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Computational rabbit models to investigate the initiation, perpetuation, and termination of ventricular arrhythmia

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ABSTRACT

Current understanding of cardiac electrophysiology has been greatly aided by computational work performed using rabbit ventricular models. This article reviews the contributions of multiscale models of rabbit ventricles in understanding cardiac arrhythmia mechanisms. This review will provide an overview of multiscale modeling of the rabbit ventricles. It will then highlight works that provide insights into the role of the conduction system, complex geometric structures, and heterogeneous cellular electrophysiology in diseased and healthy rabbit hearts to the initiation and maintenance of ventricular arrhythmia. Finally, it will provide an overview on the contributions of rabbit ventricular modeling on understanding the mechanisms underlying shock-induced defibrillation.

Contents

1. Introduction

The rabbit animal model is used extensively in experimental cardiac electrophysiological studies due to its lower housing costs compared to larger animals (eg., dogs, sheep, pigs) and its

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reasonable approximation of human cardiac electrophysiological activity compared to smaller animals (eg rats, mice, guinea pigs). Rabbit cardiac electrophysiological characteristics have been shown to reasonably match the human's in terms of the relationship between wavelength and cardiac size (Hill et al., 2013), the presence of a strong transient outward I_{to} current (Varró et al., 1993), as well as the similar dynamics of the repolarizing I_{Kr} and I_{Ks} currents (Husti et al., 2015; Zicha et al., 2003).

Over the past ~35 years, computational modeling has emerged as an important tool that can explain cardiac electrophysiological mechanisms that cannot be easily elucidated from experimental techniques alone. To complement the use of rabbit ventricles in experimental studies, much effort has been devoted to the development of computational modeling tools and techniques for representing the electrophysiology of the rabbit heart at the cell, tissue, and organ scales. The focus of this paper is to summarize recent contributions of studies utilizing computational models of the rabbit ventricles in uncovering the mechanisms of arrhythmia induction, maintenance, and termination. The works reviewed below developed and utilized rabbit ventricular models of varying complexity, in healthy and diseased states, to advance the understanding of how structural and electrophysiological heterogeneities affect cardiac electrical function.

2. Multi-scale building blocks for modeling rabbit cardiac electrophysiology

At the cell scale, the basic units of computational electrophysiology are action potential (AP) models, which describe membrane kinetics via coupled systems of nonlinear ordinary differential equations (ODEs). These equations represent current flow through ion channels, pumps, and exchangers as well as subcellular calcium cycling and are solved to observe how states (transmembrane potential [V_m] and ionic concentrations) evolve over time as they interact with one another and respond to perturbations. Many rabbit-specific models have been developed, with variants representing the behavior of several different parts of the heart, all of which provide important building blocks for the execution of realistic multi-scale simulations.

The first rabbit-specific AP model for ventricular myocytes was developed by Puglisi and Bers (Puglisi and Bers, 2001). In subsequent years, this model was carefully refined to incorporate a more realistic representation of high-gain Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum (Shannon et al., 2004) and to reproduce the emergence of Ca^{2+} transient alternans during rapid pacing (Mahajan et al., 2008; Romero et al., 2011). Models from this lineage have been used subsequently to demonstrate that execution of simulations with a range of conductance values for repolarizing currents results in the reproduction of physiologically relevant variability in rabbit ventricular AP shape (Fig. 1A) (Gemmell et al., 2014). A more recent innovation has been the development of rabbit-specific AP models geared towards representing specialized cells of the atrioventricular node (AVN) and penetrating His bundle (Inada et al., 2009) as well as fibers of the Purkinje system (PS) (Aslanidi et al., 2010; Corrias et al., 2011).

A smaller number of studies have even attempted to characterize tissue-scale electrophysiological properties in rabbit hearts. For example, Tice et al. developed a slice model of the rabbit ventricles with regional phase 1A ischemia by incorporating realistic transmural gradients in extracellular potassium concentration ($[K^+]_e$), ion channel expression, and adenosine triphosphate (ATP) availability (Tice et al., 2007).

Finally, at the organ scale, numerous groups have published detailed descriptions of the macroscopic geometry of the rabbit ventricles. A seminal example is the work of Vetter and McCulloch, who cast the rabbit myocardium in dental rubber and then analyzed the full stack of 2–3 mm-thick short-axis slices to produce a 3-dimensional reconstruction of ventricular geometry including a detailed description of myofiber architecture (Vetter and McCulloch, 1998). The same ventricular geometry (sometimes called the UC San Diego rabbit heart) has been re-discretized by several different groups (Fig. 1B) (Boyle et al., 2010; Deo et al., 2013; Fenton et al., 2005; Hill et al., 2016; Meunier et al., 2002; Sampson and Henriquez, 2005) and used in a majority of the computational studies of rabbit ventricular electrophysiology described elsewhere in this review. More recently, the advent of powerful new magnetic resonance imaging (MRI) tools has enabled the reconstruction of even more detailed cardiac models, such as the rabbit ventricular model developed as part of the Oxford 3D Heart Project (Bishop et al., 2010b; Burton et al., 2006; Vadakkumpadan et al., 2009, 2010). Such MRI-based models are sufficiently high-resolution (25 μm) that is possible to incorporate detailed representations of fine-grain anatomical features such as blood vessels, endocardial trabeculations, and fibrous tissue bundles. Diffusion tensor MRI, which measures diffusivity of water in the tissue, has been used to obtain accurate representation of fiber architecture in the rabbit ventricles (Benson et al., 2008; Higham et al., 2011; Krishnamoorthi et al., 2014). Moreover, heterogeneous AP properties can be assigned to histologically distinct regions (e.g., PS fibers), which can be manually or automatically segmented via image processing techniques (Fig. 1C) (Bishop et al., 2010b; Vadakkumpadan et al., 2009). Finally, organ-scale models of several components of the rabbit's specialized conduction system have been developed and coupled with ventricular models for use in computational studies aiming to study the AVN (Inada et al., 2009) and the PS (Atkinson et al., 2011; Behradfar et al., 2014; Bordas et al., 2011; Boyle et al., 2010; Vigmond and Clements, 2007).

3. Initiation and perpetuation of ventricular arrhythmia

3.1. Contributions of the cardiac conduction system

In addition to its critical role in the coordination of ventricular excitation, the PS has been implicated as a factor in the initiation and maintenance of arrhythmias, including catecholaminergic polymorphic ventricular tachycardia (CPVT) (Cerrone et al., 2007) and idiopathic ventricular fibrillation (Haissaguerre et al., 2002; Hooks et al., 2015). However, complete understanding of these contributions has been elusive because bioelectric activity in the PS must be inferred from low-amplitude electrograms (Robichaux et al., 2010). Consequently, computational simulations have been an important driver for improving understanding of PS-related arrhythmias in the past decade. Rabbit models have been particularly useful in this context due to similarities between human and rabbit arrhythmia dynamics (Panfilov, 2006) and PS geometric structure (unlike in dogs, pigs, and larger ungulates, human and rabbit PS fibers barely penetrate the endocardial surface) (Coghlan et al., 2006; Tranum-Jensen et al., 1991).

One of the most recent findings facilitated by simulation-based research involving a rabbit model is that stochastically-timed cell-scale Spontaneous Calcium Release (SCR) events in the PS are much more likely to overcome source-sink imbalance and trigger organ-scale Premature Ventricular Contractions (PVCs) compared to SCRs occurring in the electrically well-coupled myocardium (Campos et al., 2015). Even though the number of ventricular cells was ~2 orders of magnitude larger than the number of PS fibers, all ectopic foci observed in this study occurred in the PS, without exception, with the majority (~68%) occurring within 1 mm of a Purkinje-myocardial junction (PMJ) (Fig. 2A). Using a similar model, Zamiri