Drug-induced arrhythmia prediction method based on voltage-dependent I_{CaL}block

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Drug-induced arrhythmia can occur under prolonged action potential duration (APD) due to block of I_{Kr}. Therefore, I_{Kr} block and APD prolongation have been used for predicting drug induced arrhythmia.However, I_{Kr} blockers have difference in risk for drug-induced arrhythmia. One of the reasons is that the occurrence of drug-induced arrhythmia under bradycardia is initiated by early afterdepolarization (EAD) at the repolarization phase in prolonged action potential. For example, terfenadine, which prolongs APD and cause EAD, is considered as a drug with a high risk for drug-induced arrhythmia. On the other hand, amiodarone, which prolongs APD but does not cause EAD in clinical practice, has been considered as a relatively safe antiarrhythmic drug. Therefore, there is a possibility that EAD occurrence can account for the difference in the risks among I_{Kr} blockers. To study the mechanisms underlying different occurrence of EAD, we examined the effects of voltage-dependent I_{CaL} block property on EAD. In the present study, we used a mathematical model of human ventricular action potential. The results showed that amiodarone-like I_{CaL} block model suppressed EAD. But, I_{CaL} block models of terfenadine-like and bepridil-like increased EAD occurrence. The different effects on EAD were accounted for by difference in voltage-dependent block of I_{CaL}, as weak I_{CaL} block in hyperpolarized potential increased the occurrence of EAD. Therefore, to predict drug-induced arrhythmia, not only APD prolongation but also voltage-dependent property of I_{CaL} block should be checked.