Original research

Rabbit-specific computational modelling of ventricular cell electrophysiology: Using populations of models to explore variability in the response to ischemia

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ABSTRACT

Computational modelling, combined with experimental investigations, is a powerful method for investigating complex cardiac electrophysiological behaviour. The use of rabbit-specific models, due to the similarities of cardiac electrophysiology in this species with human, is especially prevalent. In this paper, we first briefly review rabbit-specific computational modelling of ventricular cell electrophysiology, multi-cellular simulations including cellular heterogeneity, and acute ischemia. This mini-review is followed by an original computational investigation of variability in the electrophysiological response of two experimentally-calibrated populations of rabbit-specific ventricular myocyte action potential models to acute ischemia. We performed a systematic exploration of the response of the model populations to varying degrees of ischemia and individual ischemic parameters, to investigate their individual and combined effects on action potential duration and refractoriness. This revealed complex interactions between model population variability and ischemic factors, which combined to enhance variability during ischemia. This represents an important step towards an improved understanding of the role that physiological variability may play in electrophysiological alterations during acute ischemia.

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1. Introduction

1.1. Rabbit-specific computational modelling of cardiac electrophysiology

Computational modelling is an increasingly powerful tool, especially when combined with experimental investigations, for the understanding of complex cardiac electrophysiological behaviour (Carusi et al., 2012; Fink et al., 2011; Noble and Rudy, 2001; Quinn and Kohl, 2013; Roberts et al., 2012; Trayanova, 2011). As with any model (whether it be computational, experimental, or conceptual), computational models of cardiac electrophysiology represent current collective understanding and are designed for specific applications (Bers and Grandi, 2011; Clancy et al., 2016; Noble, 2011; Quinn and Kohl, 2011; Trayanova et al., 2006;

Vigmond and Stuyvers, 2016; Winslow et al., 2012). While models exist for a variety of species, rabbit-specific models are a prevalent small animal model, as rabbit cardiac electrophysiology is generally more similar to human than that of small rodents (Bers, 2002; Nattel et al., 2008; Nerbonne, 2000). They are highly relevant for understanding human pathophysiology (Janse et al., 1998; Lawrence et al., 2008), as, for instance, responses of the rabbit heart to ischemia and to pharmacological interventions are also more similar to human than other small animal models (Harken et al., 1981) and the ratio of rabbit heart size to excitation wavelength, which dramatically affects arrhythmogenic wave patterns, is closer to human than even dog or pig (Panfilov, 2006).

In this paper, we first review existing rabbit-specific computational models of cardiac cell electrophysiology and their use in multi-cellular simulations exploring the influence of physiological and pathological cellular heterogeneity on electrical activity, to establish their utility and the current state-of-the-art. This is followed by an original investigation presenting a new methodology using experimentally-calibrated populations of rabbit-specific computational models for the study of variability in the

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Abbreviations

2D	two-dimensional	$I_{Ca,L}$	L-type Ca^{2+} current
AP	action potential	I_{K1}	inward rectifier K^+ current
APD	action potential duration	$I_{K,ATP}$	ATP-inactivated K^+ current
APD$_{90}$	APD at 90% repolarisation	I_{Kr}	rapid delayed rectifier K^+ current
$[Ca^{2+}]_i$	intracellular Ca^{2+} concentration	I_{Ks}	slow delayed rectifier K^+ current
DAD	delayed after-depolarisation	I_{Na}	fast Na^+ current
dV_m/dt_{max}	maximum rate of V_m change	I_{NaK}	Na^+-K^+ pump current
EAD	early after-depolarisation	I_{NCX}	Na^+-Ca^{2+} exchanger current
ECG	electrocardiogram	I_{stim}	stimulus current
ERP	effective refractory period	I_{to}	transient outward potassium current
f	current conductance scaling factor	$[K^+]_o$	extracellular potassium concentration
g	variable current conductance	SR	sarcoplasmic reticulum
h,j	I_{Na} inactivation gates	V_m	membrane potential
		V_{max}	maximum V_m
		V_{rest}	resting V_m

electrophysiological response to acute ischemia, which represents an innovative tool for future studies of the contribution of physiological variability to arrhythmic risk.

1.2. Rabbit-specific modelling of ventricular cell electrophysiology

Numerous biophysically-detailed action potential (AP) models for specific rabbit heart cell types have been generated. Based on the abundance of available experimental data, the earliest and most prevalent are sinoatrial node cell models, which have been vital for the integration and interpretation of results, helping explain key mechanisms underlying the beat-to-beat regulation of cardiac pacemaker function (as reviewed by others (Ravagli et al., 2016; Wilders, 2007)). Rabbit-specific models of atrioventricular node (Inada et al., 2009; Liu et al., 1993), Purkinje (Corrias et al., 2011; Inada et al., 2009) and atrial (Hilgemann and Noble, 1987; Lindblad et al., 1996) cell electrophysiology also exist, but their use for the study of physiological and pathological function has been limited. The first rabbit-specific ventricular myocyte model was developed by Puglisi and Bers (2001), and has been revised as new knowledge regarding cellular function has become available (Mahajan et al., 2008b; Morotti et al., 2012; Shannon et al., 2004, 2012).

1.2.1. Puglisi-Bers model

The Puglisi-Bers rabbit ventricular cell model was developed as an interactive computer program (LabHEART), to provide an easily accessible tool for student learning and for researchers to explore experimentally-testable hypotheses (Puglisi and Bers, 2001). The model was a rabbit-specific modification of the Luo-Rudy guinea pig model (Luo and Rudy, 1991, 1994; Zeng et al., 1995), the most commonly used ventricular cell model at the time. Changes to the model included: (i) introduction of transient outward K^+ (I_{to}) and Ca^{2+}-activated chloride currents; (ii) adjustment of T-type Ca^{2+} and rapid delayed rectifier K^+ (I_{Kr}) currents' kinetics; (iii) and rescaling of fast Na^+ (I_{Na}), inward rectifier K^+ (I_{K1}), plateau K^+, and Na^+-Ca^{2+} exchanger (I_{NCX}) currents' conductance to reproduce the electrophysiological and Ca^{2+} transport characteristics of rabbit ventricular myocytes.

Control simulations demonstrated that the model reproduced normal rabbit ventricular myocyte currents and AP and Ca^{2+} transient morphology. The model was then used to simulate heart failure by reducing I_{to}, I_{K1}, and sarcoplasmic reticulum (SR) Ca^{2+}-ATPase activity and increasing I_{NCX}. Simulations helped further validate the model, while defining the cellular basis of heart failure-induced changes in AP and Ca^{2+} transient morphology and the

propensity for triggered arrhythmias. Simulations reproduced the increase in AP duration (APD; especially at longer cycle lengths) and the reduction in Ca^{2+} transient amplitude that are observed experimentally. They demonstrated that the increase in I_{NCX} or decrease in I_{K1} with heart failure equally lower the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) threshold for Ca^{2+}-triggered excitation, and in combination have a nearly additive effect.

The fact that the model was able to reproduce electrophysiological activity of both normal and heart failure rabbit ventricular cells, and be used to investigate the contribution of different factors to arrhythmogenesis, represented a major step forward in the use of computational modelling to study physiological and pathological function with rabbit experimental models. It should be noted, however, that not all aspects of the Luo-Rudy model were updated based on rabbit data (most notably, ion fluxes involved in intracellular Ca^{2+} handling were generally left unmodified, as was the Na^+-K^+ pump current, I_{NaK}). This lack of species-specificity highlights the fact that model 're-use' is common, so that even 'species-specific' models are based on experimental data acquired from a host of different species (under different experimental conditions, in various preparations), and as a result some outputs may differ from actual function (Niederer et al., 2009).

1.2.2. Shannon model

The first modification of the Puglisi-Bers model came from Shannon et al., which updated the balance of Ca^{2+} removal mechanisms (i.e., SR Ca^{2+}-ATPase vs. Na^+-Ca^{2+} exchange activity) to match data from rabbit ventricular cells and to reproduce the nonlinear dependence of gain and fractional SR Ca^{2+} release on SR Ca^{2+} load (Shannon et al., 2004, 2012). Specifically, the model was modified to include: (i) a sub-sarcolemmal compartment (in addition to the existing junctional and bulk cytosolic compartments - the first computational model to do this); (ii) updated cytosolic Ca^{2+} buffering parameters; (iii) a reversible SR Ca^{2+} pump; (iv) a scheme for Na^+-Ca^{2+} exchange transport that is dependent on intracellular Na^+ concentration ($[Na^+]_i$) and allosterically regulated by $[Ca^{2+}]_i$; and (v) a practical model of SR Ca^{2+} release including both inactivation/adaptation and SR Ca^{2+}-load dependence.

Most significantly, the last feature, that binding of Ca^{2+} to ryanodine receptors on their SR luminal site increased the affinity of the cytosolic activation site for Ca^{2+}, while simultaneously decreasing the affinity of the cytosolic inactivation site, allowed the model to reproduce experimentally-observed relationships between SR Ca^{2+} load and characteristics of SR Ca^{2+} release. The model was used in subsequent simulations to generate the