Cardiac repolarization: Insights from mathematical modeling and electrocardiographic imaging (ECGI)

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Cardiac repolarization is a complex rate dependent process. At the cellular level, it depends on a delicate dynamic balance of ion channel currents. At the heart level, it is spatially heterogeneous, leading to spatial gradients of potential and excitability.

This article provides insights into the molecular mechanisms of the delayed rectifiers I_{Kr} (rapid) and I_{Ks} (slow) that underlie effective function of these channels as repolarizing currents during the cardiac action potential (AP). We also provide noninvasive images of cardiac repolarization in humans. Methodologically, computational biology is used to simulate ion channel function and to incorporate it into a model of the cardiac cell. ECG imaging (ECGI) is applied to normal subjects and Wolff-Parkinson-White (WPW) patients to obtain epicardial maps of repolarization. The simulations demonstrate that I_{Kr} and I_{Ks} generate their peak current late during the AP, where they effectively participate in repolarization. I_{Kr} maximizes the current by fast inactivation and gradual recovery during the AP. I_{Ks} does so by generating an available reserve of channels in closed states from which the channels can open rapidly. ECGI shows that in the human heart, normal repolarization epicardial potential maps are static with 40 ms dispersion between RV and LV. In WPW, ECGI located the accessory pathway(s) and showed a large base-to-apex repolarization gradient that resolved to normal one month post-ablation, demonstrating presence of "cardiac memory". We conclude that computational biology can provide a mechanistic link across scales, from the molecular functioning of ion channels to the cellular AP. ECGI can noninvasively image human cardiac repolarization and its alteration by disease and interventions. This property makes it a potential tool for noninvasive risk stratification and evaluation of treatment by drugs and devices.

KEYWORDS Cardiac repolarization; Ion channels; Imaging; WPW

ABBREVIATIONS AP = action potential; **ECGI** = electrocardiograph imaging; **WPW** = Wolff-Parkinson-White

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Introduction

Repolarization of the cardiac action potential (AP) is a precisely controlled process, allowing adaptation of the AP duration to changes in heart rate. Tight control is achieved by a delicate dynamic balance between several inward and outward transmembrane currents. While this multiple-current mechanism is necessary for precise control and normal rate dependence of the AP, the delicate balance is easily perturbed by abnormal ion channel function and by interventions such as drugs. A major focus of the Cape Town Symposium was on hereditary arrhythmias and sudden death associated with abnormal repolarization. In recent years, major advances have been made in our understanding of the molecular processes that underlie mutation—induced alterations in ion channel function. However, ion channel function is studied in expression systems (e.g., in Xenopus oocyte or HEK cells), removed from the physiological myocyte environment where channels participate in highly dynamic, nonlinear, and complex interactions to generate the AP. A challenge therefore remains to integrate the ion channels into the physiological system of the functioning cell. By doing so, a mechanistic link could be established between channel function (normal or altered by disease or drug) and functioning of the cell, organ, and whole organism. Genetically engineered animals (mostly transgenic mice) have been used to make genotype-phenotype mechanistic connections in the context of cardiac ion channel mutations and arrhythmia; we have developed and applied computational biology approaches to this problem.[1]

This article summarizes my two presentations at the Cape Town Symposium. The first part (first presentation) focuses on two major repolarizing currents I_{Kr} (rapid delayed rectifier) and I_{Ks} (slow delayed rectifier) carried by K^+ ions. Using computational biology, it provides mechanistic insights into how these channel gating processes determine their role in AP repolarization. The second, imaging part (second presentation) provides images of normal and abnormal repolarization of the intact human heart, which were obtained using a noninvasive electrocardiographic imaging modality (ECGI). The material presented in this conference proceedings article has been pub-

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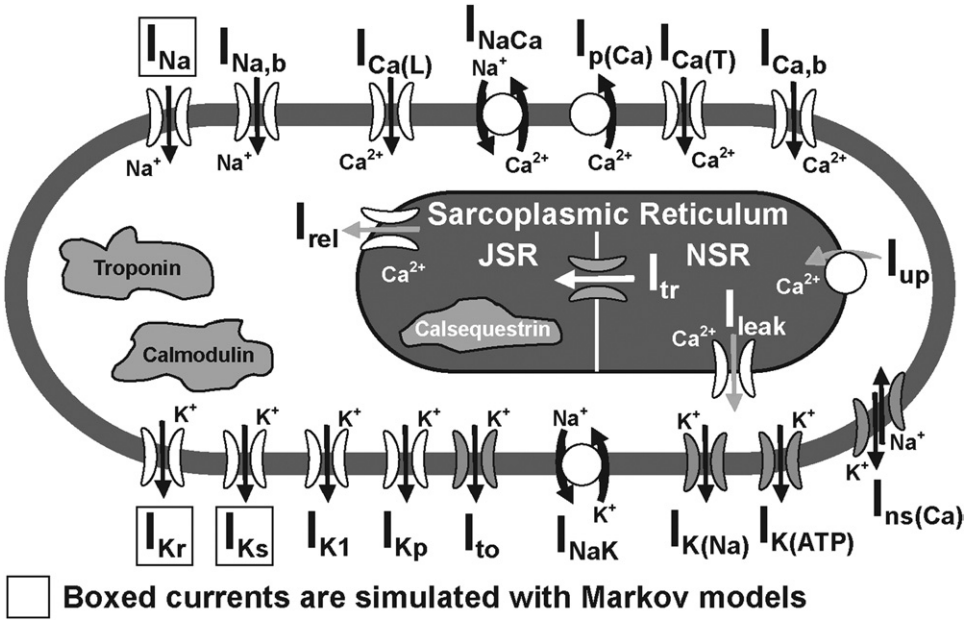

Figure 1 A schematic of the Luo-Rudy dynamic (LRd) model of a cardiac ventricular cell. The model is based mostly on guinea pig data. Details of the model can be found in reference 4 and at http://rudylab.wustl.edu, where the model code is also available. Boxed currents are simulated with Markov models.

lished previously[2–7]; additional details can be found in the original articles and at http://rudylab.wustl.edu.

Methods

The general approach for modeling the AP is the same as described elsewhere.[4] Single-channel-based Markov models are used to compute kinetic states occupancies and transition between the states during the AP. Figure 1 shows the cardiac ventricular cell model used in the simulations. A detailed discussion of methodology, including fitting of the Markov models to experimental data, can be found in the original publications[1–4] and at http://rudylab.wustl.edu.

ECGI combines 250 body surface ECGs with computed tomography (CT) of the heart-torso geometry to compute potentials, electrograms (typically 600), activation sequences (isochrones), and repolarization patterns on the epicardial surface of the heart. All protocols of studies presented here were approved by the respective Institutional Review Boards of University Hospitals of Cleveland and Washington University in St. Louis. A diagram of the ECGI procedure is included in the imaging section of this article; for details, including properties and limitations of ECGI, see[5–7] and http://rudylab.wustl.edu.

Results

Role of I_{Kr} in AP repolarization

I_{Kr} is a tetrameric channel formed by four identical α-subunits that are encoded by the HERG gene. The Markov model of I_{Kr} (Figure 2A) consists of three closed states (C3, C2, C1), an open state (O), and an inactivated state (I). Figures 2B and 2C show the AP and I_{Kr} (top) and occupancy of the channel kinetic states (bottom) during the AP at slow (cycle length [CL] = 1000 ms; panel B) and fast (CL = 300 ms; panel C) pacing. During the AP upstroke, channels move rapidly from the deep closed state (C3) through C2 to C1, from which they can either open (O) or inactivate directly (I). Channels that open during this rapid activation process move very quickly from O to I through a very fast inactivation process. Consequently, during most of the AP the balance between activation and inactivation favors inactivation and residency in I (Figure 2B, 2C). As the AP plateau repolarizes, channels recover gradually from inactivation and transition from I to O, generating a pronounced peak of occupancy in the open state during the late plateau phase (Figure 2B, 2C). Thus, as a consequence of fast inactivation at early AP and gradual recovery during the plateau, I_{Kr} current intensifies during the late phase of the AP. At this phase, the AP is determined by a very delicate balance between inward and outward currents. Increasing I_{Kr} at this time maximizes its effect on AP repolarization and the action potential duration (APD). After this peak in open state occupancy, channels deactivate slowly, moving from O back to C1 and the deeper closed states.

Role of I_{Ks} in AP rate adaptation

Similar to I_{Kr}, I_{Ks} is a tetrameric structure of four α-subunits (KCNQ1), each containing a voltage sensor that moves upon depolarization to cause channel opening. While KCNQ1 can form a functional channel, a modulatory β-subunit (KCNE1) is also included in the I_{Ks} channel assembly, most likely with a 4α:2β stoichiometry.[8] It has been shown that during activation each of the four voltage sensors undergoes at least two transitions before channel opening.[9,10] It starts from a resting position (R1) and then moves to an intermediate position (R2) from which it transitions into an activated position (A). When all four voltage sensors are in the A position, the channel can open via a transition that involves cooperation among the four α-subunits.[11,12] Con-