A computational framework facilitating analyses of fundamental cellular electrophysiological features of clinically-used antiarrhythmic drugs

Introduction: Cardiac arrhythmias remain a major cause of death and disability worldwide. Despite the improved understanding of arrhythmia mechanisms, progress in the development of new antiarrhythmic drugs (AADs) has been limited and clinical application of currently available AADs remains suboptimal, likely in large part due to the incomplete understanding of the complex mechanisms-of-action of AADs. Here, we present a novel user-friendly computational framework to facilitate a better understanding of AADs (the Maastricht Antiarrhythmic Drug Evaluator; MANTA).

Methods: MANTA integrates widely-used computational cardiomyocyte models of different species (mouse, guinea-pig, rabbit, dog, human), regions (atrial, ventricular, purkinje) and disease conditions (atrial fibrillation- and heart failure-related remodeling; Fig. A). It enables simulations of the effects of clinically available AADs (Vaughan-William Classes I, III, IV and multi-channel blockers) on action potential (AP) properties and the occurrence of proarrhythmic effects such as early-afterdepolarizations. AAD effects were simulated based on published IC50 values for each cardiac ion channel and by integrating state-dependent block of INa by Class I AADs using a Markov-model approach in all cardiomyocyte models (Fig. B-C).

Result: Markov model parameters were optimized to replicate published INa characteristics (voltage-dependent activation, inactivation, recovery from inactivation) and AP upstroke velocity in all cardiomyocyte models and reproduced experimental use-dependent onset and recovery of INa inhibition by flecainide, lidocaine and vernakalant. MANTA provides a user-friendly graphical user interface (Fig. C) allowing users to select and compare different AADs, concentrations, and experimental conditions (rate, electrolyte concentrations). Using MANTA, we characterized important species-, rate-, and condition-specific AAD effects, including 1) a stronger effect of Class III AADs in large mammals than in rodents (Fig. D1); 2) a frequency-dependent decrease in upstroke velocity with Class I AADs and reverse use-dependence of Class III AADs (Fig. D2); 3) ventricular-predominant effects of pure IKr blockers and preferential reduction in atrial AP upstroke velocity with vernakalant; and 4) excessive AP prolongation with Class III AADs during hypokalemia (Fig. D3).

Conclusion: The effects of AADs are complex and highly dependent on the experimental or clinical conditions. MANTA is user-friendly, freely available framework able to reproduce a wide range of AAD characteristics that enables analyses of the underlying ionic mechanisms. Use of MANTA is expected to improve understanding of AAD effects on cellular electrophysiology under a wide range of conditions, which can provide clinically-relevant information on the safety and efficacy of AAD treatment.