Multiscale Modelling and Simulation Investigation of Variability and Abnormalities in Repolarization: Application to Drug Cardiotoxicity

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Abstract

Abnormalities in cardiac repolarization have been implicated in cardiac arrhythmogenesis caused by disease, mutations and drugs. Of particular concern for regulatory agencies, pharmaceutical industry and society is the fact that certain drugs, in particular those not designed to affect the heart, can exhibit cardio-toxicity (i.e.unwanted side effects), which can put patients at risk of developing lethal arrhythmias. Drug cardiotoxicity is often related to abnormalities in repolarization caused by drug-induced alterations at the ionic level. Given the limitations of in vitro and in vivo testing in preclinical prediction of drug cardiotoxicity, there is increasing interest in computational methods to complement experimental findings. The paper describes how state-of-the-art computational cardiac electrophysiology is being used to investigate the mechanisms of drug cardiotoxicity and the role of biological variability in its many forms in determining pro-arrythmic responses to drugs. The work described here is being conducted under the umbrella of the European funded grant preDiCT. The main aim is to unravel the mechanisms of drug-induced arrhythmic risk in the context of high inter-subject electrophysiological variability, and to propose novel arrhythmic risk biomarkers based on this research.

1. Introduction

Drug side-effects have a huge socio-economic cost: they represent a major cause of mortality in industrialised societies and also account for most late product development failures. Many unwanted drug side-effects affect the heart, resulting in potentially increased pro-arrhythmic risk. Since these can be fatal, potential electrophysiological cardiotoxicity is among the most stringent exclusion criteria in the release of new drugs to the market, contributing to the exorbitant cost of bringing new compounds to market.

Currently, screening of drug cardiotoxicity focuses predominantly on the rapid component of the delayed rectifier potassium current, I_{Kr} (hERG) at the ionic level, action potential (AP) duration at the cellular level and QT interval at the whole organism level. HERG block, as well as AP and QT prolongation are commonly regarded as risk factors for arrhythmias such as Torsades de Pointes. However, the fact that a compound blocks I_{Kr}, or even causes AP duration or QT prolongation, does not necessarily translate to increased arrhythmic risk.

Mechanisms of drug-induced arrhythmias are complex usually involving multiple ion channel effects and non-linear dynamics resulting in abnormalities in repolarization. An additional difficulty is that drug-induced arrhythmias are rare events, with incidence often below 10%. This makes unravelling the causes and mechanisms of drug cardiotoxicity even a more challenging task.

The work presented in this paper is based on the premise that understanding causes of variability in its many different forms (i.e. temporal, spatial, anatomical) is key in the investigation of drug-induced repolarization abnormalities and their implications for cardiac safety. Furthermore, we believe that, due to the complex and non-linear nature of the mechanisms modulating repolarization in the heart, multiscale modelling and simulation can help in understanding the causes of variability in repolarization and the pro-arrhythmic consequences of drug effects.

2. Modelling and simulation of drug cardiotoxicity

Drug-induced arrhythmias originate from drug-induced effects at the ionic level and involve the multiscale mechanisms illustrated in Figure 1. Causes vary but often include alterations in multiple ion channel properties caused by both drugs and disease. As a consequence, the balance of inward and outward currents across the cellular membrane is altered, potentially leading to abnormalities in cellular repolarization such as early afterdepolarizations. Repolarization properties and mechanisms are often spatially variable due to heterogeneity in ion channel properties, for instance, and therefore the dispersion of electrophysiological properties in tissue could also be affected by drug effects at the ionic level. Specifically, increased dispersion of repolarization and conduction velocity have been implicated in providing the substrate for the establishment of reentrant arrhythmia circuits.

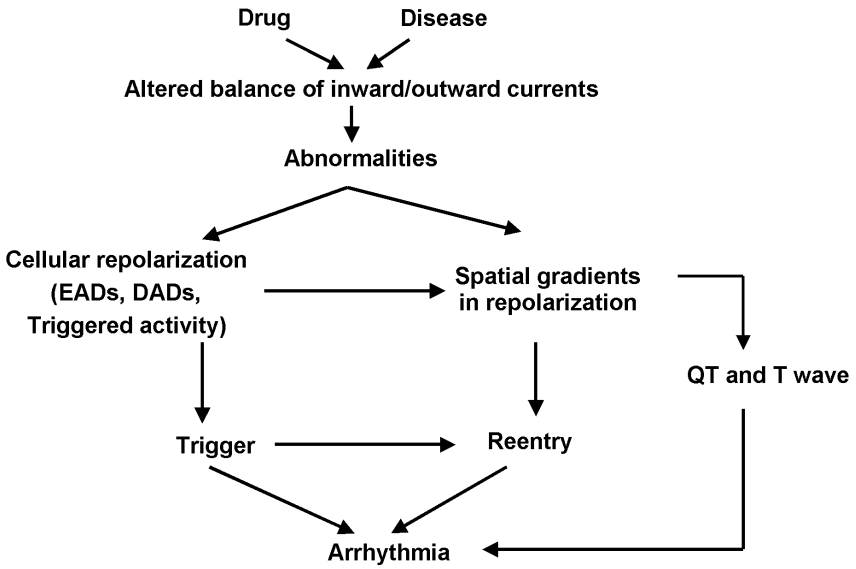

Figure 1. Multiscale mechanisms of drug-induced arrhythmias: from ion channels to whole organ.

The challenges in investigating drug-induced negative side-effects include (but are not limited) to the multiscale nature of the mechanisms, as illustrated in Figure 1, spatio-temporal heterogeneity in cellular properties, high inter-individual electrophysiological and structural properties. In our recently published paper (1), we argue that, in light of these complexities, an iterative combination of experimental and computational work represents the only promising way towards a systematic understanding of multiple drug actions and the role of variability in repolarization in determining different outcomes for the same drug-related cause.

One of the various initiatives supporting the application of those principles is the European Union-funded project preDiCT (http://www.vph-predict.eu/), which is developing the computational infrastructure to specifically allow in silico modelling and simulation of drug action, for the identification of new biomarkers of electrophysiological cardiotoxicity. The consortium involves academic partners and five major pharmaceutical companies (AstraZeneca, GSK, Pfizer, Novartis, and Roche), as well as a major IT company (Fujitsu) and a biotech firm (Aureus Pharma). In the next section, we describe some of the work conducted within the preDiCT project to investigate mechanisms of variability in repolarization and its implications for drug cardiotoxicity.

3. Modelling and simulation of variability in repolarization and its implications in cardiac safety

During the last half century, simulation has been an essential tool in cardiac electrophysiology research, both in academia and in industry. The use of computational modelling and simulation has a long history of productive insights relevant to mechanisms of arrhythmia. We can now simulate electrophysiological activity using anatomically-based whole organ models with detailed representation of membrane kinetics and myocardial 'fibre' orientation to investigate the contributions of individual ion channels and transporters to normal and disturbed heart rhythms. This requires the development of complicated modelling and simulation techniques, including dedicated software such as the open source package Chaste developed at Oxford (2).

Cardiotoxic risk stratification needs a thorough understanding of high electrophysiological variability (such as in terms of sex, age and ethnicity, for instance). For example, the risk of Torsades de Pointes is larger in women than in men. This is believed to be related to differences in ion channel expression that explain differences in the occurrence of repolarization abnormalities in women and men, as we have recently explored using modelling and simulation techniques (3).

Indeed, sex and age are known to determine response to cardiotoxicity. However, variability and heterogeneity in repolarization take many forms. Ionic current and cellular electrophysiological properties are known to exhibit a significant variability even for cells from the same heart and the same region (4). In recent studies, we used sensitivity analysis performed on single cell action potential models to investigate the role of biological variability in modulating electrophysiological behaviour of human (5) and rabbit ventricular myocytes (6), human atrial cardiomyocytes (7) and rabbit Purkinje cells (8).

Another form of variability is beat-to-beat variability in action potentials and ECG-based biomarkers, whose enhancement by drugs or disease has been related to arrhythmic risk in a large number of papers. One of the hypotheses we are testing is that stochasticity in ion channel behaviour could be the cause of beat-to-beat variability in repolarization properties and that this could be enhanced by drug block of HERG. To test the hypothesis, we developed stochastic models of the action potential using both biophysically-detailed formulations (8) and most recently a phenomenological approach (4). The models allow exploring the ionic causes of beat-to-beat variability and the role of intercellular coupling and drug block in modulating beat-to-beat and cell-to-cell variability in repolarization in tissue.

Furthermore, variability in cardiac anatomy and structure could also explain variability in cardiac electrophysiological function and cardiotoxic responses. In a recent study (10), we described the technological pipeline developed to extract the free-running Purkinje anatomy from high resolution MRI images, to build the Purkinje mesh, to integrate it in a whole ventricular model, to then conduct electrophysiological simulations using the Chaste software. The pipeline is illustrated in Figure 2. Electrophysiological simulations are been conducted to investigate how inter-subject differences in free-running Purkinje anatomy could explain differences in whole-ventricular electrophysiological function and drug-induced arrhythmias.

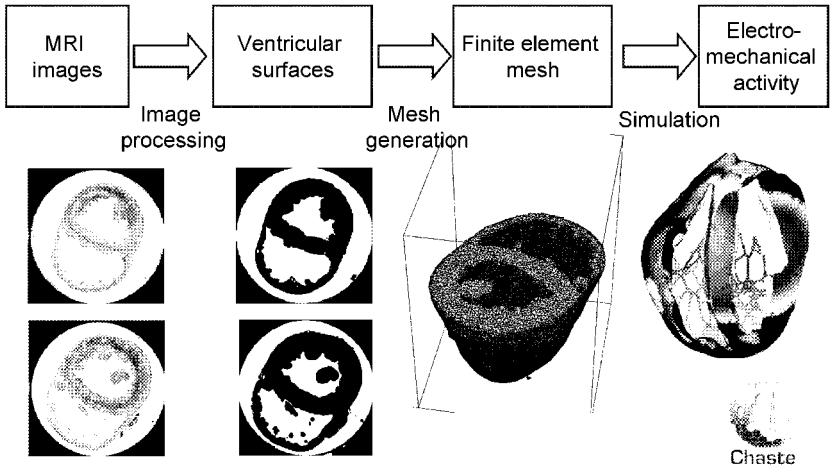

Figure 2. Linking cardiac structure and electromechanical function using modeling and simulation. Technological pipeline required to simulate cardiac electromechanical activity using highly detailed whole ventricular models developed based on MRI images.

4. Conclusions

Understanding the causes of temporal, spatial and anatomical variability is key in unravelling mechanisms determining the occurrence of repolarization abnormalities and their implications for cardiac safety. This is a challenging endeavour due to the variety and complexity of mechanisms, causes and modulators of repolarization properties, which include (but are not limited to) ion channel properties, spatial heterogeneity, intercellular coupling, inter-subject variability in anatomical structures, rate dependent properties (restitution and memory), structural heterogeneity, mechano-electric feedback and beta-adrenergic stimulation. The synergistic combination of modelling and simulation, experimental and clinical approaches is the most promising way forward to dissect mechanisms of repolarization abnormalities and the role of variability in modulating drug-induced cardiotoxic

responses. A truly collaborative engagement between pharmaceutical and academic researchers is required to apply this interdisciplinary approach to drug development and cardiac safety.

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