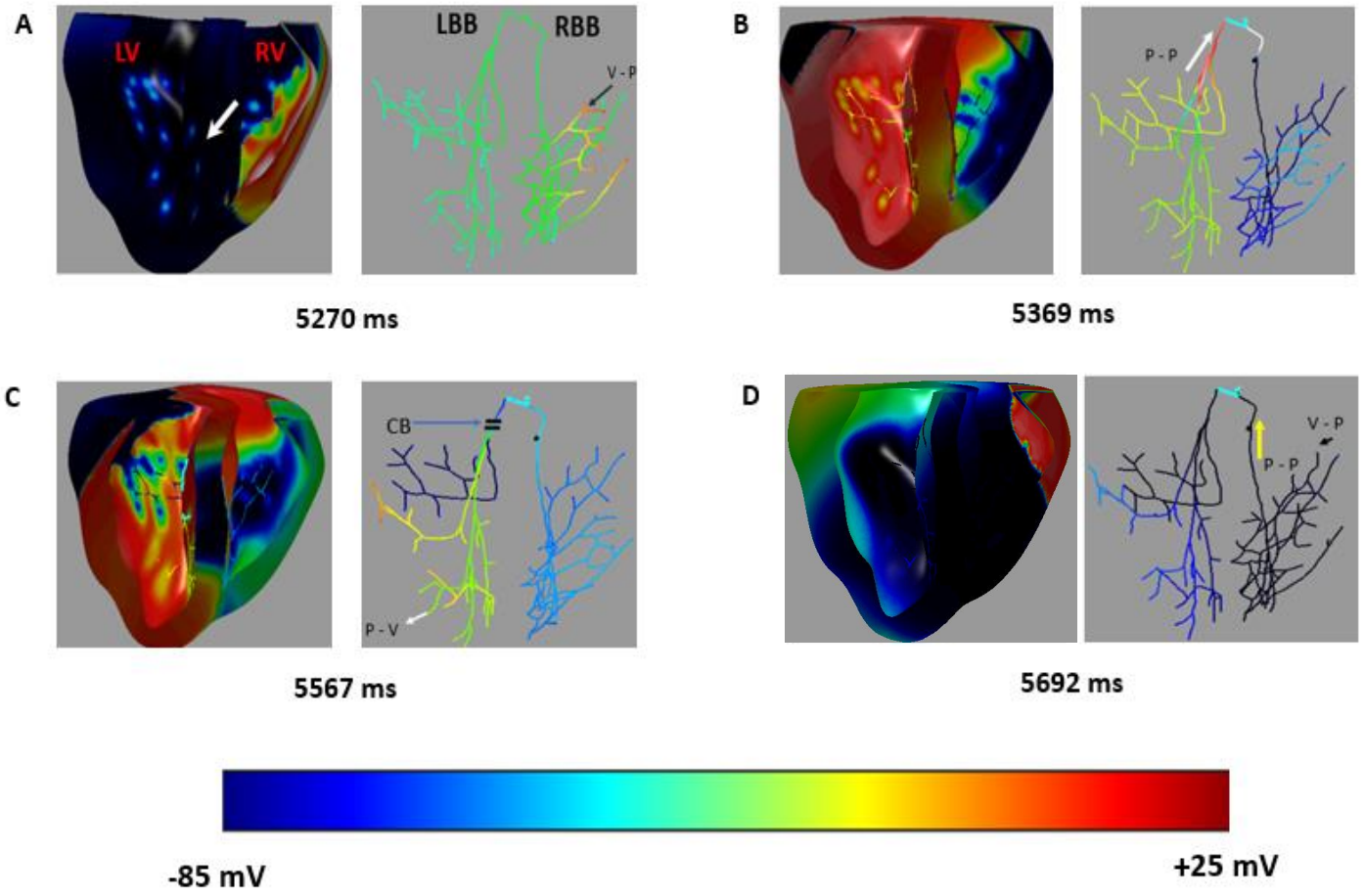
- If S2 stimulus occurred too soon, it was blocked by the refractory tissue (grey).
- Whereas if S2 occurred too late, it was conducted by the entire ventricular tissue causing a premature excitation (blue).
- If the S2 stimulus occurred when the tissue is partially excitable, more complex interactions were observed (Red) – Reentry & Ventricular tachycardia.
- S1-S2 window for tachycardia extended significantly during the I_{Kr} block (233% prolongation for 100% I_{Kr} block).





Activations in Ventricles During Reentry

Simulated Reentry Mechanism (S2 at 5240 ms)



RBB- Right Bundle Branch, **LBB-** Left Bundle Branch, **V-P**: ventricular myocardium to Purkinje propagation; **P-V**: Purkinje to ventricular myocardium propagation; **P-P**: propagation within the Purkinje system; **CB**: conduction block.

A:5270 ms. An ectopic stimulus in the region of RV excites neighboring myocytes and excitation spread towards the RBB (V-P; black arrow). The excitation is blocked by the RBB, preventing retrograde propagation to the LBB.

B:5369 ms. LBB excitable after applying the ectopic stimulus. The activation excites the LBB, and the LV and excitation is propagated retrogradely to the RBB, exciting it and RV (P-P; white arrow).

C:5567ms. Retrograde propagation from the LBB to RBB experiences a conduction block (CB) (CB; blue arrow).

D:5692 ms. RBB and LBB are both excitable. Excitation from the ventricle (V-P; black arrow) excites the RBB. Retrograde propagation (P-P; yellow arrow) through the RBB reached the LBB, exciting it and the LV.

Conclusions

- We presented a multiscale numerical simulation study to investigate the arrhythmogenic effects of HERG channel block producing an LQT2 phenotype.
- Our model was able to reproduce clinically observed QT prolongation in ECG as a result of I_{Kr} block.
- Our study revealed that a complete I_{Kr} blockade results into more severe phenotype in Purkinje cells than in ventricular myocytes.
- The window of susceptibility to reentry that degrades into tachycardia was significantly prolonged in presence of I_{Kr} block.

Thank you!