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Simulation of early after-depolarisation in non-failing human ventricular myocytes: Can this help cardiac safety pharmacology?

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Abstract:
Background: Identified as being the primary mechanism involved in the induction of torsades de pointes (TdP), early after-depolarisation (EAD) formation is an important parameter in cardiac safety pharmacology. Easily observed experimentally at the cellular or tissue level, EAD can also be simulated by computer algorithms using animal or human models. During the last decade, confidence in these algorithms has greatly increased. We investigated the putative usefulness of EAD simulation for cardiac safety pharmacology.
Methods: EAD simulations were performed in non-failing human ventricular myocytes using the O'Hara-Rudy dynamic model. The role of each cardiac current was investigated by modifying the amplitude of its activity in the model. Prediction of EAD induction by drugs was based on the ratio of their 50% inhibitory concentration values for various cardiac ionic currents to their maximal effective free therapeutic plasma concentration ($EFTPC_{max}$).
Results: In the ventricular endocardial myocytes, EAD was only induced by at least 85% inhibition of the rapid delayed rectifier K^+ current (I_{Kr}). The other currents can either induce or prevent EAD under sub- (80% I_{Kr} inhibition) or up-threshold conditions (87% I_{Kr} inhibition) of EAD. The study of the ability of drugs to induce EAD resulted in a classification which was in agreement with the Tdp risk classification.
Conclusion: Based on EAD computer simulation within the human situation, the present study identified the role of various cardiac currents in the EAD formation and suggested that prediction of EAD formation can be useful for early cardiac safety pharmacology.

Key words:
early after-depolarisation, safety pharmacology, cardiac action potential simulation, ORd model, maximal effective free therapeutic plasma concentration