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Review article

Lessons learned from multi-scale modeling of the failing heart

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ABSTRACT

Heart failure constitutes a major public health problem worldwide. Affected patients experience a number of changes in the electrical function of the heart that predispose to potentially lethal cardiac arrhythmias. Due to the multitude of electrophysiological changes that may occur during heart failure, the scientific literature is complex and sometimes ambiguous, perhaps because these findings are highly dependent on the etiology, the stage of heart failure, and the experimental model used to study these changes. Nevertheless, a number of common features of failing hearts have been documented. Prolongation of the action potential (AP) involving ion channel remodeling and alterations in calcium handling have been established as the hallmark characteristics of myocytes isolated from failing hearts. Intercellular uncoupling and fibrosis are identified as major arrhythmogenic factors.

Multi-scale computational simulations are a powerful tool that complements experimental and clinical research. The development of biophysically detailed computer models of single myocytes and cardiac tissues has contributed greatly to our understanding of processes underlying excitation and repolarization in the heart. The electrical, structural, and metabolic remodeling that arises in cardiac tissues during heart failure has been addressed from different computational perspectives to further understand the arrhythmogenic substrate.

This review summarizes the contributions from computational modeling and simulation to predict the underlying mechanisms of heart failure phenotypes and their implications for arrhythmogenesis, ranging from the cellular level to whole-heart simulations. The main aspects of heart failure are presented in several related sections. An overview of the main electrophysiological and structural changes that have been observed experimentally in failing hearts is followed by the description and discussion of the simulation work in this field at the cellular level, and then in 2D and 3D cardiac structures. The implications for arrhythmogenesis in heart failure are also discussed including therapeutic measures, such as drug effects and cardiac resynchronization therapy. Finally, the future challenges in heart failure modeling and simulation will be discussed.

Contents

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1. Introduction. Experimental heart failure

The definition of heart failure (HF) is still changing and evolving. Indeed, definitions of heart failure depend on the contexts in which this term is used, but it is generally considered a syndrome in which the pumping action of the heart fails to provide sufficient amount of blood and oxygen to the organs, including the heart itself [1]. HF is the final common pathway of various cardiac pathologies such as myocardial infarction, hypertrophy, congenital cardiac abnormalities, valve disease, hypertension, dilated cardiomyopathy, and tachycardia-dependent cardiomyopathy. The primary electrophysiological changes and the mechanisms of arrhythmogenesis associated with HF depend on the etiology [2]. However, there are some common features, which are described in this section.

At the cellular level, there is a prolongation of the action potential, resulting from the remodeling of some ion currents, such as the late sodium current (I_{NaL}) [4,5] which is significantly enhanced. Also, reductions of the inward rectifier K^+ current (I_{K1}), the transient outwart K^+ current (I_{to}), and the Na^+/K^+ pump (I_{NaK}) [3] have been experimentally measured. The increased I_{NaL} and elevated cytosolic Na^+ ($[Na^+]_i$) in HF is linked to the cellular Ca^{2+} overload via the Na^+–Ca^{2+} exchanger (NCX) [6]. NCX activity is critically regulated by $[Na^+]_i$, and even a modest increase in $[Na^+]_i$ causes a decrease in the exchanger to extrude less Ca^{2+}, raising the cellular Ca^{2+} content [7,6]. Also upregulation of the NCX in HF may magnify the functional impact of altered $[Na^+]_i$, and thus Ca^{2+} overload. Alterations in calcium handling, i.e. an increase of diastolic $[Ca^{2+}]_i$, a decrease of systolic $[Ca^{2+}]_i$ peak, and a slow $[Ca^{2+}]_i$ decay, as well as intracellular sodium accumulation, have been established as the hallmark characteristics of myocytes and tissues isolated from failing hearts, especially in terminal HF [8–10]. Detubulation and changes in the beta adrenergic system have also been observed in failing hearts and have been related to the above mentioned alterations of Ca^{2+} transients [11,12].

Animal studies [13,14] have shown that the gap junctional protein connexin43 (Cx43) is redistributed from the intercalated disk to the lateral ventricular myocyte borders and that the amount of hypophosphorylated Cx43 is increased, leading to intercellular uncoupling and reduced conduction velocity in HF [15,16]. In addition, remodeling of the extracellular matrix including the presence of cardiac myofibroblasts [17–20] and their interactions with cardiomyocytes, alters electrical conduction, which is determinant in HF arrhythmogenesis.

During HF, electrophysiological remodeling and Ca^{2+}-handling alterations can lead to focal activity initiated by either early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs), that may lead to a triggered premature beat [2]. If the altered myocardial structure represents a suitable substrate, characterized by repolarization heterogeneities, fibrosis and/or uncoupling, reentry may ensue. Reentrant rhythms have been observed in failing hearts and an improved understanding of the responsible mechanisms is much needed.

The complexity and variability of the experimental and clinical studies performed to characterize the HF pathology justify the need of further assistance to fully understand HF etiology and the underlying arrhythmogenic mechanisms. Computer models emerge as a complementary and very effective tool to fill this gap. Indeed, personalized multi-scale models are able to establish the link between the cellular or even genetic or molecular changes during disease and the consequent arrhythmogenic mechanisms. Simulation studies allow also component dissection, which is hardly feasible in experiments or in clinical environments, and enrich our understanding of these complex mechanisms.

2. Computational modeling of heart failure at the cellular level

2.1. Electrophysiological remodeling and altered Ca^{2+} handling

Multiple electrophysiological changes have been experimentally observed in isolated failing cardiac cells. Computational models have helped to analyze the cellular electrophysiological consequences of these changes. The first simulation study that focused on heart failure induced electrical alterations (at the cellular level) was carried out by Priebe and Beuckelmann in 1998 [21]. In this work, the AP of a human ventricular myocyte was modeled and modified to simulate HF. Selected ion currents (see Table 1), based on experimental data, were remodeled leading to HF phenotype, characterized by a longer action potential duration (APD) and a corresponding altered Ca^{2+} transient. Priebe and Beuckelmann [21] also showed that EADs could develop in HF conditions following the block of the rapid delayed K^+ current (I_{Kr}). They used the model results to propose how spontaneous calcium release triggered a premature AP in HF; the reduction of repolarization currents (I_{K1} and I_{NaK}) rather than an increase of the depolarizing current (I_{NaCa}) seemed to be responsible for the enhanced likelihood of triggered APs in failing myocytes. Because the effects of altered Ca^{2+} transients in HF are widely suggested to be critical for proarrhythmic phenomenon, a number of models have since been developed that describe in detail the behavior of intracellular calcium pathways.

Since the first study, a number of computational works have focused on describing HF phenotype on the basis of new emerging experimental data. Table 1 summarizes the HF computational models that have been developed to date. As shown in Fig. 1, several computational models reproduce not only APD prolongation, but also elevated diastolic $[Ca^{2+}]_i$ levels, the reduction of peak systolic $[Ca^{2+}]_i$ and the slow decay of Ca^{2+} transient observed experimentally in failing cells [22,23]. Specifically, Winslow et al. [24] defined the minimum model of 'end-stage heart failure' focusing on the protein levels of SR Ca^{+2} ATPase and NCX in canine cardiac ventricular failing myocytes. The model estimated a range for NCX upregulation and SERCA pump downregulation responsible for altered Ca^{2+} transients.

Using a similar approach, Puglisi et al. [25] developed a computational model to analyze the electrophysiological and Ca^{2+} transport properties of failing rabbit ventricular myocytes. They showed that combining enhanced Na^+/Ca^{2+} exchange with reduced I_{K1} (as occurs in HF) lowers the $[Ca^{2+}]_i$ threshold to trigger an AP.

A more detailed description of Ca^{2+} dynamics was developed by Shannon et al. [26], who predicted that increased Ca^{2+} affinity of the ryanodine receptors (RyR) increased the probability of delayed afterdepolarizations (DADs) when heart failure was simulated. Calcium calmodulin kinase II (CaMKII) pathway, another important factor for Ca^{2+} dynamics especially in HF, was recently introduced in AP models [27–29]. CaMKII is upregulated in HF and strongly affects Ca^{2+} handling. CaMKII shifts sodium current availability to more negative voltages, enhances intermediate inactivation, and slows recovery from inactivation, but also enhances the activity of the I_{NaL}. CaMKII also increases Ca^{2+} and K^+ currents (ICa and I_{to}). CaMKII-induced alterations of sodium current (I_{Na}), Ca^{2+} current (ICa), and transient outward K^+ current (I_{to}) were modeled by Grandi et al. [29] to analyze the complexity of CaMKII-dependent AP changes. Simulation results showed a