

Mathematical Approaches to Understand Changes in Cardiac Action Potential Morphology Caused by Non-Specific Drugs

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Changes to action potential duration and morphology are key factors in the development of cardiac arrhythmias. Torsades de pointes is a well-known arrhythmia that results from the prolongation of the QT interval. Prolongation of the QT interval is a direct result of extended action potential duration (APD) of cardiac myocytes. Action potential duration may be extended as a consequence of a congenital disorder, such as Long QT Syndrome, or it may be extended via pharmacological agents. Many drugs have been pulled off the market for causing toxic and sometimes lethal cardiac side effects. Terfenadine, an antihistamine, was removed from the market after exhibiting these types of lethal side effects. Prolongation of the action potential duration is not the only factor that can have potentially fatal consequences. Shortening of the action potential duration, when coupled with morphological changes, can lead directly to ventricular fibrillation. Unfortunately, some pharmacological agents are not shown to be lethal until the agent is exposed to a large enough population. Therefore, prediction of changes to action potential duration is of high importance for the development of safe drugs.

Action potential duration and morphology are a result of a delicate system of ionic currents which bridge the intracellular space to the extracellular space of ventricular myocytes. These currents run through a network of channels that allow and restrict the flow of different ions at key instances. Blocking one or more of these channels can therefore have a dramatic effect on the action potential. One channel that has been shown to be of high importance to the action potential duration is the channel through which the rapid delayed rectifier current (I_{Kr}) flows. This current is responsible for the repolarization of the cellular membrane, so a pharmacological agent which blocks the I_{Kr} channel will extend the duration of the action potential. Some drugs may not be specific for I_{Kr} only and as a result may block other channels in addition to I_{Kr} . How combinatorial blocks affect the action potential is difficult and expensive to test experimentally. Moreover, if a pharmacological agent is affecting action potential duration and/or morphology, how can a drug developer determine the channels responsible for the change? Computational simulations can be used to address these issues. Using a model of a ventricular myocyte, one can block different channels and observe the changes to the action potential. Mathematical analysis of the results can then lead to an understanding of how to discover probable channel blocks which lead to changes to action potential duration.