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Review article

Calcium flux balance in the heart

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ABSTRACT

This article reviews the consequences of the need for the cardiac cell to be in calcium flux balance in the steady state. We first discuss how this steady state condition affects the control of resting $[Ca^{2+}]_i$. The next section considers how sarcoplasmic reticulum (SR) Ca content is controlled by a feedback mechanism whereby changes of SR Ca affect the amplitude of the Ca transient and this, in turn, controls sarcolemmal Ca fluxes. Subsequent sections review the effects of altering the activity of individual Ca handling proteins. Increasing the activity of the SR Ca-ATPase (SERCA) increases both the amplitude and rate constant of decay of the systolic Ca transient. The Ca flux balance condition requires that this must be achieved with no change of Ca efflux placing constraints on the magnitude of change of amplitude and decay rate. We analyze the quantitative dependence of Ca transient amplitude and SR content on SERCA activity. Increasing the open probability of the RyR during systole is predicted to have no steady state effect on the amplitude of the systolic Ca transient. We discuss the effects of changing the amplitude of the L-type Ca current in the context of both triggering Ca release from the SR and loading the cell with calcium. These manoeuvres are considered in the context of the effects of β-adrenergic stimulation. Finally, we review calcium flux balance in the presence of Ca waves. This article is part of a Special Issue entitled "Calcium Signaling in Heart".

Contents

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1. Introduction

The Ca that activates cardiac contraction in the heart comes from two sources: (i) influx from the extracellular fluid, largely via the L-type Ca current and (ii) release from the sarcoplasmic reticulum via the Ryanodine Receptor, RyR. Relaxation requires the removal of Ca from the cytoplasm by a combination of Ca pumping out of the cell (largely via Na–Ca exchange, NCX) and Ca uptake into the SR via the SR Ca ATPase (SERCA). Each of these mechanisms is subject to multiple and often complex regulation. However, no matter how complicated the controls on each Ca source or sink, it is important to note that, in the steady state, the Ca influx into the cell on each beat must equal the efflux of Ca. Equally, the amount of Ca released from the SR must equal that taken back up. Indeed this simple argument can be applied to all potential sources and sinks of Ca including mitochondria. In the article we review some of the many consequences of this Ca flux balance. Some, such as the effects of changing the open probability of the RyR, have been discussed before but we feel that their consequences are ignored often enough that it is important to restate them. Others are less well known and will be enumerated here.

2. The need for Ca flux balance in the heart

It is axiomatic that, if a steady state is to occur, Ca influx and efflux must be equal. It follows from this that, in the steady state, if influx is unaltered then efflux must also remain constant. Obviously there are important conditions in which influx does not equal efflux. One good example is during the onset of β-adrenergic stimulation. Under these conditions the increase of L-type Ca current and stimulation of SERCA activity result in Ca influx being greater than efflux. This will result in an increase of cell (SR) Ca content. However, a new steady state will then be reached at which influx and efflux will again be in balance with the increased Ca transient amplitude providing the mechanism for increasing Ca efflux and thus balancing the increased Ca influx occurring on the L-type Ca current. We argue therefore that, when analyzing cardiac Ca cycling, it is essential to ensure that any proposed mechanisms are consistent with the requirement for Ca flux balance during steady-state conditions.

3. The control of resting calcium

Obviously the heart is not normally at rest but beats constantly. Nevertheless, if only for experimental purposes, it is useful to consider what controls resting Ca. On a simple model resting intracellular Ca concentration ($[Ca^{2+}]_i$) would be expected to be controlled by the surface membrane. This is because, in the steady state there can be no net flux of Ca into, or out of, intracellular organelles such as the SR or mitochondria [1,2]. The exact level of resting $[Ca^{2+}]_i$ will depend on the relative activities of Ca entry and removal mechanisms. The Ca removal is provided by a combination of Na–Ca exchange (NCX) and the plasma membrane Ca-ATPase (PMCA). The routes for Ca entry are less clear. During the action potential the major Ca entry process is the L-type Ca current. However the open probability of this channel is very low at the normal resting membrane potential of a ventricular myocyte (~−80 to 90 mV) [3] and it is doubtful that there is much Ca entry through this route. Under some conditions, in some species, there may be Ca entry via reverse NCX but with normal Na concentrations and membrane potential Ca efflux via NCX is thermodynamically favoured. There is evidence that Ca can enter the cell even when NCX and L-type Ca channels are inhibited but the exact pathway has not been identified [4].

The argument that the control of resting $[Ca^{2+}]_i$ depends on the surface membrane, whilst correct, needs, however, some refinement [2]. There is good evidence that the NCX does not always simply experience the bulk cytoplasmic $[Ca^{2+}]_i$ [5–7]. During systole Ca is released from the SR into the narrow space between SR and t-tubular membrane making the local $[Ca^{2+}]_i$ (sub-sarcolemmal $[Ca^{2+}]_i$) transiently much greater than the bulk cytoplasmic $[Ca^{2+}]_i$. This produces an extra activation of the NCX current and thus Ca efflux. During diastole much of the Ca loss from the SR occurs as Ca sparks [8] which will increase Ca in the locality of the NCX (sub-sarcolemmal $[Ca^{2+}]_i$). There is every reason to expect an extra increase of NCX activity in association with the spark. This raises the possibility that much of the Ca efflux from the cell is determined by Ca sparks and other release of Ca from the SR e.g. putative IP_3 receptors [9,10]. In other words the Ca efflux from the cell would not be governed by the background global diastolic $[Ca^{2+}]_i$ but, rather, by the frequency and amplitude of Ca sparks. This concept is related to what has been proposed in smooth muscle and other cell types where Ca release from intracellular stores is vectorially directed to sarcolemmal Ca pumps [11]. In this context it is worth noting that SERCA inhibitors such as thapsigargin can elevate diastolic $[Ca^{2+}]_i$ [12,13]. One possible explanation of this is that the decay of the systolic Ca transient becomes so slow that the Ca transient does not relax fully between beats. This, however, does not account for the observation since SERCA inhibition elevates diastolic $[Ca^{2+}]_i$ even at very low rates of stimulation or in the absence of stimulation. It is possible that the increase of diastolic $[Ca^{2+}]_i$ results from emptying of the SR abolishing Ca sparks and thereby decreasing the local $[Ca^{2+}]_i$ sensed by NCX resulting in a rise of diastolic $[Ca^{2+}]_i$ until NCX activity recovers to control levels (via the overall increase in bulk, and thus, by diffusion, sub-sarcolemmal $[Ca^{2+}]_i$). However, a cautionary note is important here. There is evidence in many cell types of the phenomenon of store-operated Ca influx. On this mechanism a decrease of SR (or endoplasmic reticulum, ER) Ca leads to the opening of sarcolemmal Ca influx channels. Such store operated channels have been reported in neonatal cardiac myocytes [14,15] but are generally thought to be absent in adult cardiac cells (but see [16]). The potential activity of such channels could provide an alternative explanation for the increase of diastolic $[Ca^{2+}]_i$ produced by emptying the SR.

In summary, future work needs to collect experimental data to shed light on the mechanisms producing both Ca influx and efflux in the resting cardiac cell.

4. SR Ca content and the amplitude of the systolic Ca transient: a two-way interaction

It is well established that most of the Ca that activates contraction, comes from the SR. The amplitude of the Ca transient depends steeply on SR Ca content [17]. Indeed, at low levels of SR Ca, the fraction of SR Ca that is released decreases to very low levels [17,18]. The relationship between SR Ca content and the amplitude of the Ca transient can be fit by a cubic relationship (see inset Fig. 1) [19,20]. The origin of this steep relationship is not entirely clear and has several causes. An increase of free SR Ca content will increase the driving force for Ca release from the SR but, in addition, will increase the open probability of the RyR [21,22]. Furthermore, as cytoplasmic Ca buffers tend to saturate, a given release of Ca from the SR will result in a larger increase of $[Ca^{2+}]_i$ [23].

Whatever its origin, the steep relationship plays a major role in the regulation of SR Ca content as illustrated in Fig. 1. The Ca transient affects both Ca influx and Ca efflux from the cell. Inactivation of the L-type Ca current is largely a Ca-dependent process; the larger the amplitude of the systolic Ca transient, the faster the rate of inactivation of this current [5,19,24]. This increased inactivation will decrease the Ca entry into the cell. An increase of the amplitude of the Ca transient will also directly increase Ca efflux from the cell via NCX. This results in a negative feedback loop: (i) an increase of SR Ca content increases the amplitude of the systolic Ca transient; (ii) the increased Ca transient increases Ca efflux and decreases influx leading to (iii) a