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Review

Atrial cardiomyocyte calcium signalling ☆

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ABSTRACT

Whereas Ca^{2+} signalling in ventricular cardiomyocytes is well described, much less is known regarding the Ca^{2+} signals within atrial cells. This is surprising given that atrial cardiomyocytes make an important contribution to the refilling of ventricles with blood, which enhances the subsequent ejection of blood from the heart. The dependence of cardiac function on the contribution of atria becomes increasingly important with age and exercise. Disruption of the rhythmic beating of atrial cardiomyocytes can lead to life-threatening conditions such as atrial fibrillation. Atrial and ventricular myocytes have many structural and functional similarities. However, one key structural difference, the lack of transverse tubules ("T-tubules") in atrial myocytes, make these two cell types display vastly different calcium patterns in response to electrical excitation. The lack of T-tubules in atrial myocytes means that depolarisation provokes calcium signals that originate around the periphery of the cells. Under resting conditions, such Ca^{2+} signals do not propagate towards the centre of the atrial cells and so do not fully engage the contractile machinery. Consequently, contraction of atrial myocytes under resting conditions is modest. However, when atrial myocytes are stimulated with a positive inotropic agonist, such as isoproterenol, the peripheral Ca^{2+} signals trigger a global wave of Ca^{2+} that propagates in a centripetal manner into the cells. Enhanced centripetal movement of Ca^{2+} in atrial myocytes leads to increased contraction and a more substantial contribution to blood pumping. This article is part of a Special Issue entitled: 11th European Symposium on Calcium.

1. Why are atrial myocytes important?

In a typical human lifetime, the heart beats over 2 billion times with the same repeated chain of events—the "cardiac cycle." The events can be divided into two key stages—diastole and systole. During the diastolic stage, the ventricular myocytes are relaxed. The systolic period refers to the contraction and consequent ejection of blood from the ventricles to the pulmonary artery or aorta. Atrial contraction and relaxation (the "P wave" in a normal electrocardiogram) occurs just before ventricular contraction.

The cardiac cycle is initiated by the sinoatrial node. This is a specialised group of non-contractile cardiac myocytes located within the right atrium that generate repetitive action potentials. From the sinoatrial node, an action potential spreads over both atria causing them to contract and push blood into the ventricles. Eventually, the action potential reaches the atrioventricular node, which temporally filters and relays the signal to the ventricles via specialised conduction tissue including the Purkinje fibres. The ventricular chambers are larger and stronger than their atrial counterparts, and are responsible for propelling blood to the lungs and body.

Although atrial contraction is not as substantial as that in the ventricles and does not generate the same force, atria can enhance the amount of blood that loads into the ventricles prior to systole. When a person is at rest, the contribution of atria to the filling of ventricles with blood is relatively low. Indeed, the majority of ventricular refilling occurs due the venous return of blood to the heart and ventricular relaxation. However, during periods of increased activity and hemodynamic demand, such as during exercise or stress, then atrial contraction can account for ~20–30% of the volume of blood entering the ventricles. The contribution of atria to ventricular refilling is sometimes called "atrial kick," and it can make a significant difference to the performance of the heart [1].

The most common form of cardiac dysrhythmia in humans is known as "atrial fibrillation." This pathology arises when electrical impulses do not solely arise from the sinoatrial node, but instead spontaneously occur with high frequency from sites around the atria (~350 discharges per minute compared to the normal sinoatrial rhythm of 60–80 beats per minute) [2]. Due to the irregular electrical discharges that occur during atrial fibrillation, the atria do not display coordinated contractions required to propel blood into the ventricles. Consequently, atrial kick is missing, and the blood pumping capacity of the heart can be reduced by a third [3]. Given that ventricles can refill substantially without atrial participation, atrial fibrillation is typically not immediately life threatening. However, thromboembolism caused by stagnation

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of blood flow is a significant complication arising from atrial fibrillation. With respect to human health, it is established that the incidence of atrial fibrillation increases with age, and ~15% of strokes occur in people with atrial fibrillation (see http://www.bhsoc.org/bhf_factfiles/bhs_factfile_dec_2000.pdf). It is therefore clear that co-ordinated atrial function is very important. Substantial evidence points to dysregulation of Ca^{2+} signalling as being a causal factor in genesis and maintenance of atrial fibrillation [4–8]. Heart failure is a progressive pathological change to the function of the heart caused by a chronic impairment in cardiovascular function, and if not managed it can be fatal. Heart failure is a common cause of atrial fibrillation, and it is evident that atrial myocytes phenotypically remodel during the disease such that they have reduced contraction, and a greater propensity to show spontaneous Ca^{2+} signals [5]. During the remodelling, atrial myocytes alter the expression of key proteins involved in Ca^{2+} homeostasis, storage and signal generation. Such changes unfortunately appear to reinforce the incidence of fibrillation [8].

2. Ca^{2+} and cardiac excitation–contraction coupling

As the action potential emanating from the sinoatrial node sweeps over the heart, it causes depolarisation of the myocytes, and consequently causes them to contract (a process known as excitation–contraction coupling; EC coupling) [9]. Ca^{2+} is the link between myocyte depolarisation and contraction. Ca^{2+} binds to troponin C within a complex of proteins that are associated with the thin (actin) filaments in myocytes. The binding of Ca^{2+} to troponin C displaces tropomyosin, and allows engagement of actin and myosin filaments. These myofilaments slide past each other and contract the cell. The simultaneous contraction of many cells within the atrial and ventricular walls generates sufficient force to propel blood around the heart, lungs and body.

Depolarisation of myocytes by the action potential causes voltage-operated Ca^{2+} channels (VOCCs) to open. These open channels permit Ca^{2+} to flow across the sarcolemma and into a narrow (~10 nm) cytosolic cleft (often referred to as the "dyadic junction") [10], which is formed by the juxtaposition of the sarcolemma and the membrane of the internal Ca^{2+} store (the sarcoplasmic reticulum; SR) (Fig. 1). The SR is studded with Ca^{2+} release channels known as ryanodine receptors (RyRs), which are activated by Ca^{2+} itself in a process known as Ca^{2+}-induced Ca^{2+} release (CICR) [11–13]. The density of RyRs is particularly high at the clefts, where the SR and sarcolemma are in close apposition, and they are therefore located directly opposite VOCCs. The Ca^{2+} that enters through VOCCs rapidly encounters RyRs and causes them to open. The release of Ca^{2+} sequestered within the SR greatly amplifies the original Ca^{2+} rise through the VOCCs. The dyadic junction is too small for visualisation with conventional imaging technologies; however, mathematical models have predicted that the Ca^{2+} concentration within this tiny volume may exceed several millimolar in the centre of the cleft [14,15].

The activation of RyR clusters via CICR within the dyadic junction leads to the generation of microscopic (diameter ~2–5 μm; lifetime ~100 ms) Ca^{2+} release events known as "Ca^{2+} sparks" [16,17]. Exactly how many RyRs participate in a Ca^{2+} spark is still debated. Estimates have suggested that Ca^{2+} sparks represent the activation of ~15 RyRs [18], although the variability in their time course and amplitude suggests that the number and/or cooperation between channels can vary [19,20]. The Ca^{2+} entry signal that activates the RyR cluster probably arises from a smaller group of closely apposed VOCCs [21]. Depending on the condition of the myocyte, Ca^{2+} sparks can represent an amplification (commonly also called "gain") of ~10-fold or more over the Ca^{2+} flux that originally entered through the VOCCs. Eventually, Ca^{2+} ions diffuse out of the cleft and trigger contraction by binding to troponin C within the myofibrils. Ca^{2+} recovers back to resting (diastolic) levels due to sequestration in the SR by an ATP-dependent enzyme known as SERCA (sarcoendoplasmic reticulum Ca^{2+} ATPase), and transports across the sarcolemma via the action of a Na^+/Ca^{2+} exchanger (NCX). Myocytes also express sarcolemmal Ca^{2+} ATPases (PMCAs). These enzymes are generally believed to have a minor effect on Ca^{2+} extrusion [22], but they may have other isoform-specific signalling roles [23].

3. Ventricular myocyte EC-coupling

Since the ventricles contribute most to blood pumping, and disturbances in their rhythmicity can be immediately life-threatening, Ca^{2+} signalling has been most extensively studied in ventricular myocytes. Depolarisation of mammalian ventricular myocytes causes homogenous whole-cell Ca^{2+} signals that activate myofilaments throughout the volume of the cells [17,24,25]. Such global Ca^{2+} signals arise from the spatial summation of Ca^{2+} ions released by thousands of simultaneously-activated Ca^{2+} spark sites. The critical ultrastructural aspect of mammalian ventricular myocytes that promotes global Ca^{2+} transients is the presence of T-tubules [26]. These inward projections of the sarcolemma arise at each of the Z-lines within cardiac muscle, and have a regular spacing (~1.8 μm) [27,28] (Figs. 1 and 2). T-tubules vary in diameter (20–400 nm) and can have highly-branched morphologies, with both transverse and longitudinal elements [29]. Despite their narrow diameter, it is estimated that T-tubules can account for ~50% of the sarcolemmal membrane [30].

Key proteins involved in the initiation and eventual recovery of Ca^{2+} signals are located along the T-tubules, with lesser amounts on the peripheral surface membrane [26]. With respect to EC-coupling, T-tubules bring VOCCs and RyRs into close proximity to form dyadic junctions within the whole volume of a ventricular myocyte. Indeed, immunostaining ventricular myocytes for VOCCs and RyRs reveals that these proteins spatially overlap throughout the cells [25,31–33] (Fig. 2). Essentially, T-tubules relay action potentials to VOCCs at dyadic junctions throughout the cell. Consequently, when a ventricular myocyte is depolarised, thousands of Ca^{2+} sparks are simultaneously triggered and a homogenous Ca^{2+} rise ensues [25,34]. Imaging ventricular myocytes at high speed during the up-stroke of a response reveals that Ca^{2+} signals originate with a striated appearance (due to discrete release at dyadic junctions) [35,36]. The rapid diffusion of Ca^{2+} from the release sites produces the subsequent homogenous global Ca^{2+} signal within tens of milliseconds [37]. The loss of T-tubules, as occurs in disease (see below), leads to clusters of RyRs that are "orphaned" in the sense that they are no longer within a functional dyad and are not activated by CICR from nearby VOCCs during EC-coupling. Imaging of myocytes with orphaned RyRs demonstrates spatial inhomogeneities within the Ca^{2+} transients. Such inhomogeneities cause myocytes to contract with less force [29].

4. Ca^{2+} signals during atrial myocyte EC-coupling

It is likely that all electrically active or contractile cell types within mammalian hearts possess some degree of T-tubule network, but that the degree of tubulation can vary between regions and species. For example, the atrial myocytes of rats, and of some other small mammals, have a more rudimentary transverse-axial tubular network that is quite different from that seen in their ventricular cells [10,25,28,38,39]. It has been suggested that in place of the T-tubules these atrial cells have prominent SR elements, termed "Z-tubules" (Fig. 1) [40]. Just like T-tubules, these structures are perpendicular to the long axis of the cells and are also spaced at ~1.8 μm intervals. Therefore, atrial cells also contain transversely-oriented tubules, but they are sometimes formed from internal SR membrane and not the sarcolemma.

The distribution of RyRs within atrial myocytes is similar to that observed in ventricular cells; the majority of RyRs are observed within transverse striations corresponding to the positions of the Z-tubules