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Review

Models of cardiac excitation–contraction coupling in ventricular myocytes

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ABSTRACT

Mathematical and computational modeling of cardiac excitation–contraction coupling has produced considerable insights into how the heart muscle contracts. With the increase in biophysical and physiological data available, the modeling has become more sophisticated with investigations spanning in scale from molecular components to whole cells. These modeling efforts have provided insight into cardiac excitation–contraction coupling that advanced and complemented experimental studies. One goal is to extend these detailed cellular models to model the whole heart. While this has been done with mechanical and electophysiological models, the complexity and fast time course of calcium dynamics have made inclusion of detailed calcium dynamics in whole heart models impractical. Novel methods such as the probability density approach and moment closure technique which increase computational efficiency might make this tractable.

1. Introduction

Mathematical and computational modeling have long played a role in understanding the physiology of the heart. This started with empirical relations derived to understand the pumping of the heart such as the Frank–Starling law. It was followed by more detailed and mechanistic descriptions as more experimental information became available. The result is that currently models spanning many spatio-temporal scales, going from single ion channels, to individual cardiac myocytes, and finally to the whole heart are being used to gain understanding into function of the heart and the disease processes that affect human health. This review paper will focus on cellular and subcellular modeling of cardiac excitation–contraction (EC) coupling.

Cardiac excitation–contraction coupling refers to the series of events initiated by the electrical excitation of the heart. With each heart beat, ions flowing through ion channels in the plasma membrane generate currents which cause characteristic changes in membrane voltage referred to as the action potential (AP). This AP triggers calcium release from internal stores (i.e., the sarcoplasmic reticulum), via a process known as calcium-induced calcium release (CICR) which results in a transient increase in internal calcium concentration. These calcium ions interact with myofilaments to initiate cell contraction (Fig. 1). Various ion pumps and exchangers then work to restore ion concentrations back to their previous levels before the next beat.

In order to understand EC coupling, we must understand the basic physiology and the closely related morphology. The basic contractile unit in the cardiac myocyte is the sarcomere, which is a repeated structure giving the myocyte its banded or striated appearance due to the arrangement of the proteins present in its different regions. During normal contraction all the sarcomeres shorten uniformly. The *z*-lines, located at the two ends of the sarcomere, are the location of the t-tubules. The t-tubules are regions of extra-cellular space created by tubular invaginations of the sarcolemma (i.e., the cell's outer membrane). EC coupling occurs in the dyadic subspaces, regions of restricted space bounded by the t-tubular and sarcoplasmic reticulum (SR) membrane (Fig. 2).

The action potential is caused by the opening of voltage-gated ion channels, proteins that span the sarcolemma and when open allow the movement of ions down their electro-chemical gradient which is generated by ion motive ATPases and exchangers in the sarcolemma. The initial depolarization phase of the AP is caused by a fast sodium current followed by opening of the voltage-sensitive L-type or dihydropyridine receptors (DHPR) calcium channels (J_{dhpr}) located primarily at in the t-tubular membrane. The L-type calcium current helps maintain the plateau phase of the action potential. The plateau and repolarization phase that follows is governed primarily by voltage-gated potassium channels.

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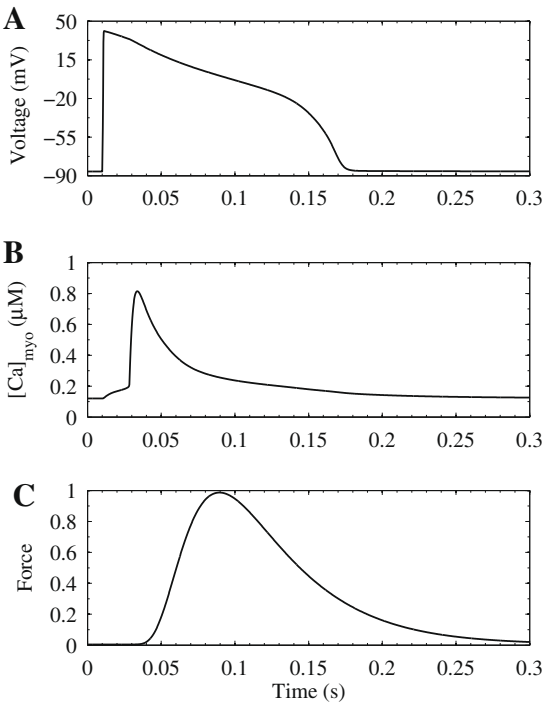

Fig. 1. Excitation–contraction (EC) coupling is the processes linking electrical excitation which triggers the action potential shown in (A) membrane potential. This leads to calcium mobilization shown in (B) bulk myoplasmic (intracellular) calcium concentration. The increase calcium binds to myofilaments and causes force generation shown in (C) normalized force. These time courses are simulated using the Jafri–Rice–Winslow model of the guinea pig ventricular myocyte coupled to the Rice–Hunter–Winslow model for isometric force generation.

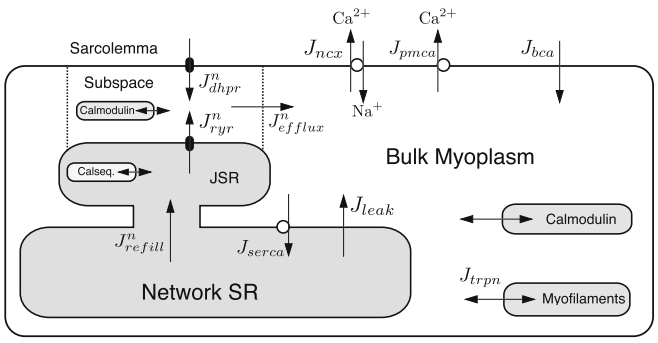

Fig. 2. Schematic diagram for cardiac EC coupling.

The opening of the L-type calcium channel allows calcium to flow down its electro-chemical gradient into dyadic subspace. This presence of calcium ions in the subspace serves two roles. First, it is responsible for triggering the opening of the calcium-sensitive intracellular ryanodine receptor calcium channel which releases calcium (J_{ryr}) from intracellular stores via CICR. Second, this elevated dyadic subspace calcium concentration induces calcium-dependent inactivation of the L-type channel by binding to calmodulin, a protein tethered to the L-type calcium channel. Calcium in the dyadic subspace is then free to diffuse (J_{efflux}) out into the myoplasm and throughout the sarcomere where it binds to the calcium binding protein troponin in the myofilaments and initiates cell contraction. Calcium is resequestered to the network SR by the sarco-endoplasmic reticulum calcium ATPase (SERCA) pump flux (J_{serca}) and then diffuses into the junctional SR (J_{refill}) where it becomes available for release. A passive SR calcium leak (J_{leak}) helps moderate SR calcium concentration. Throughout this process calcium is buffered by calcium binding proteins such as calmodulin and troponin. Homeostasis of total cellular calcium is maintained predominantly by the sodium–calcium exchanger (J_{ncx}) and the plasma membrane calcium ATPase (J_{pmca}).

2. Deterministic common-pool, whole myocyte models

2.1. History

The earliest mathematical model of cardiac EC coupling was the Noble model for the Purkinje cell published in 1962 [1]. The model was an enhanced version of the Hodgkin–Huxley model for the action potential in the nerve axon [2] which included a second type of potassium channel, but lacked any calcium currents. Further enhancements followed with the addition of an inward calcium current in [3] and the 1985 DiFrancesco and Noble model [4]. The DiFrancesco–Noble model of the Purkinje fiber, while intended to describe a multicellular preparation, included membrane bound ion channels and transporters (used to generate the action potential) and also a description of intracellular concentration changes. This was the first biophysically detailed model of excitation contraction coupling as it included a more complete description of the ion channels and ionic homeostasis mechanisms. This model increased the understanding of the action potential by integrating knowledge about the ionic mechanisms to show that they could account for the action potential. Hilgemann and Noble [5] developed a model of rabbit atrial cell that included calcium dynamics including SR uptake and release mechanisms as well as transarcolemmal fluxes. Later work by Demir et al. [6] in rabbit sinoatrial cells used a modified form of the this model.

The first model for the ventricular myocyte was developed by Beeler and Reuter in 1977 [7]. It followed the earlier models of McAllister, Noble and Tsien, but added a slow inward current to give an action potential and included changes of intracellular calcium. The first published biophysically detailed model of the ventricular cell was developed by Luo and Rudy in 1991 [8] as it contained experimentally verified descriptions of the many membrane currents found in the guinea pig ventricular myocyte. This was followed by their Phase II model in 1994 [9,10] that included dynamic equations for ion concentrations. Another family of models for the ventricular myocyte was developed by the Noble group based upon their previous work which are reviewed in [11].

The Luo–Rudy phase II model produces robust action potential wave trains under a number of experimental protocols. The model and its improvements [12–14] allow the study of many phenomena involved in EC coupling and suggested that the action potential in guinea pig ventricular myocytes show decreased action potential duration with decreased interbeat intervals (i.e., increased pacing frequency) due to the incomplete deactivation of the potassium currents between beats. These more recent modeling efforts, while describing ionic currents and exchangers constrained by biophysical data, included empirical descriptions of calcium dynamics.

Many early models are termed common-pool models [15] as calcium release by the SR is controlled by a single compartment into which release occurs. In some cases this is the myoplasmic calcium concentration that is described by one continuously stirred pool. The release of calcium from the sarcoplasmic reticulum was formulated to give the desired calcium transient behavior, but lacked physiologically realistic descriptions of the ryanodine receptor. This was due in part to the difficulties introduced by the strong positive feedback caused by the regenerative nature of CICR, a fundamental property of the ryanodine receptor.

2.2. Models with detailed calcium dynamics

The Jafri–Rice–Winslow guinea pig ventricular myocyte model (1998), was the first ventricular myocyte model to provide a