Benchmarking In Silico Models and Candidate Metrics for Assessing the Risk of Torsade de Pointes

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Goal of the In Silico Working Group

- **To develop and validate a computer model of the human ventricular myocyte based on experimentally derived electrophysiology and pharmacology data to reconstruct the electrophysiological response of human cardiac cells to drugs**
- **Using this model, to identify and characterize candidate metrics that predict the risk of clinical Torsade de pointes (TdP)**
- **Starting point: O'Hara-Rudy as the consensus model recommended at the 2013 CiPA In Silico Expert Workshop**

O'Hara T, Virag L, Varro A, Rudy Y (2011) Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation. PLoS Comput Biol 7(5)

Talk overview

A. **Compare action potential reconstructions using the O'Hara Rudy human ventricular myocyte model to other models recently used to classify TdP risk**

B. **Benchmark the performance of a set of candidate metrics recently proposed to asses TdP risk**

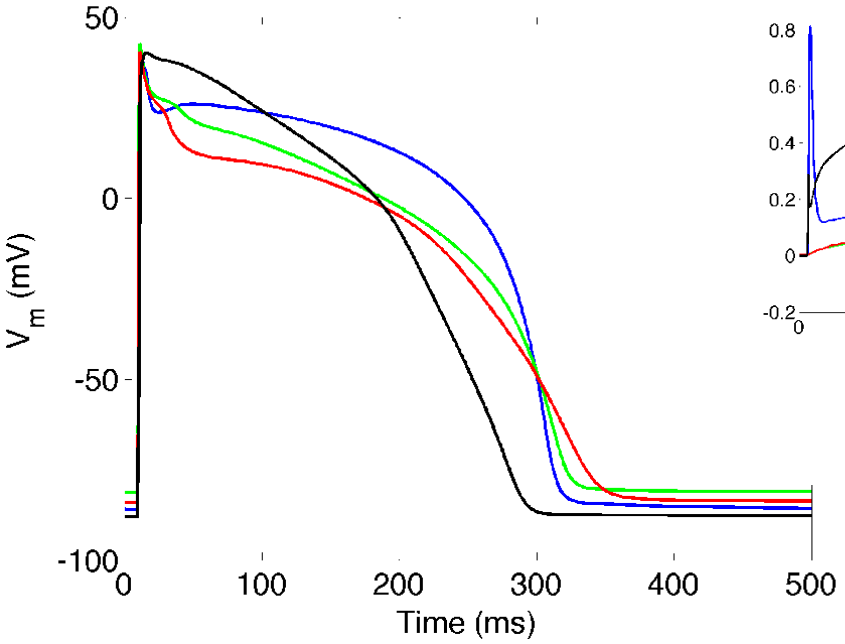
Recent computer models of the adult human ventricular myocyte

- **O'Hara-Rudy (2011) – based directly on experimentally derived human ventricular myocyte data**
- **ten Tusscher (2006) – simplified, 'computationally efficient' model derived from a variety of models and data sources**
- **Grandi (2010) – derived from the Shannon rabbit ventricular myocyte model**
- **Carro (2011) – derived from the Grandi (rabbit myocyte) model**

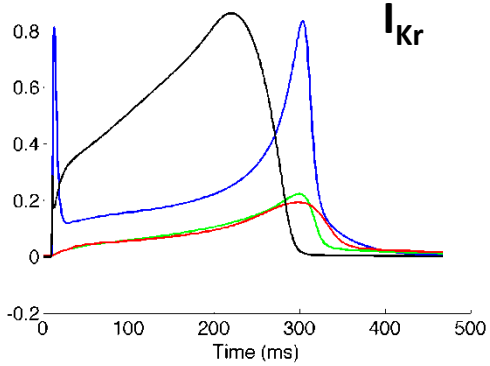
O'Hara Rudy model uses experimental data obtained in adult human ventricular cells and validated against human cellular electrophysiological behaviors

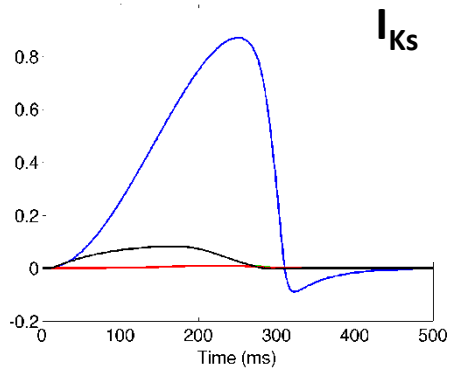
Comparison of AP reconstructions

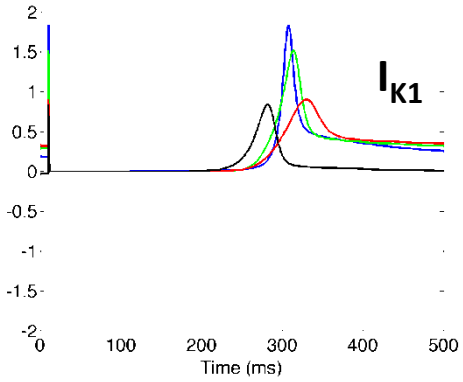
- **All 4 computer models reproduce the basic waveform of the ventricular myocyte action potential but differ in the amount and contributions of some repolarization currents**



Reconstructed Endocardial AP







O'Hara-Rudy
ten Tusscher
Grandi
Carro

Sotalol as an initial test case

- **D,l-sotalol is an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties**
- **Identified by the CiPA Compound Selection WG as "high risk"**
- **FDA drug product label contains detailed information about the ability of sotalol to prolong ventricular repolarization (QTc) and generate TdP**

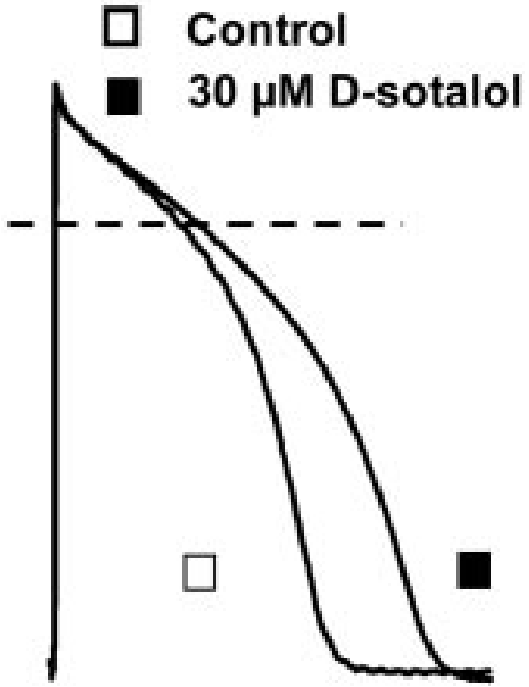
Percent Incidence of Torsade de Pointes and Mean QT_c Interval by Dose For Patients With Sustained VT/VF

Daily Dose (mg)	Incidence of Torsade de Pointes	Mean QT_c [a] (msec)
80	0 (69)[b]	463 (17)
160	0.5 (832)	467 (181)
320	1.6 (835)	473 (344)
480	4.4 (459)	483 (234)
640	3.7 (324)	490 (185)
>640	5.8 (103)	512 (62)

a) highest on-therapy value
b) Number of patients assessed

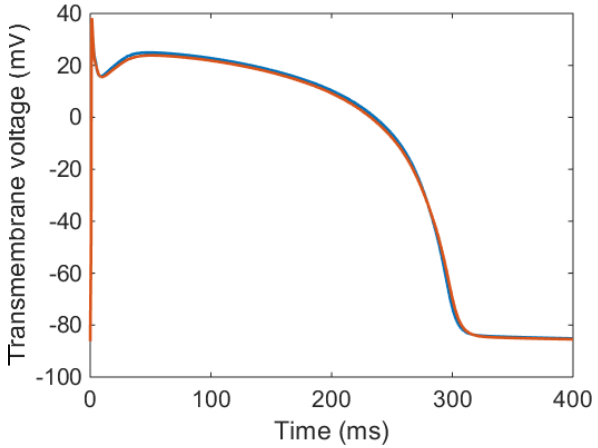
Source: Betapace® (sotalol HCL) product label

Sotalol effects on human ventricular cells

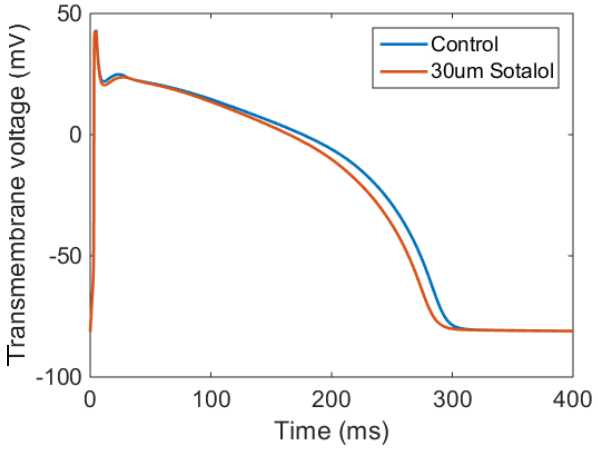


(Jost et al., 2005)

- Data are available showing the effects of sotalol on human ventricular papillary muscle action potentials (30µM, 60 bpm)
- This prolongation is not replicated in either the Grandi or ten Tusscher models using the IC50s for hERG, Cav1.2 and Nav1.5 in Kramer et al. (2013)

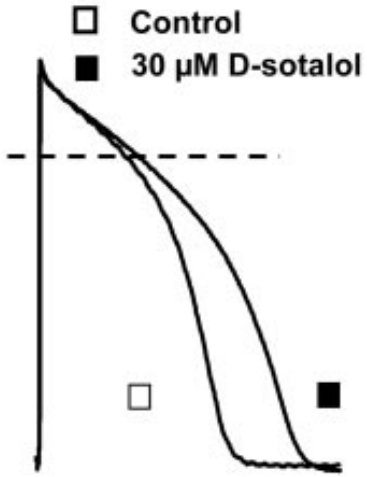


ten Tusscher



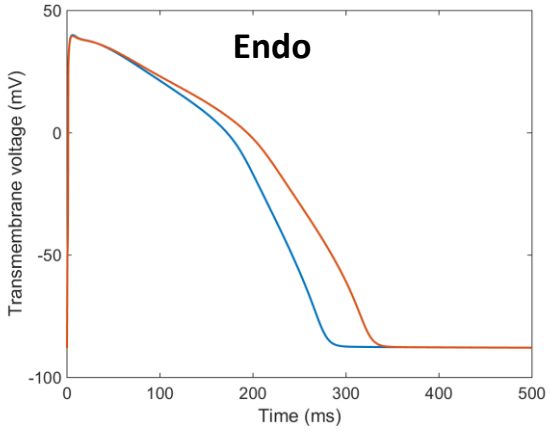
Grandi

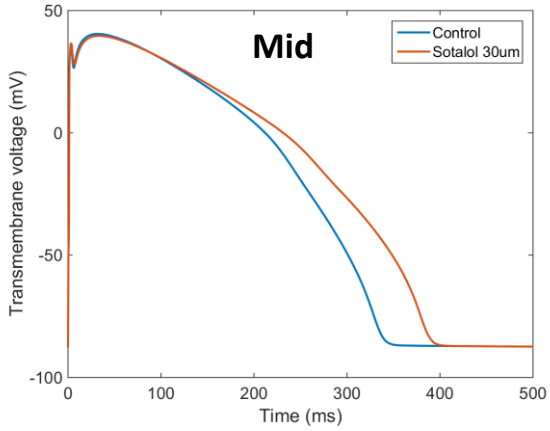
Sotalol effects on human ventricular cells

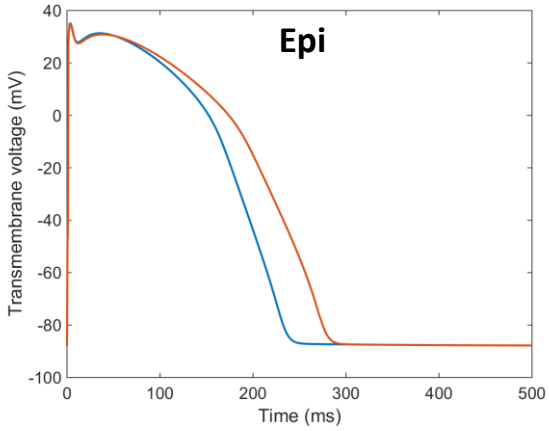


(Jost et al., 2005)

- **Using the IC50s for hERG, Cav1.2 and Nav1.5 in Kramer et al. (2013), the O'Hara Rudy model is able to reconstruct the prolongation of the human ventricular action potential seen experimentally**

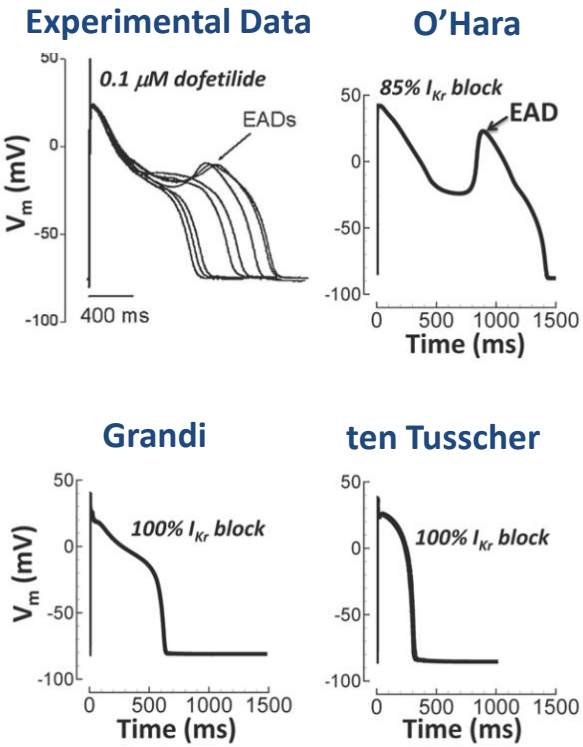




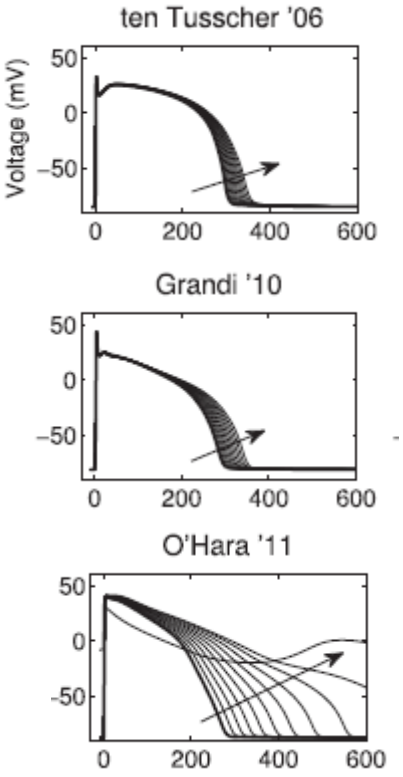


Early afterdepolarizations (EADs) and TdP

- **Only the O'Hara-Rudy model is able to generate EADs, a primary mechanism for triggering TdP**



O'Hara et al., 2011



Mirams et al., 2014

Pilot evaluation of TdP risk metrics

IN PROGRESS

- **An initial set of candidate metrics have been evaluated using the O'Hara Rudy model in an exploratory study to assess their ability to rank the clinical risk of TdP**
  - Against the Redfern et al. (2002) classification scheme (class 1-5)
  - IC50s taken from Mirams et al. (2013)
  - Drug list taken from Mirams et al. (2013)
- **The metrics tested included:**

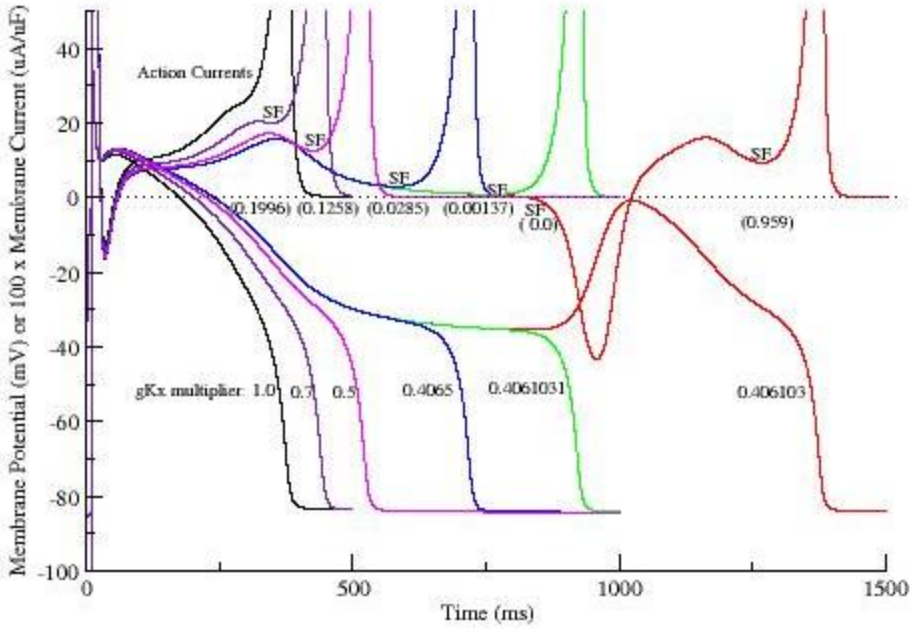
Action potential properties
- APD_{90}
- APD_{50}
- APD triangulation (90-50)
- Peak AP
- Max upstroke velocity

Calcium transient properties
- Ca Peak
- Ca_{90}
- Ca_{50}

Restitution properties
- S1-S2 maximal slope
- Dynamic restitution

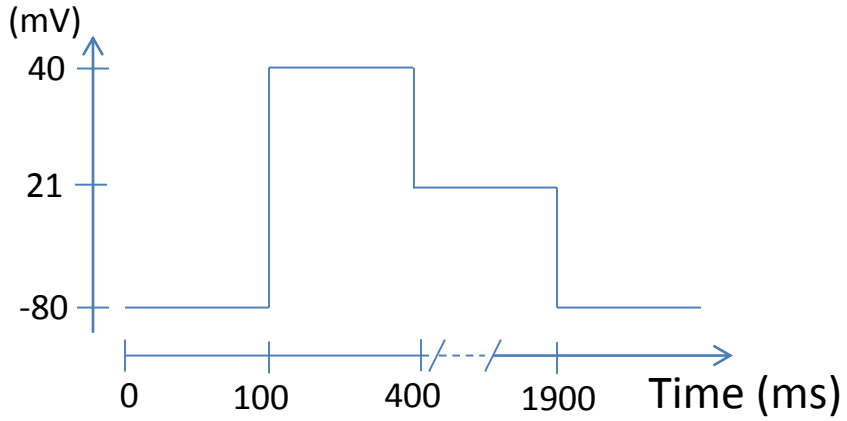
Net repolarizing current as a candidate metric

- **Mechanistic approach to assess amount of residual net repolarizing current available for repolarization under a "worse case" EAD scenario (where $I_{net} = I_{Kr} + I_{Ks} + I_{K1} + I_{NaL} + I_{CaL}$)**



Starmer (https://frank.itlab.us/ead/)

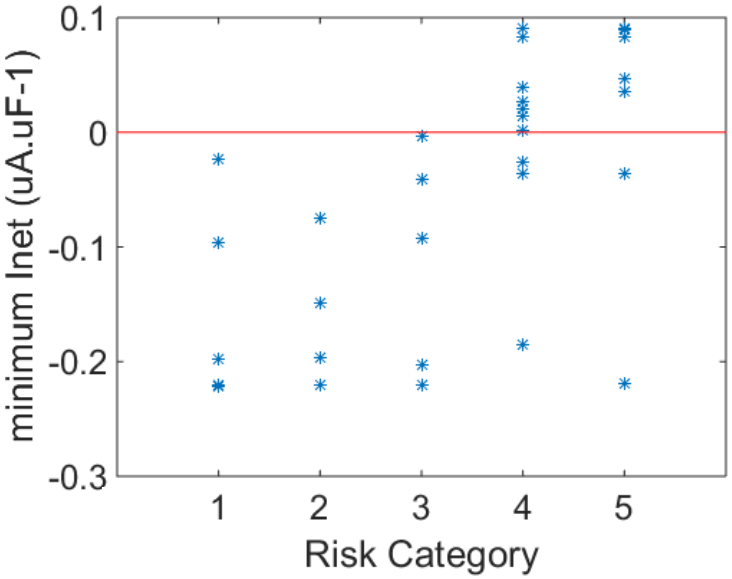
- **When Inet crosses 0 during repolarization EAD occurs**
- **Voltage step procotol**



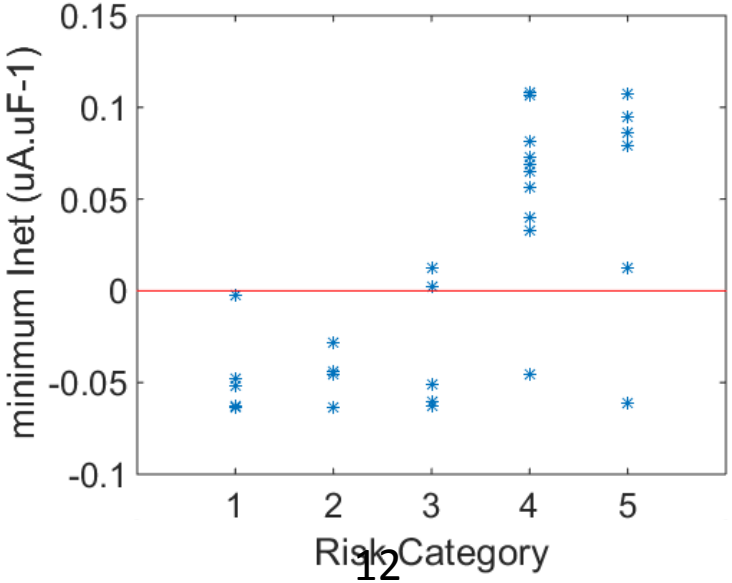
Net repolarizing current vs. drug risk category

- **Net repolarizing current metric on 31 drugs listed in Mirams et al. (2013) using their table of IC50s**
- **Caveats: Redfern (2002); IC50s, relative to effective drug concentrations vs. absolute risk**

Grandi model



O'Hara-Rudy model



Summary and next steps

- **The O'Hara Rudy human ventricular myocyte model is derived from the most consistent and complete set of experimental measurements in adult human cells**
- **Unlike other models, O'Hara Rudy reconstructs a prolongation of the AP duration with sotalol and generates EADs**
- **An initial pool of candidate metrics is being assembled, along with an explorations of protocols with the potential to enhance metric performance**
- **Further development of the model and assessment of candidate metrics will :**
  - Await the availability of "new" multi-ion channel pharmacology data from the Ion Channel Working Group
  - Development/validation of kinetic models for channel pharmacology
  - Separation of the current CiPA drug list into (a) testing and (b) validation subsets

Acknowledgements

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