Predicting drug-induced arrhythmic risk using simulated afterdepolarisations

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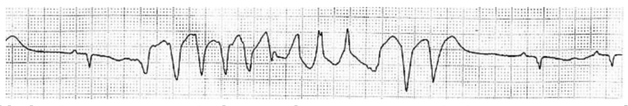
Abstract: We created a novel afterdepolarisation-based, patient-specific method of predicting pro-arrhythmic risk.

Introduction



New drug candidates must be shown not to cause life-threatening Torsades de Pointes arrhythmia. The present metrics used to predict this are block of the hERG potassium current, and prolongation of the QT interval. However, some drugs which are strong hERG blockers are not torsadogenic [1] and not all drugs which prolong the QT interval cause Torsades [2]. In an effort to find a more specific marker of drug- induced pro-arrhythmic risk, we used multi-ion channel block in combination with mathe- matical electrophysiological modelling to investigate the link between ion channel effects and susceptibility to early afterdepolarisations (EADs).

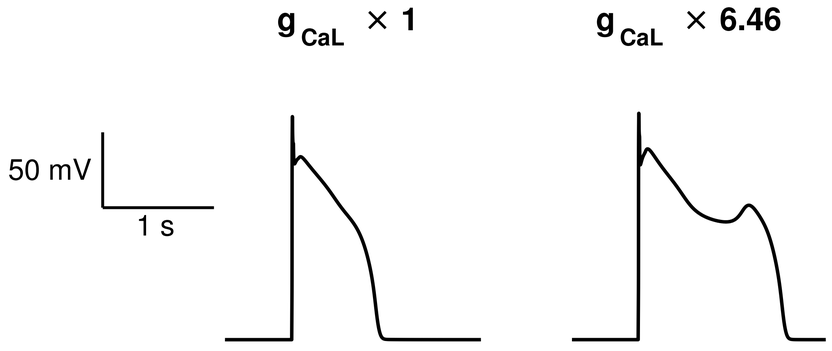
Methods

Using data for drug effects on multiple ion channels, we reduced ion channel conductances to mimic the effects of drug block in mathematical cardiac cell models. We created EAD-inducing interventions based on disease states that cause afterdepolarisations, including increasing L-type calcium current conductance, decreasing rapid delayed rectifier potassium current conductance, increasing late sodium current [3], and shifting the voltage inactivation curve of the fast sodium current.

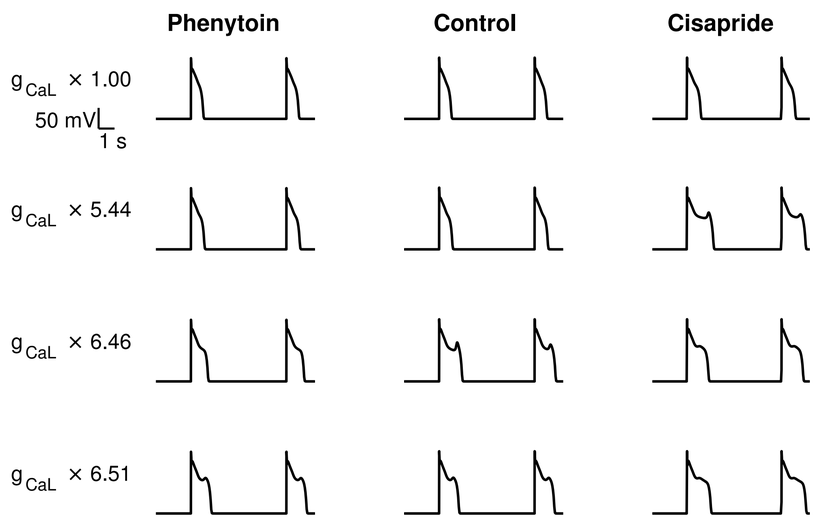
We implemented these effects in mathematical models of cardiac cells by altering conductances, concentrations, and ion channel kinetics. The level of these interventions necessary to cause afterdepolarisations were measured for each drug of interest.

Receiver operating characteristics were calculated for each intervention. The test set of drugs was then classified into the torsadogenic risk categories proposed in [4], using linear discriminant analysis. The threshold data were normalised between -1 and 1 and used for cluster analysis to determine which drugs were grouped together.

EADs can be induced in cell models



Thresholds change with drug effects



Receiver operating characteristics

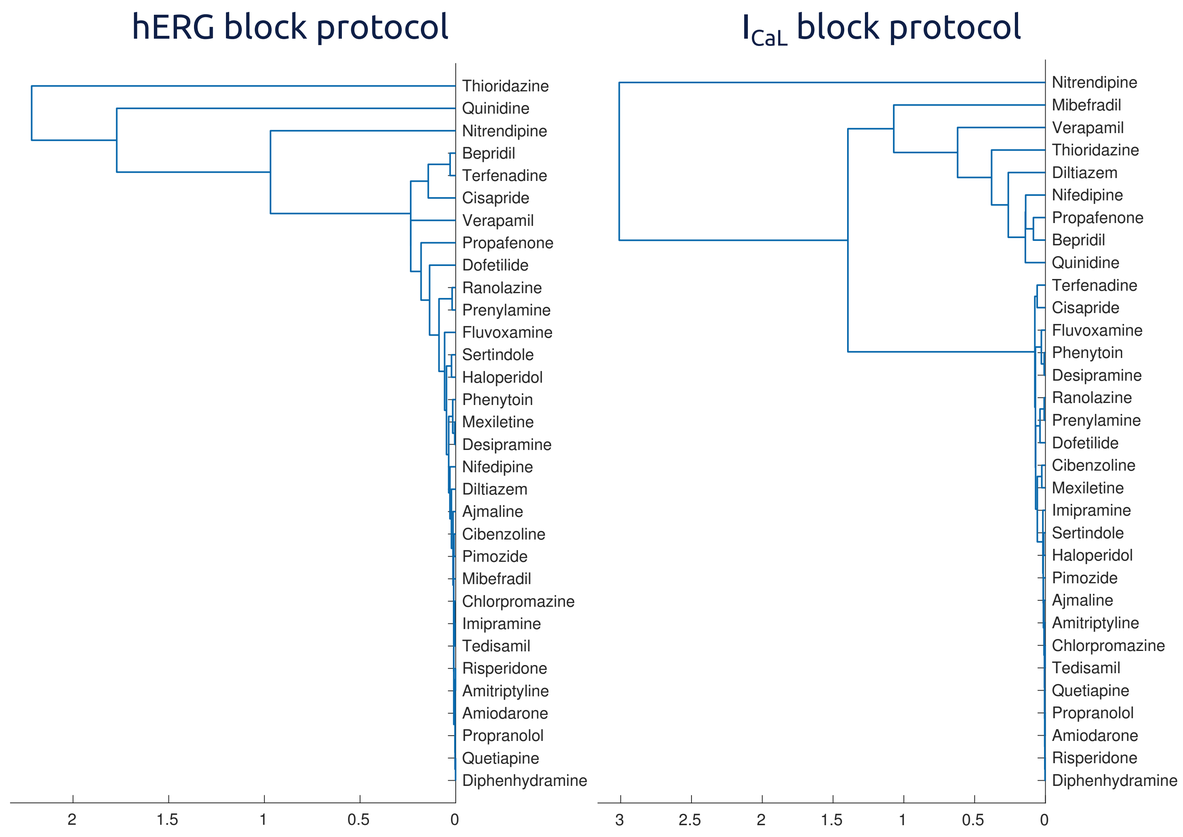
All but two of the intervention-model pairs tested had ROC accuracy values of over 0.5, meaning that the method was more predictive than a random allocation. The most predictive protocol was the hERG block intervention in the ten Tusscher 2006 model, which had an accuracy of 0.61767. The average accuracy score was 0.565.

Classification

All but five of the interventions were more predictive than hERG-only risk markers, which had a mean error of 1.5, with a standard deviation of 1.2. The lowest error was the L-type calcium current increase protocol in the Ten Tusscher 2006 M cell model, with mean error 0.48 and standard deviation 0.62, the same mean error as the APD90 measure from [5].

Cluster analysis

Different EAD-inducing protocols produced different groupings, indicating that this method has the potential to differentiate between drug effects in different patient groups.



Conclusion

Simulating afterdepolarisation tendency offers a patient-specific way to predict Tosades de Pointes. While the technique offers useful information on the similarities between compounds, it is not yet capable of accurately separating drugs into risk categories.

These results indicate that simulating afterdepolarisation tendency has potential for use in the early stages of drug development as an improved marker for CiPA and drug companies to use for predicting drug-induced arrhythmic risk.

References

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[5] Mirams et al. (2011) Cardiovascular Research, 91(1), 53-61

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