Simulation of TRIaD markers of arrhythmic risk in acquired long QT syndrome

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Acquired long QT syndrome occurs most commonly as a result of block of the human ether-à-go-go related gene (hERG) potassium channel. Disturbances in repolarisation of the cardiac action potential which occur as a result of this can cause the potentially lethal arrhythmia *torsades de pointes*, and this is a common reason for drug restriction or withdrawal from market. However, the relationship between block of hERG and proarrhythmic propensity is complex - drugs with similar IC_{50} values in equilibrium binding assays are known to have very different proarrhythmic properties. The TRIaD (Triangulation, Reverse use-dependence, Instability, and Dispersion) system of markers of repolarisation abnormality is an alternative method used to identify drugs likely to promote arrhythmia. However, the underlying mechanisms of how individual drugs differentially contribute to TRIaD are unclear. In this study we use single and multicellular simulations of cardiac electrical activity to examine this question. Specifically we have developed Markov state models of drug binding to hERG channels that are incorporated into models of the human ventricular action potential. Using these descriptions of drug-hERG interaction, the full range of arrhythmic phenomena can be reproduced. Importantly, each of the individual components of TRIaD is shown to arise from hERG block alone, and the different pro-arrhythmic properties of drugs, as assessed by TRIaD, can be explained by differences in the *kinetics* of hERG-drug interactions. We envisage that this better understanding of the kinetic properties that give rise to the TRIaD profiles of different drugs can be employed to more intelligently guide development of anti-arrhythmic therapy and will lead to greater safety of other novel agents.